REVIEW ARTICLE

Progression in Moyamoya Disease: Clinical Features, Neuroimaging Evaluation, and Treatment

Xin Zhang[1,2,3,4,5,#], Weiping Xiao[1,2,3,4,5,#], Qing Zhang[6,#], Ding Xia[7], Peng Gao[7], Jiabin Su[1,2,3,4,5], Heng Yang[1,2,3,4,5], Xinjie Gao[1,2,3,4,5], Wei Ni[1,2,3,4,5], Yu Lei[1,2,3,4,5,*] and Yuxiang Gu[1,2,3,4,5,*]

[1]Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China; [2]Neurosurgical Institute of Fudan University, Shanghai, China; [3]Shanghai Clinical Medical Center of Neurosurgery, Shanghai, China; [4]Shanghai Key Laboratory of Brain Function and Restoration and Neural Regeneration, Shanghai, China; [5]Department of Neurosurgery, Huashan Hospital North, Fudan University, Shanghai, China; [6]Department of Nursing, Huashan Hospital North, Fudan University, Shanghai, China; [7]Department of Radiology, Huashan Hospital North, Fudan University, Shanghai, China

Abstract: Moyamoya disease (MMD) is a chronic cerebrovascular disease characterized by progressive stenosis of the arteries of the circle of Willis, with the formation of collateral vascular network at the base of the brain. Its clinical manifestations are complicated. Numerous studies have attempted to clarify the clinical features of MMD, including its epidemiology, genetic characteristics, and pathophysiology. With the development of neuroimaging techniques, various neuroimaging modalities with different advantages have deepened the understanding of MMD in terms of structural, functional, spatial, and temporal dimensions. At present, the main treatment for MMD focuses on neurological protection, cerebral blood flow reconstruction, and neurological rehabilitation, such as pharmacological treatment, surgical revascularization, and cognitive rehabilitation. In this review, we discuss recent progress in understanding the clinical features, in the neuroimaging evaluation and treatment of MMD.

1. INTRODUCTION

Moyamoya disease (MMD) is a chronic cerebrovascular disease characterized by progressive stenosis of the terminal segment of the internal carotid artery and the circle of Willis, resulting in the formation of a collateral vascular network at the base of the brain [1]. The clinical manifestations of this disease are complicated. Since it was first reported in the 1950s, numerous studies [2-5] from different parts of the world have attempted to clarify its epidemiological characteristics in different regions. Furthermore, studies of its genomics and pathophysiology have also promoted understanding of the unclear etiology of this disease [6, 7]. With the development and application of radiological techniques, various neuroimaging methods with different advantages have furthered the understanding of MMD in terms of its structural, functional, spatial, and temporal aspects [8, 9].

At present, the main treatment for MMD focuses on neurological protection, cerebral blood flow reconstruction, and neurological rehabilitation, including pharmacological treatment, surgical revascularization, and cognitive rehabilitation

[10-12]. In this review, we discuss recent advances in the understanding of its clinical features, its neuroimaging evaluation, and its treatment, to highlight prospective future directions in these fields.

2. EPIDEMIOLOGY

2.1. Incidence and Prevalence

MMD apparently has regional and ethnic characteristics. The incidence of MMD is higher in Asia than in Europe, America, Africa, and Latin America. Japan has a robust case-information registration mechanism and also has the highest incidence of MMD. According to 2 Japanese nationwide epidemiological surveys, the total number of patients diagnosed with MMD nearly doubled from 3,900 (95% confidence Interval [CI] 3,500-4,400) in 1994, to 7700 (95% confidence interval, 6,300-9,300) in 2003. During this time period, the prevalence and incidence rates increased from 3.16 and 0.35 per 100,000 population to 6.03 and 0.54 per 100,000 population, respectively, partly due to the development of neuroimaging techniques and improvement of the diagnostic criteria [13, 14]. Another epidemiology survey of unilateral MMD (typical angiographic evidence of MMD unilaterally, with equivocal contralateral findings) and quasi-MMD (MMD present with inherited or acquired disorders) conducted in 2013 estimated that there were about 6671

*Address correspondence to these authors at the Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China; E-mails: piliyouxia_lei@126.com; guyuxiang1972@126.com
[#]These authors contributed equally to this work.*

MMD patients, 841 unilateral MMD patients, and 430 quasi-MMD patients in Japan. The annual incidence rates of MMD, unilateral MMD, and quasi-MMD were estimated as 1.13, 0.23, and 0.11/100,000, and the prevalence rates as 5.22, 0.66, and 0.34/100,000, respectively [15].

Other southeast Asian regions, like China and South Korea, have also reported high incidences of MMD. A South Korean nationwide and population-based study estimated the number of patients with MMD to be 8,154 in 2011 and the incidence increased from 1.7 to 2.3 per 100,000 population from 2007 to 2011 [16]. A regional multi-center epidemiological survey by 15 hospitals in Nanjing, China, suggested that prevalence and incidence rates of MMD were 3.92 and 0.43/100,000 [17]. In Taiwan, China, an investigation by 7 hospitals revealed that the average incidence rate was 0.48/100,000 during a 12-year period [18]. In addition, a recent epidemiological single-center study in China identified 4,128 patients with MMD, with the highest prevalence observed in the Central Plains and surrounding regions, such as Henan province (1.050/100,000), Hebei province (0.818/100,000), Beijing (0.765/100,000), and Shandong province (0.660/100,000) [19].

Relatively lower incidence and prevalence rates of MMD were reported in Europe. For example, a Danish population-based study indicated an incidence rate of 0.07 per 100,000 person-years from 2008 onwards [2]. The prevalence of MMD among Irish Caucasians was calculated as 0.33/100,000, with a mean annual incidence of 0.04/100,000 [20]. America presented varying incidence rates of MMD in its different regions. Incidences in the USA ranged from 0.05/100,000 in Iowa, and 0.086/100,000 in Washington State and California, to 0.17/100,000 in Hawaii, per 100,000 patient-years [21-24]. Approximately 7,473 patients had been diagnosed with MMD in the USA from 2005 to 2008 [25]. Literature from different regions all over the world is compared in Fig. (**1**).

2.2. Age Distribution

Relative studies have suggested that the youngest patient diagnosed with MMD could be less than 4 years old [14, 16]. In Japan, previous studies have suggested that there are 2 peaks of MMD in terms of age distribution: approximately 10-19 years and 40-49 years [13]. However, these values were modified in the 2003 nationwide epidemiological survey, which revealed 3 peaks in men: 10-14 years, 35-39 years, and 55-59 years, and 2 peaks in women: 20-24 years and 50-54 years [14]. While in Korea, the first peak occurred at age 10-19 years and the second peak occurred at age 50-59 years [16]. Three epidemiological studies conducted in China revealed the same age distribution peaks in pediatric patients, *i.e.*, 5-9 years, but differed in the peak for adult patients, *i.e.* 40-44 years in both sexes, in Taiwan, China, and 35-39 years, in Nanjing province and the Central Plains and surrounding regions [17-19].

MMD patients of European Caucasian ethnic background demonstrated a tendency to present at a younger age: 35.8 ± 14.8 (range 1.6-72 years) [26]. Among patients enrolled in a German retrospective study, the youngest patient was reported to be 1 year old, while the median age of onset was 32.9 years (median 32 years, range 1-74 years, standard deviation

14.04 years) [27]. A long-term follow-up study in a Finnish population revealed that the mean age at the start of the follow-up ranged from 3 to 77 years (with a median age of 35 years) [28].

In the USA, there was a single age peak, at 1-10 years, in Iowa, while there was another peak, at 55-59 years, in California and Washington [23]. The age of onset also differed by ethnicity, as African Americans demonstrated an earlier onset, with a median age of onset of 18 years [24].

2.3. Sex Ratio

A female predominance was reported by several regional investigations, as the female to male ratios ranged from 2.8:1 in Iowa [25] to as high as 4.25:1 in Europe [29]. Moreover, 2 large epidemiological studies conducted in Japan in 1997 and 2003 presented the female to male ratio as 1.8:1 [13,14]. However, this was different from the figures in some Chinese studies, where this ratio was reported to be 1.15:1 and 1.3:1 in Nanjing and Taiwan, respectively [17,18]. In addition, Bao *et al.* [19] found a 1:1 sex ratio in a recent single-center epidemiological study in China. This suggests that sex factors in the clinical characteristics of MMD patients in China are different from those in Japan, South Korea, and other Asian countries, which may be related to differences among races, regions, and environments.

3. GENETICS

In addition to region-specific incidences, family history was found in 12.1% of MMD patients [14]. Identical twins have a higher rate of MMD co-prevalence, and the offspring of MMD patients are about 34 times more likely to develop MMD than the general population [30]. Some cases have been reported to have co-existing MMD and genetic diseases, such as Down syndrome, neurofibromatosis and Turner syndrome, were reported [31, 32]. Multiple systems and organs are involved in these genetic disorders and cerebrovascular diseases could be one of their complications. A retrospective analysis also revealed a significantly higher prevalence of other diseases, particularly type 1 diabetes mellitus, hyperlipidemia, and thyroid disease, among MMD patients [33]. Taken together, genetic factors appear to play an important role in the pathogenesis of MMD.

An investigation of 16 Japanese families with MMD (total: 77 patients) in 1999 reported 3p24.2−26 as an early genetic locus associated with MMD [34]. This locus was also found in a study in a Greek twin-pair with MMD by Zafeiriou *et al.* [35] in 2003. Several other genetic loci were demonstrated to be related to Japanese familial MMD, *i.e.*, 6q25, 8q23, 12p12, and 17q25 [36-38]. Notably, a rare 17q25 allele was much more frequent in Asian populations (Japanese, Korean, and Chinese), but was not detected in Caucasian cases [39]. The association of human leukocyte antigen (HLA) with various diseases also sparked some genetic investigations into MMD. For instance, significant association of HLA-DQB1*0502 [40], HLA-B51, and HLA-DR4 [41] was found with MMD in the Japanese population, and of HLA-DRB1(*)1302, HLA-DRB1(*)0609 [42], and HLA-B35 [43] with MMD in Korean patients. Moreover, the frequencies of HLA-DRB1*03, HLA-DRB1*13, HLA-A*02, HLA-B*08, and HLA-DQB1*03 were increased in
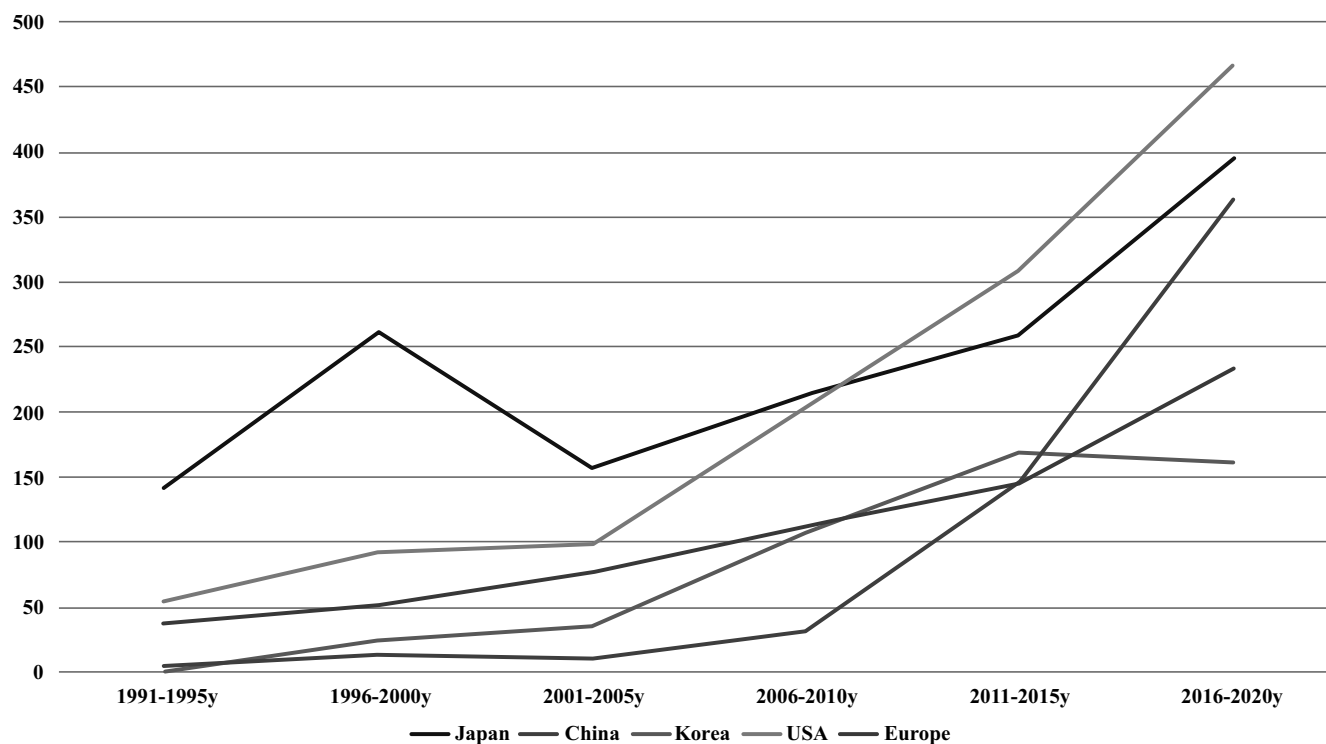
Fig. (1). Publications concerning moyamoya disease from various countries and regions during the past 30 years.

Caucasian MMD patients [44]. Other studies mainly focused on gene polymorphism of the tissue inhibitor of metalloproteinase (TIMP) [45], the vascular smooth muscle cell (SMC)-specific isoform of alpha-actin (ACTA2) [46], and ring-finger protein 213 (RNF213) [47, 48]. Mutations in RNF213, a zinc ring-finger protein that is related to intracranial major artery stenosis/occlusion [49], may affect the expression of some micro-RNAs and proteins associated with signaling processes involved in angiogenesis and immune activities that underlie the pathology and progression of MMD [50]. The amino acid substitution p.R4859K, the first identified RNF213 polymorphism associated with MMD, was found in 95% of patients with familial MMD, 80% of those with sporadic MMD, and 1.8% of control individuals in a Japanese population, in a genome-wide linkage and exome analysis study [51]. Other studies revealed the predictive role of this variant on the age of onset and Posterior Cerebral Artery (PCA) involvement in MMD cases [52]. In addition, several other variants in RNF213 were identified among Caucasian cases, namely p.N3962D, p.D4013N, p.R4062Q, and p.P4608S [53]. Additional mutations tended to be associated with ischemic- or hemorrhagic-type MMD in specific populations [54] and require further investigation.

4. PATHOPHYSIOLOGY

4.1. Immunity and Inflammation

In 1993, an autopsy conducted by Masuda *et al.* on 6 MMD patients revealed infiltration of macrophages and T cells in the thickened intima of the arteries in the circle of Willis composed predominantly of smooth muscle cells [55]. This provided insight into the participation of the immune system and inflammation in the pathophysiology of MMD

[56]. Chronic inflammation may damage the vessel wall and cause microthrombi, leading to ischemic stroke. Moreover, the pro-inflammatory environment formed by the abnormal secretion of cytokines may also stimulate activation of endothelial cells and macrophages [57, 58], the proliferation of smooth muscle cells [59, 60], and neovascularization [61]. One investigation has found the higher expression of an M2 macrophage marker-sCD163 in the serum of MMD patients, indicating the possible role of macrophage in the progression of MMD. Transforming Growth Factor-β (TGF-β) is among these pro-inflammatory cytokines, capable of regulating various cell functions, such as proliferation, differentiation, and migration [62]. Peripheral TGF-β was found to be increased in MMD patients and showed a positive correlation with Suzuki's stage MMD [63]. Increased expression of TGF-β could induce substantial extracellular matrix production, accompanied by intimal and medial hyperplasia in normal porcine arteries [64]. Similarly, higher serum levels of IL-1β, TNF-α, and IL-12 were also found in MMD patients than in age- and sex-matched healthy individuals; these levels also correlated with those detected in the cerebrospinal fluid (CSF) of these subjects [65].

Co-existence of MMD and some autoimmune diseases, such as type 1 diabetes mellitus [66], Graves' disease [67], or thrombocytopenia [68] also urged investigation into the mechanism of immune regulation disorder and abnormal expression of immune proteins in the progression of MMD. Yanagawa *et al.* [69] reported an MMD case with positive findings for rheumatoid factor and myeloperoxidase-anti-neutrophil cytoplasmic antibody. Protein array data analysis followed by bioinformatics analysis has helped to identify 165 significantly overexpressed autoantibodies in sera from MMD patients, which were associated with post-translational

modification, inflammatory responses, and DNA damage repair and maintenance [70]. Moreover, the deposition of IgG and IgM was found under the internal elastic lamina of the internal carotid artery and the anterior and middle cerebral arteries in 15 human autopsies of MMD cases [71]. The deposition of immune complexes may cause degeneration, tortuosity, and rupture of the inner elastic layer of the main cerebral vessels and their branches and can cause mass migration of the smooth muscle cells of the middle membrane to the subintima, leading to intima thickening and vascular lumen narrowing.

4.2. Endothelial Progenitor Cells

With the potential of differentiating into mature vascular endothelial cells, Endothelial Progenitor Cells (EPCs) participate in post-natal angiogenesis events, such as tumor angiogenesis [72] and vasculogenesis [73], within ischemic tissues [74], as well as in the maintenance of vascular homeostasis [75], in addition to embryonic vascular development [76]. Higher levels of circulating EPCs were found in MMD patients than in patients with atherosclerotic cerebrovascular disease and in healthy controls [77]. Moreover, this was observed in patients with angiographic moyamoya vessels, but not in patients with major cerebral artery occlusion (or severe stenosis) who did not have moyamoya vessels [78]. A prospective clinical trial also found a significant correlation between EPC count and good post-operative collateral circulation in 116 MMD patients [79]. However, seemingly contradicting reports found decreased levels of blood EPCs in a group of adult Caucasian MMD patients who had not undergone surgery [80] and in a group of children with MMD [81].

In addition to quantitative anomalies, the functional abnormality of EPCs may also play a role in the progression of MMD [81, 82]. This phenomenon exists due to a lack of standardized protocols for isolation, cultivation and identification of these cells, as different investigations were conducted using various techniques and with non-unified cell surface markers, concentrating on different subgroups of EPCs [82]. Early EPCs possess 3 specific surface markers: CD34, CD133, and vascular endothelial growth factor receptor 2 (VEGFR-2) [83], while late EPCs only express 2 markers: CD34 and VEGFR-2 [84]. EPCs at various stages could play different roles in the pathophysiology of MMD.

4.3. Nitric Oxide and Angiogenesis Related Cytokines

Nitric Oxide (NO), by binding to its only known receptor, guanylate cyclase (sGC) [85], plays an important biochemical role as a neurotransmitter and second messenger that is involved in various physiological and pathophysiological activities, including vascular smooth muscle remodeling [86] and vasoconstriction regulation [87], through an NO–sGC–cyclic guanosine monophosphate (cGMP) pathway [88]. This was confirmed by the dilatory effect of L-arginine, a precursor of NO, on murine cerebral arterioles and the constrictive effect of N(G)-monomethyl-L-arginine (L-NMMA), an NO synthesis inhibitor [89]. Additionally, the level of NO in the CSF obtained from 23 MMD patients was significantly higher than that of control specimens from 16 non-MMD patients [89]. Additionally, disrupted NO signaling due to sGC mutation could lead to MMD [90, 91]. It could be spec-

ulated that changes in NO levels can influence vascular smooth muscle and promote the formation of abnormal vascular networks in the skull base, by expanding small vessels in the collateral circulation; however, the specific underlying mechanisms remain to be elucidated. In addition, caveolin-1 (Cav-1), a repressive modulator of NO, was found reduced in MMD patients and further in vitro study showed that Cav-1 downregulation suppressed angiogenesis in the endothelial cells and induced the smooth muscle cells apoptosis, indicating its negative role in arterial remodeling in MMD.

MMD patients exhibit significantly altered plasma concentrations of cytokines, including growth factors like Vascular Endothelial Growth Factor (VEGF), platelet-derived growth factor BB (PDGF-BB) [92] and angiogenesis related cytokines. The expression of VEGF [93] could be induced by hypoxia [94]. It is currently considered to be the most effective pro-angiogenesis growth factor. Significantly higher plasma concentration of VEGF was found in MMD patients.

During the progression of MMD, local cerebral hypoxia could give rise to changes in the expression of VEGF, which may contribute to the formation of moyamoya vessels. In addition, receptors responsible for VEGF-soluble VEGF receptor-1 (sVEGFR-1) and sVEGFR-2 were found to be reduced in MMD patients and MMD patients who underwent indirect bypass surgery tended to have better collateral formation with lower sVEGFR-1 and sVEGFR-2 levels. As a kind of angiogenesis related cytokines and targeting at collagen IV, matrix metalloproteinase-9 (MMP-9) causes endothelial basal lamina destabilization by degrading cell-cell and cell-matrix contacts and may participate in the disruption of the blood−brain barrier [92]. Sporadic studies have reported elevated expression of some other cytokines like basic Fibroblast Growth Factor (bFGF), Hepatocyte Growth Factor (HGF), and Platelet-Derived Growth Factor (PDGF-BB) and Monocytes Chemoattractant Protein-1 (MCP-1) in MMD patients' serum or cerebrospinal fluid [95]. These cytokines mainly cause the proliferation of endothelial cells and migration of smooth muscle cells, leading to intima hyperplasia and pathological collateral vessel formation. However, whether these cytokines play initiating roles or are simply intermediate products during the progression of MMD remains unknown and deserves further investigation.

5. NEUROIMAGING EVALUATIONS

5.1. Digital Subtraction Angiography

MMD was first named as such in 1969 by Suzuki and Takaku because the appearance of this angiopathy on angiography is reminiscent of a puff of smoke (the meaning of "moyamoya" in Japanese) [96]. Digital subtraction angiography (DSA) is always the criterion standard for diagnosis of MMD [97]. DSA can not only evaluate the severity of stenosis in the terminal part of the internal carotid artery, but can also assess the degree of compensation from the external carotid artery and posterior circulation [98, 99]. Bonasia *et al.* [100] described the compensatory vascular systems in MMD and found 3 different types of anastomoses with different compensatory abilities, resulting from various perfusion needs of the anterior circulation. Recent studies based on DSA have mainly focused on the prediction of clinical

outcomes and prognosis in MMD [101-103]. Funaki *et al.* [104] demonstrated that choroidal anastomosis and posterior cerebral artery involvement are characteristic of intracranial hemorrhage in MMD, and might be risk factors for hemorrhagic MMD. Yamamoto and Hori *et al.* [105, 106] suggested that the longitudinal shift in collateral channels from the anterior to the posterior component might be closely related to the onset of hemorrhagic stroke in MMD, and may also be associated with ethnic differences. Zhang *et al.* [107] also found that direct anastomoses of the parasylvian cortical arteries with anterograde hemodynamic sources from the middle cerebral artery had a high risk of postoperative complications in MMD. Notably, the literature has increasingly confirmed the value of DSA in the assessment of MMD [108], as it allows evaluation of hemodynamic characteristics and compensation [109], and possibly prediction of clinical outcomes [110]. However, a shortcoming of this method is that it cannot truly reflect the perfusion status of the brain parenchyma. Moreover, with increased understanding of DSA, the modified Suzuki grading system may facilitate risk stratification and prognosis prediction in patients with MMD [111].

5.2. Magnetic Resonance Imaging

There is no doubt that with advances in Magnetic Resonance Imaging (MRI) and development of different sequences, marked progress has been made in the understanding of MMD [112, 113]. Previous studies have suggested that different sequences of structural MRI (sMRI) can contribute to the objective evidence of MMD [114-116], showing gray matter atrophy and white matter deterioration with high spatial resolution [117]. Kazumata *et al.* [118] reported that the combination of diffusion tensor imaging and sMRI is potentially useful for tracking subtle anatomical changes, even though hemodynamic compensation may mask ischemic status in advanced stages of MMD. In addition, Susceptibility-Weighted Imaging (SWI) and time-of-flight magnetic resonance angiography (TOF-MRA) allows highly reproducible detection of the bleeding point in hemorrhagic MMD, which is a prognostic factor for rebleeding and assessing the degree of preventive effects [119, 120]. High-resolution vessel wall imaging also has potential utility for diagnosis as well as for indicating disease activity with the presence of wall thickening and enhancement in MMD [121, 122].

Functional MRI (fMRI) provides the opportunity to understand the functional connectivity between brain regions at neural, regional, and network levels [123]. Blood Oxygen Level Dependence (BOLD) is an emerging technique for the assessment of cerebrovascular reactivity in MMD [124, 125]. It is a very promising tool for hemodynamic evaluation and holds potential for becoming a routine examination in the pre- and postoperative evaluation of MMD patients in the future [126, 127]. Working memory and performance speed scores are inversely correlated to the degree of disruption of the default mode network changes, and can be detected by using resting-state fMRI [128]. This suggests a possible relationship between higher cognitive function and orderliness of fundamental brain networks. Analysis of resting state networks may produce potential biomarkers for cognition in MMD [129]. Using fMRI, Lei *et al.* [130] clarified static and

dynamic organizational principles behind network changes in MMD, which provided some new insights into the pathophysiology and treatment direction.

Furthermore, different types of perfusion sequence MRI can provide hemodynamic information and have recently become hot research topics for MMD [131, 132]. Lin *et al.* [133] developed standardized Time-to-Peak maps and a scoring system *via* perfusion-weighted MRI to evaluate longitudinal perfusion changes in MMD and confirmed the predictive value of preoperative perfusion status. Arterial spin Labeling (ASL) is another MR perfusion method that relies on endogenous water molecules for signal and is increasingly used for quantitative cerebral blood flow measures in MMD [97, 113, 134]. Lee *et al.* [135] determined that ASL could be used as a noninvasive monitoring tool to identify perfusion changes, including cerebral blood flow, collateral blood flow, and anastomosis site patency after revascularization in MMD patients. Numerous modified methods [136, 137], such as velocity-selective ASL, offer a powerful approach to cerebral perfusion imaging with high accuracy, which holds marked research prospects for MMD.

5.3. Advanced Neuroimaging

Cerebral hemodynamic imaging, such as single-photon emission computed tomography, can evaluate the level of blood perfusion, and detects misery perfusion with high sensitivity in MMD [138, 139]. Positron-Emission computed Tomography (PET) seems to be more sensitive in detecting cerebral perfusion reserves, such as the Oxygen Extraction Fraction (OEF) and cerebrovascular reserve capacity, to clarify the mechanism of cognitive impairment for MMD [140-142]. Hara *et al.* [143] found that chronic ischemia in patients with MMD may induce decreased neurite and axonal density and simplified network complexity, which may lead to neurocognitive dysfunction. Lee *et al.* [144] also confirmed that severe hemodynamic impairment, indicated by increased OEF ratios on PET is associated with decreased cortical thickness in MMD. More importantly, hemodynamic evaluation is essential for MMD, to clarify vascular territories at risk of stroke [145, 146]. A previous study [127] found that the incidence of ischemic events was low and that cognitive function was stable in MMD without cerebral misery perfusion, which strengthened the surgical indications and concepts for MMD [147].

Electroencephalogram (EEG) can reflect the overall electrophysiological effects and the function of the brain network [148]. It is a noninvasive method with high temporal resolution that can reflect neuronal activities in patients with MMD [149]. A previous study has confirmed that EEG is useful for evaluating transient neurological events in MMD to distinguish seizures and epileptiform changes [150]. Additionally, postoperative transient neurological dysfunction resulting from transient cortical depression often occurs in MMD [151]. This can be detected by EEG, as low amplitude arrhythmic slowing in the corresponding hemisphere [152]. Some studies [153, 154] have also found that focal ischemic events as well as epileptic waves monitored on EEG correlated with clinical outcomes in MMD. Electrocorticography (ECoG) is another method for evaluating suppression of neurophysiologic activity and comparing spectral power

Table 1.   Different grading systems for moyamoya disease based on different neuroimaging methods.

Year	Author	Basis for Grading	Objective	Significance
2011	Czabanka, *et al.*	DSA, MRI & CVRC	Degree of stenosis of intracranial artery & compensation Sign of ischemia CVRC	Such system can stratify for clinical symptomatology
2014	Hung, *et al.*	Color-coded parametric quantitative DSA DSC-PWI	Delay time of maximal opacification between ICA and MCA	Such system correlates with angioarchitecture and hemodynamic impairment status
2015	Sahoo, *et al.*	Angiographic outcome score	Reformation of distal MCA and ACA Regression of basal moyamoya vessels Leptomeningeal collaterals and overall perfusion	Such score can reflect angiographic changes after revascularization
2017	Ladner, *et al.*	Prior infarcts, reactivity & angiography	DSA Structural and hemodynamic MRI	Such system correlates with symptomatology to evaluate hemodynamic severity
2018	Yin, *et al.*	CT perfusion	Cerebral perfusion status	Such system can evaluate cerebral perfusion status and predict the efficacy of revascularization
2019	Zhi-Wen, *et al.*	Collateral circulation and Suzuki stage	Anatomic extent of blood flow of intracranial and pial perforator	Such system correlates with clinical symptoms, hemodynamic status, and therapeutic prognosis which may facilitate risk stratification and prognosis predictions in MMD patients
2019	Lin, *et al.*	MRI perfusion	Standardized TTP maps using cerebellar reference values	Preoperative perfusion status is the only predictor of indirect revascularization outcome
2020	Moinay, *et al.*	Demographics, multimodal imaging Surgical revascularization types	Hyperlipidemia & smoking Cerebral infarction on preoperative CT or MRI Reduced regional CVRC	Such system reveals the importance of smoking and hyperlipidemia to predict clinical outcome
2020	Mario, *et al.*	DSA, MRI & Xenon-CT	Structural intracranial vessels criteria Sign of ischemia/hemorrhage/atrophy CVRC	Such system can stratify hemispheric symptomatology and predict stroke events

(CVRC: Cerebrovascular Reserve Capacity; DSC-PWI: Dynamic Susceptibility Contrast Perfusion-Weighted Imaging; ICA: Internal Carotid Artery; MCA: Middle Cerebral Artery, ACA: Anterior Cerebral Artery; CT: Computer Tomography; MRI: Magnetic Resonance Imaging; TTP: Time To Peak)

between different regions in the surgical area, which may provide insight into the potential neuromodulatory role of revascularization surgery [155, 156].

5.4. Future Directions

Various types of neuroimaging modalities have different clinical significance in the diagnosis and evaluation of MMD [157]. DSA and sMRI may be more sensitive for distinguishing characteristic structural changes and yield a higher spatial resolution. ASL as well as EEG may have better temporal resolution and could be more suitable for individual application. On the other hand, BOLD and PET are superior in functional evaluation of the brain and provides some new insights into MMD. Moreover, it cannot be refuted that neuropsychological evaluation is also a valuable assessment, because cognitive impairment resulting from MMD can also be detected on functional neuroimaging, which is of great significance in identifying asymptomatic MMD and disease progression [158]. Multiple studies [130, 150] have found abnormalities on fMRI and EEG, which correlated strongly with cognitive changes and clinical manifestations. Investi-

gation of the connection between cognitive status and advanced neuroimaging have become a focus in MMD, with marked potential [159]. Yet, each neuroimaging modality has its own limitations, which might be complemented by using multimodal image fusion techniques. The Berlin grading system [160] involves DSA, sMRI, and functional cerebrovascular assessment of hemodynamic impairment, and correlates with disease severity. More importantly, it allows stratification of the individual risks of surgical therapy. Although there are many types of staging systems for MMD, based on clinical characteristics and imaging findings (Table **1**), an appropriate grading system for MMD that can clarify the true progression of the disease is still lacking.

6. TREATMENT

6.1. Medical Treatment

In terms of treating the common symptoms of MMD, the use of antiplatelet and many other agents focuses on symptomatic control [10, 161]. The results of a nationwide survey in Japan [162] showed that the selection of antiplatelet drugs

varied widely across facilities and there is no consensus treatment. Notably, some researches [163] showed that cilostazol improves cerebral perfusion as well as cognition better than other antiplatelet drugs for ischemic MMD patients. Meanwhile, a recent 10-year follow-up evaluation has demonstrated that the use of antiplatelet agents did not influence the rate of cerebral infarction in patients with MMD [163]. Treatment indications for asymptomatic MMD are currently being revisited in the AMORE trial [164]; more research evidence is needed to confirm the efficiency of conservative therapy with antiplatelet drugs [165]. Given the vascular cognitive impairment caused by MMD [114], acetylcholinesterase inhibitors, such as donepezil and rivastigmine, have generally been approved for modest cognitive benefits [166]. Moreover, butylphthalide may alleviate perioperative neurological deficits in cases with unfavorable preoperative status [167]. Taken together, effectiveness of medical treatment for MMD remains unclear and further investigations are urgently needed [168].

6.2. Revascularization

Surgical treatment is the most effective method to restore the blood supply and increase cerebral perfusion in order to prevent secondary stroke in ischemic MMD and to stabilize cerebrovascular hemodynamics to regress fragile moyamoya vessels to prevent bleeding in hemorrhagic MMD [11, 169], which then improves neurocognitive outcomes [170]. In surgical practice, endovascular treatment and revascularization are often applied; the latter includes indirect, direct, and combined revascularization [171].

6.2.1. Endovascular Treatment

Endovascular treatment (EVT) has become the current main-stream treatment for MMD-associated aneurysms [172]. Previous reports have shown that endovascular embolization is safe and efficacious for treating intracranial aneurysm with liquid embolic agents or coils in most locations in patients with MMD [173, 174]. Moreover, some studies [175, 176] have reported that while EVT can be applied in atherosclerotic moyamoya syndrome, it is a major challenge to perform EVT for MMD in stenosed arteries in which super-selective catheterization is technically difficult [177]. Indeed, there are plenty of attempts to treat MMD by EVT in order to improve forward blood flow of target vessels. Due to the pathogenesis of MMD being vasculitis-liked angiopathy with concentric stenosis of intracranial artery, both angioplasty and stenting may promote inflammatory reaction in the artery, of which the long-term clinical outcomes remain controversial.

6.2.2. Direct Revascularization

Direct revascularization *via* anastomosis of the superficial temporal artery to the middle cerebral artery (STA-MCA bypass) has been the most common procedure for addressing the MCA territory [178], but also supports the anterior cerebral artery territory *via* leptomeningeal anastomoses [179, 180]. Particularly, Kurihara *et al.* [181] reported that the posterior auricular artery can also be used as the donor artery using a double direct bypass technique for cases with poor development of the STA. Multiple reports have confirmed that direct revascularization is more effective in preventing recurrent ischemic strokes for adult ischemic-type MMD

[182, 183], while, direct bypass is challenging in children, where bypass patency rates have been reported to be lower [184, 185].

6.2.3. Indirect Revascularization

Indirect revascularization relies on neovascularization of the cortical surface using angiogenic mechanisms from pedicle-based grafts, such as pial synangiosis, and temporal muscle grafts, which are generally easier to perform [186, 187]. However, the hemodynamic protective effects may take months to develop and are not very predictable [188]. A previous study confirmed that indirect bypass surgery could provide satisfactory long-term improvement in overall clinical outcomes and prevention of recurrent stroke in children with MMD [189]. Another previous study proved that encephalo-duro-arterio-synangiosis was beneficial for patients with hemorrhagic MMD through long-term follow-up [190]. Mirone *et al.* [191] also emphasized the good success rate of using multiple burr holes in pediatric MMD, which could be an effective support to produce good collateral revascularization and improve cerebral perfusion. Such burr-hole surgery could provide satisfying clinical symptom control with low perioperative risk. In addition to the abovementioned coverage of the brain surface, other strategies, such as Encephalo-Duro-Myo-Synangiosis (EDMS) and omental transplantation have also been applied to stimulate transcranial angiogenesis [192]. There are a wide variety of indirect techniques, but which of these techniques is superior to the others remains unknown.

6.2.4. Combined Revascularization

Combined revascularization includes direct and indirect bypasses; the latter aims to achieve both immediate and later hemodynamic improvement and serves as a fallback strategy in case the direct bypass fails [193]. Multiple reports [194, 195] have confirmed that combined revascularization would be the best choice for preventing not only further ischemic events, but also hemorrhagic stroke, by improving anterior choroidal artery-posterior communicating artery dilation and extension. Additionally, Kazumata *et al.* [196] reported that combined revascularization may improve cognitive function, including processing speed and attention in MMD patients with evidence of postsurgical structural brain changes. However, we encountered a patient with intraventricular hemorrhage (IVH) who was diagnosed with MMD accompanied with a pseudoaneurysm in our center (Figs. **2A**, **2B**; white arrow), in whom combined revascularization was performed (Fig. **2C**). Long-term angiographic follow-up showed good patency of the donor artery, satisfactory compensation from EDMS, and disappearance of the pseudoaneurysm (Figs. **2D-F**). After 1 year, the patient suffered from headache and Computed Tomography (CT) showed IVH, as before, but showed no significant findings on DSA (Figs. **2G-I**). SWI revealed multiple right paraventricular microbleeds (Fig. **2J**; dotted arrow). It remains unclear what should be done for such patients, and how rebleeds should be prevented [173]. In addition, postoperative hyperperfusion syndrome, such as aphasia, epileptic seizures, and even new cerebral hemorrhage or ischemia, are experienced frequently in the acute phase after such combined revascularization processes, and these can progress to irreversible sequelae [197]. Therefore, appropriate methods with sufficient evidence are urgently needed.
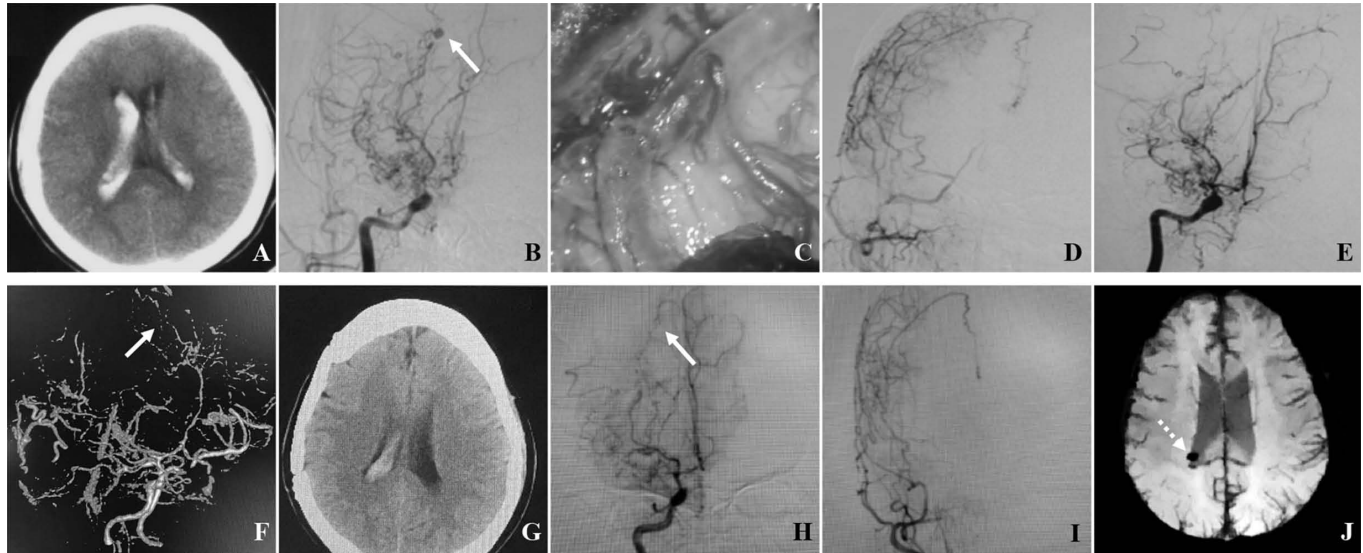
Fig. (2). This patient was found to have Intraventricular Hemorrhage (IVH) and was diagnosed with moyamoya disease accompanied with pseudoaneurysm (**A**, **B**, white arrow) at our center. Combined revascularization (superficial temporal artery to the middle cerebral artery by-pass and encephalo-duro-myo-synangiosis) was performed (**C**). The 6-months follow-up with digital subtraction angiography (DSA) showed good compensation from the external carotid artery and disappearance of the pseudoaneurysm (**D**, **E**, **F**). After 1 year, the patient suffered from headache. IVH was found on computed tomography, but there was no significant finding on DSA (**G**, **H**, **I**). Susceptibility-weighted imaging was performed and revealed multiple right paraventricular microbleeds (**J**; dotted arrow). *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*
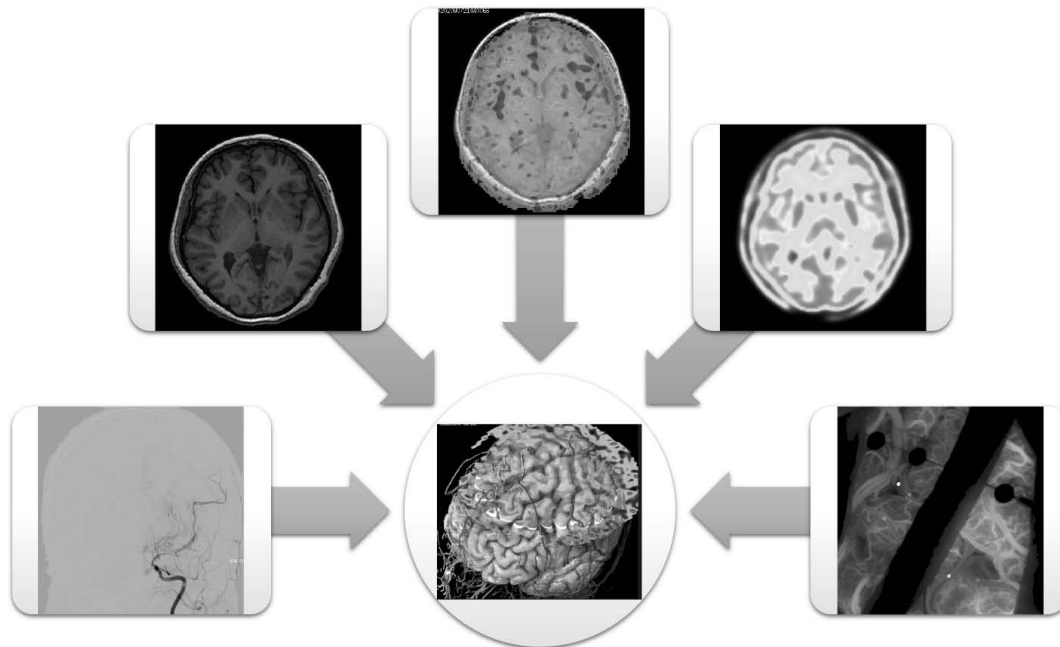

Fig. (3). Evaluating methods, including Digital Subtraction Angiography (DSA), structural Magnetic Resonance Imaging (sMRI), Arterial Spin Labeling (ASL), positron emission tomography (PET), indocyanine green angiography (ICG-FLOW800) and electrocorticography (ECoG) can reflect different characteristics, such as angioarchitecture, cerebral perfusion, and metabolic status in different hemispheres from the perspective of structure to function. Such modified revascularization based on multimodal neuroimaging guidance aims to provide objective evidence for surgical decision-making and can decrease peri-operative complications of moyamoya disease. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

6.3. Neurological Rehabilitation

Neurological rehabilitation also plays an important role in vascular cognitive impairment caused by MMD. Perng *et al.* [198], in their meta-analysis, found that systematic cogni-tive training is an effective intervention for MMD. Formica *et al.* [199] also found that specific motor and neuropsycho-logical rehabilitative treatments provided advantages in the care of MMD patients with disorders of consciousness. In

particular, psychological intervention for pediatric MMD patients is important to improve post-operative quality of life and physical, emotional, social, and school functional outcomes [200]. Choi *et al.* [201] also confirmed the effectiveness of remote ischemic pre- and post-conditioning in reducing neurological complications and the duration of hospitalization in MMD patients undergoing STA-MCA anastomosis. Taken together, neuroprotection and neurorecovery enhancement have marked potential as MMD treatments. A standard neurological rehabilitation protocol needs to be established [202].

6.4. Future Directions

Although surgical revascularization is the most successful treatment for improving cerebral perfusion and reducing the risk of stroke events in MMD patients, the rate of complications, such as hyperperfusion syndrome, cerebral infarction, and epilepsy, remains very high due to hemodynamic abnormalities. Nevertheless, the distribution of global and regional perfusion, metabolism, as well as neuronal activity, are also important influencing factors in surgical decision-making regarding bypass surgeries [203]. Additionally, the choice of recipient vessel is currently based on the experience of the surgeon, without objective evidence. A modified method of operation is needed to reduce the incidence of complications [104]. With multi-dimensional neuroimaging evaluations of MMD, assessment that includes angioarchitecture, cerebral perfusion and metabolism, regional hemodynamic parameters, and neuronal activities by means of DSA, ASL, PET-CT, indocyanine green angiography (ICG-FLOW 800), and intraoperative electrocorticography [204]. With such evaluations, the ischemic as well as dysfunctional cortical area can be accurately confirmed so as to choose the appropriate recipient artery, and the clinical outcomes of bypass surgery may improve and the complication rate decrease (Fig. **3**).

CONCLUSION

Taken together, not only are the clinical features of MMD complicated, but the diagnostic criteria and treatment strategy for MMD need to be developed further. More nationwide studies are urgently needed to clarify the mechanism and risk factors of MMD and explore more efficient preventative measures. There are numerous neuroimaging methods that can be used to evaluate the progression of MMD, in terms of different aspects, which can also be useful in facilitating an appropriate bypass.

AUTHORS' CONTRIBUTION

XZ and WPX performed all data acquisition and interpretation, and drafted the manuscript. QZ assisted with data interpretation and revised the manuscript. DX and PG assisted with neuroimaging and helped to draft the manuscript. JBS, HY, and XJG assisted with data collection. WN, YL, and YXG guided article revision. All authors contributed to the article and approved the submitted version.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

REFERENCES

[1]   Scott, R.M.; Smith, E.R. Moyamoya disease and moyamoya syndrome. *N. Engl. J. Med.,* **2009**, *360*(12), 1226-1237.
        http://dx.doi.org/10.1056/NEJMra0804622 PMID: 19297575
[2]   Birkeland, P.; Tharmabalan, V.; Lauritsen, J.; Ganesan, V.; Bjarkam, C.R.; von Weitzel-Mudersbach, P. Moyamoya disease in a European setting: A Danish population-based study. *Eur. J. Neurol.,* **2020**, *27*(12), 2446-2452.
        http://dx.doi.org/10.1111/ene.14439 PMID: 32668488
[3]   Miyakoshi, A.; Funaki, T.; Fushimi, Y.; Nakae, T.; Okawa, M.; Kikuchi, T.; Kataoka, H.; Yoshida, K.; Mineharu, Y.; Matsuhashi, M.; Nakatani, E.; Miyamoto, S. Cortical distribution of fragile periventricular anastomotic collateral vessels in moyamoya disease: An exploratory cross-sectional study of japanese patients with moyamoya disease. *AJNR Am. J. Neuroradiol.,* **2020**, *41*(12), 2243-2249.
        http://dx.doi.org/10.3174/ajnr.A6861 PMID: 33154076
[4]   Kwon, H.S.; Kim, Y.S.; Lee, J.M.; Koh, S.H.; Kim, H.Y.; Kim, C.; Lee, S.H.; Jung, K.H.; Kim, Y.D.; Kwon, H.M.; Kim, B.J.; Kim, J.M.; Kim, B.J.; Heo, S.H.; Chang, D.I.; Investigators, S.K.Y. Causes, risk factors, and clinical outcomes of stroke in Korean young adults: Systemic lupus erythematosus is associated with unfavorable outcomes. *J. Clin. Neurol.,* **2020**, *16*(4), 605-611.
        http://dx.doi.org/10.3988/jcn.2020.16.4.605 PMID: 33029967
[5]   Ge, P.; Ye, X.; Zhang, Q.; Liu, X.; Deng, X.; Zhao, M.; Wang, J.; Wang, R.; Zhang, Y.; Zhang, D.; Zhao, J. Clinical features, surgical treatment, and outcome of intracranial aneurysms associated with moyamoya disease. *J. Clin. Neurosci.,* **2020**, *80*, 274-279.
        http://dx.doi.org/10.1016/j.jocn.2020.09.006 PMID: 33099360
[6]   Zhu, B.; Liu, X.; Zhen, X.; Li, X.; Wu, M.; Zhang, Y.; Zhao, Z.; Zhang, D.; Zhao, J. RNF213 gene polymorphism rs9916351 and rs8074015 significantly associated with moyamoya disease in Chinese population. *Ann. Transl. Med.,* **2020**, *8*(14), 851.
        http://dx.doi.org/10.21037/atm-20-1040 PMID: 32793695
[7]   Kuribara, T.; Mikami, T.; Komatsu, K.; Kimura, Y.; Kim, S.; Miyata, K.; Akiyama, Y.; Enatsu, R.; Hirano, T.; Mikuni, N. Preoperatively estimated graft flow rate contributes to the improvement of hemodynamics in revascularization for Moyamoya disease. *J. Stroke Cerebrovasc. Dis.,* **2021**, *30*(1), 105450.
        http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2020.105450 PMID: 33171424
[8]   Fan, H.; Su, P.; Huang, J.; Liu, P.; Lu, H. Multi-band MR fingerprinting (MRF) ASL imaging using artificial-neural-network trained with high-fidelity experimental data. *Magn. Reson. Med.,* **2021**, *85*(4), 1974-1985.
        http://dx.doi.org/10.1002/mrm.28560 PMID: 33107100

[9]   Eisenmenger, L.B.; Rivera-Rivera, L.A.; Johnson, K.M.; Drolet, B.A. Utilisation of advanced MRI techniques to understand neuro-vascular complications of PHACE syndrome: A case of arterial stenosis and dissection. *BMJ Case Rep.,* **2020**, *13*(9), e235992.
http://dx.doi.org/10.1136/bcr-2020-235992 PMID: 32928832

[10]   Qiu, S.; Gao, J.; Liu, J.; Wang, C.; Li, A.; Wang, J. Study on Novel Nanoparticle Slow-Release Drugs for Moyamoya Disease. *J. Nanosci. Nanotechnol.,* **2021**, *21*(2), 1008-1017.
http://dx.doi.org/10.1166/jnn.2021.18682 PMID: 33183437

[11]   Raper, D.M.S.; Rutledge, W.C.; Winkler, E.A.; Meisel, K.; Callen, A.L.; Cooke, D.L.; Abla, A.A. Controversies and Advances in Adult Intracranial Bypass Surgery in 2020. *Oper. Neurosurg. (Hagerstown),* **2020**, *20*(1), 1-7.
http://dx.doi.org/10.1093/ons/opaa276 PMID: 32895706

[12]   Krisht, K.; Orenday-Barraza, J.M.; Saad, H.; Krisht, A.F. Continuous interrupted double throw suturing method: a novel suturing technique for extracranial-intracranial Bypass. *World Neurosurg.,* **2021**, *146*, 113-117.
http://dx.doi.org/10.1016/j.wneu.2020.10.167 PMID: 33171321

[13]   Wakai, K.; Tamakoshi, A.; Ikezaki, K.; Fukui, M.; Kawamura, T.; Aoki, R.; Kojima, M.; Lin, Y.; Ohno, Y. Epidemiological features of moyamoya disease in Japan: Findings from a nationwide survey. *Clin. Neurol. Neurosurg.,* **1997**, *99*(Suppl. 2), S1-S5.
http://dx.doi.org/10.1016/S0303-8467(97)00031-0 PMID: 9409395

[14]   Kuriyama, S.; Kusaka, Y.; Fujimura, M.; Wakai, K.; Tamakoshi, A.; Hashimoto, S.; Tsuji, I.; Inaba, Y.; Yoshimoto, T. Prevalence and clinicoepidemiological features of moyamoya disease in Japan: Findings from a nationwide epidemiological survey. *Stroke,* **2008**, *39*(1), 42-47.
http://dx.doi.org/10.1161/STROKEAHA.107.490714 PMID: 18048855

[15]   Hayashi, K.; Horie, N.; Suyama, K.; Nagata, I. An epidemiological survey of moyamoya disease, unilateral moyamoya disease and quasi-moyamoya disease in Japan. *Clin. Neurol. Neurosurg.,* **2013**, *115*(7), 930-933.
http://dx.doi.org/10.1016/j.clineuro.2012.09.020 PMID: 23041378

[16]   Ahn, I.M.; Park, D.H.; Hann, H.J.; Kim, K.H.; Kim, H.J.; Ahn, H.S. Incidence, prevalence, and survival of moyamoya disease in Korea: A nationwide, population-based study. *Stroke,* **2014**, *45*(4), 1090-1095.
http://dx.doi.org/10.1161/STROKEAHA.113.004273 PMID: 24595588

[17]   Miao, W.; Zhao, P.L.; Zhang, Y.S.; Liu, H.Y.; Chang, Y.; Ma, J.; Huang, Q.J.; Lou, Z.X. Epidemiological and clinical features of Moyamoya disease in Nanjing, China. *Clin. Neurol. Neurosurg.,* **2010**, *112*(3), 199-203.
http://dx.doi.org/10.1016/j.clineuro.2009.11.009 PMID: 20004511

[18]   Chen, P.C.; Yang, S.H.; Chien, K.L.; Tsai, I.J.; Kuo, M.F. Epidemiology of moyamoya disease in Taiwan: A nationwide population-based study. *Stroke,* **2014**, *45*(5), 1258-1263.
http://dx.doi.org/10.1161/STROKEAHA.113.004160 PMID: 24676775

[19]   Bao, X.Y.; Wang, Q.N.; Zhang, Y.; Zhang, Q.; Li, D.S.; Yang, W.Z.; Zhang, Z.S.; Zong, R.; Han, C.; Duan, L. Epidemiology of Moyamoya Disease in China: Single-Center, Population-Based Study. *World Neurosurg.,* **2019**, *122*, e917-e923.
http://dx.doi.org/10.1016/j.wneu.2018.10.175 PMID: 30404059

[20]   Doherty, R.J.; Caird, J.; Crimmins, D.; Kelly, P.; Murphy, S.; McGuigan, C.; Tubridy, N.; King, M.D.; Lynch, B.; Webb, D.; O'Neill, D.; McCabe, D.J.H.; Boers, P.; O'Regan, M.; Moroney, J.; Williams, D.J.; Cronin, S.; Javadpour, M. Moyamoya disease and moyamoya syndrome in Ireland: Patient demographics, mode of presentation and outcomes of EC-IC bypass surgery. *Ir. J. Med. Sci.,* **2021**, *190*(1), 335-344.
http://dx.doi.org/10.1007/s11845-020-02280-w PMID: 32562218

[21]   Graham, J.F.; Matoba, A. A survey of moyamoya disease in Hawaii. *Clin. Neurol. Neurosurg.,* **1997**, *99*(Suppl. 2), S31-S35.
http://dx.doi.org/10.1016/S0303-8467(97)00037-1 PMID: 9409401

[22]   Kleinloog, R.; Regli, L.; Rinkel, G.J.; Klijn, C.J. Regional differences in incidence and patient characteristics of moyamoya disease: A systematic review. *J. Neurol. Neurosurg. Psychiatry,* **2012**, *83*(5), 531-536.
http://dx.doi.org/10.1136/jnnp-2011-301387 PMID: 22378916

[23]   Uchino, K.; Johnston, S.C.; Becker, K.J.; Tirschwell, D.L. Moyamoya disease in Washington State and California. *Neurology,* **2005**, *65*(6), 956-958.
http://dx.doi.org/10.1212/01.wnl.0000176066.33797.82 PMID: 16186547

[24]   Wetjen, N.M.; Garell, P.C.; Stence, N.V.; Loftus, C.M. Moyamoya disease in the midwestern United States. *Neurosurg. Focus,* **1998**, *5*(5), e1.
http://dx.doi.org/10.3171/foc.1998.5.5.4 PMID: 17112204

[25]   Kainth, D.; Chaudhry, S.A.; Kainth, H.; Suri, F.K.; Qureshi, A.I. Epidemiological and clinical features of moyamoya disease in the USA. *Neuroepidemiology,* **2013**, *40*(4), 282-287.
http://dx.doi.org/10.1159/000345957 PMID: 23445954

[26]   Acker, G.; Goerdes, S.; Schneider, U.C.; Schmiedek, P.; Czabanka, M.; Vajkoczy, P. Distinct clinical and radiographic characteristics of moyamoya disease amongst European Caucasians. *Eur. J. Neurol.,* **2015**, *22*(6), 1012-1017.
http://dx.doi.org/10.1111/ene.12702 PMID: 25847099

[27]   Kraemer, M.; Schwitalla, J.C.; Diesner, F.; Aktas, O.; Hartung, H.P.; Berlit, P. Clinical presentation of Moyamoya angiopathy in Europeans: Experiences from Germany with 200 patients. *J. Neurol.,* **2019**, *266*(6), 1421-1428.
http://dx.doi.org/10.1007/s00415-019-09277-1 PMID: 30868219

[28]   Savolainen, M.; Mustanoja, S.; Pekkola, J.; Tyni, T.; Uusitalo, A.M.; Ruotsalainen, S.; Poutiainen, E.; Hernesniemi, J.; Kivipelto, L.; Tatlisumak, T. Moyamoya angiopathy: Long-term follow-up study in a Finnish population. *J. Neurol.,* **2019**, *266*(3), 574-581.
http://dx.doi.org/10.1007/s00415-018-9154-7 PMID: 30560456

[29]   Kraemer, M.; Heienbrok, W.; Berlit, P. Moyamoya disease in Europeans. *Stroke,* **2008**, *39*(12), 3193-3200.
http://dx.doi.org/10.1161/STROKEAHA.107.513408 PMID: 18787200

[30]   Kuroda, S.; Houkin, K. Moyamoya disease: Current concepts and future perspectives. *Lancet Neurol.,* **2008**, *7*(11), 1056-1066.
http://dx.doi.org/10.1016/S1474-4422(08)70240-0 PMID: 18940695

[31]   Byworth, M.T.; Moffatt, J.I.; Perera, K.S. Novel vascular anastomoses and moyamoya disease in a woman with down syndrome. *Can. J. Neurol. Sci.,* **2021**, *48*(3), 417-418.
http://dx.doi.org/10.1017/cjn.2020.195 PMID: 32892767

[32]   Santoro, C.; Palladino, F.; Bernardo, P.; Cinalli, G.; Mirone, G.; Giugliano, T.; Piluso, G.; Perrotta, S. Report on a child with neurofibromatosis type 2 and unilateral moyamoya: Further evidence of cerebral vasculopathy in NF2. *Neurol. Sci.,* **2019**, *40*(7), 1475-1476.
http://dx.doi.org/10.1007/s10072-019-3728-8 PMID: 30666475

[33]   Bower, R.S.; Mallory, G.W.; Nwojo, M.; Kudva, Y.C.; Flemming, K.D.; Meyer, F.B. Moyamoya disease in a primarily white, midwestern US population: Increased prevalence of autoimmune disease. *Stroke,* **2013**, *44*(7), 1997-1999.
http://dx.doi.org/10.1161/STROKEAHA.111.000307 PMID: 23652271

[34]   Ikeda, H.; Sasaki, T.; Yoshimoto, T.; Fukui, M.; Arinami, T. Mapping of a familial moyamoya disease gene to chromosome 3p24.2-p26. *Am. J. Hum. Genet.,* **1999**, *64*(2), 533-537.
http://dx.doi.org/10.1086/302243 PMID: 9973290

[35]   Zafeiriou, D.I.; Ikeda, H.; Anastasiou, A.; Vargiami, E.; Vougiouklis, N.; Katzos, G.; Gombakis, N.; Gioula, G.; Matsushima, Y.; Kirkham, F.J. Familial moyamoya disease in a Greek family. *Brain Dev.,* **2003**, *25*(4), 288-290.
http://dx.doi.org/10.1016/s0387-7604(02)00224-3 PMID: 12767463

[36]   Inoue, T.K.; Ikezaki, K.; Sasazuki, T.; Matsushima, T.; Fukui, M. Linkage analysis of moyamoya disease on chromosome 6. *J. Child Neurol.,* **2000**, *15*(3), 179-182.
http://dx.doi.org/10.1177/088307380001500307 PMID: 10757474

[37]   Sakurai, K.; Horiuchi, Y.; Ikeda, H.; Ikezaki, K.; Yoshimoto, T.; Fukui, M.; Arinami, T. A novel susceptibility locus for moyamoya disease on chromosome 8q23. *J. Hum. Genet.,* **2004**, *49*(5), 278-281.
http://dx.doi.org/10.1007/s10038-004-0143-6 PMID: 15362573

[38]   Yamauchi, T.; Tada, M.; Houkin, K.; Tanaka, T.; Nakamura, Y.; Kuroda, S.; Abe, H.; Inoue, T.; Ikezaki, K.; Matsushima, T.; Fukui, M. Linkage of familial moyamoya disease (spontaneous occlusion

of the circle of Willis) to chromosome 17q25. *Stroke,* **2000**, *31*(4), 930-935.
http://dx.doi.org/10.1161/01.STR.31.4.930 PMID: 10754001

[39] Liu, W.; Hashikata, H.; Inoue, K.; Matsuura, N.; Mineharu, Y.; Kobayashi, H.; Kikuta, K.; Takagi, Y.; Hitomi, T.; Krischek, B.; Zou, L.P.; Fang, F.; Herzig, R.; Kim, J.E.; Kang, H.S.; Oh, C.W.; Tregouet, D.A.; Hashimoto, N.; Koizumi, A. A rare asian founder polymorphism of raptor may explain the high prevalence of moyamoya disease among east asians and its low prevalence among caucasians. *Environ. Health Prev. Med.,* **2010**, *15*(2), 94-104.
http://dx.doi.org/10.1007/s12199-009-0116-7 PMID: 19921495

[40] Inoue, T.K.; Ikezaki, K.; Sasazuki, T.; Matsushima, T.; Fukui, M. Analysis of class II genes of human leukocyte antigen in patients with moyamoya disease. *Clin. Neurol. Neurosurg.,* **1997**, *99*(Suppl. 2), S234-S237.
http://dx.doi.org/10.1016/S0303-8467(97)00051-6 PMID: 9409445

[41] Aoyagi, M.; Ogami, K.; Matsushima, Y.; Shikata, M.; Yamamoto, M.; Yamamoto, K. Human leukocyte antigen in patients with moyamoya disease. *Stroke,* **1995**, *26*(3), 415-417.
http://dx.doi.org/10.1161/01.STR.26.3.415 PMID: 7886716

[42] Hong, S.H.; Wang, K.C.; Kim, S.K.; Cho, B.K.; Park, M.H. Association of HLA-DR and -DQ genes with familial moyamoya disease in koreans. *J. Korean Neurosurg. Soc.,* **2009**, *46*(6), 558-563.
http://dx.doi.org/10.3340/jkns.2009.46.6.558 PMID: 20062572

[43] Han, H.; Pyo, C.W.; Yoo, D.S.; Huh, P.W.; Cho, K.S.; Kim, D.S. Associations of Moyamoya patients with HLA class I and class II alleles in the Korean population. *J. Korean Med. Sci.,* **2003**, *18*(6), 876-880.
http://dx.doi.org/10.3346/jkms.2003.18.6.876 PMID: 14676447

[44] Kraemer, M.; Horn, P.A.; Roder, C.; Khan, N.; Diehl, R.R.; Berlit, P.; Heinemann, F.M. Analysis of human leucocyte antigen genes in Caucasian patients with idiopathic moyamoya angiopathy. *Acta Neurochir. (Wien),* **2012**, *154*(3), 445-454.
http://dx.doi.org/10.1007/s00701-011-1261-5 PMID: 22234791

[45] Kang, H.S.; Kim, S.K.; Cho, B.K.; Kim, Y.Y.; Hwang, Y.S.; Wang, K.C. Single nucleotide polymorphisms of tissue inhibitor of metalloproteinase genes in familial moyamoya disease. *Neurosurgery,* **2006**, *58*(6), 1074-1080.
http://dx.doi.org/10.1227/01.NEU.0000215854.66011.4F PMID: 16723886

[46] Guo, D.C.; Papke, C.L.; Tran-Fadulu, V.; Regalado, E.S.; Avidan, N.; Johnson, R.J.; Kim, D.H.; Pannu, H.; Willing, M.C.; Sparks, E.; Pyeritz, R.E.; Singh, M.N.; Dalman, R.L.; Grotta, J.C.; Marian, A.J.; Boerwinkle, E.A.; Frazier, L.Q.; LeMaire, S.A.; Coselli, J.S.; Estrera, A.L.; Safi, H.J.; Veeraraghavan, S.; Muzny, D.M.; Wheeler, D.A.; Willerson, J.T.; Yu, R.K.; Shete, S.S.; Scherer, S.E.; Raman, C.S.; Buja, L.M.; Milewicz, D.M. Mutations in smooth muscle alpha-actin (ACTA2) cause coronary artery disease, stroke, and Moyamoya disease, along with thoracic aortic disease. *Am. J. Hum. Genet.,* **2009**, *84*(5), 617-627.
http://dx.doi.org/10.1016/j.ajhg.2009.04.007 PMID: 19409525

[47] Morito, D.; Nishikawa, K.; Hoseki, J.; Kitamura, A.; Kotani, Y.; Kiso, K.; Kinjo, M.; Fujiyoshi, Y.; Nagata, K. Moyamoya disease-associated protein mysterin/RNF213 is a novel AAA+ ATPase, which dynamically changes its oligomeric state. *Sci. Rep.,* **2014**, *4*, 4442.
http://dx.doi.org/10.1038/srep04442 PMID: 24658080

[48] Lin, J.; Sheng, W. RNF213 Variant diversity predisposes distinct populations to dissimilar cerebrovascular diseases. *BioMed Res. Int.,* **2018**, *2018*, 6359174.
http://dx.doi.org/10.1155/2018/6359174 PMID: 30671466

[49] Kim, J.; Park, Y.S.; Woo, M.H.; An, H.J.; Kim, J.O.; Park, H.S.; Ryu, C.S.; Kim, O.J.; Kim, N.K. Distribution of intracranial major artery stenosis/occlusion according to RNF213 Polymorphisms. *Int. J. Mol. Sci.,* **2020**, *21*(6), 1956.
http://dx.doi.org/10.3390/ijms21061956 PMID: 32182997

[50] Lee, M.J.; Fallen, S.; Zhou, Y.; Baxter, D.; Scherler, K.; Kuo, M.F.; Wang, K. The Impact of Moyamoya Disease and *RNF213* mutations on the spectrum of plasma protein and microrna. *J. Clin. Med.,* **2019**, *8*(10), 1648.
http://dx.doi.org/10.3390/jcm8101648 PMID: 31658621

[51] Kamada, F.; Aoki, Y.; Narisawa, A.; Abe, Y.; Komatsuzaki, S.; Kikuchi, A.; Kanno, J.; Niihori, T.; Ono, M.; Ishii, N.; Owada, Y.; Fujimura, M.; Mashimo, Y.; Suzuki, Y.; Hata, A.; Tsuchiya, S.;

Tominaga, T.; Matsubara, Y.; Kure, S. A genome-wide association study identifies RNF213 as the first Moyamoya disease gene. *J. Hum. Genet.,* **2011**, *56*(1), 34-40.
http://dx.doi.org/10.1038/jhg.2010.132 PMID: 21048783

[52] Wang, Y.; Zhang, Z.; Wei, L.; Zhang, Q.; Zou, Z.; Yang, L.; Li, D.; Shang, M.; Han, C.; Mambiya, M.; Bao, X.; Li, Q.; Hao, F.; Zhang, K.; Wang, H.; Liu, S.; Liu, M.; Zeng, F.; Nie, F.; Wang, K.; Liu, W.; Duan, L. Predictive role of heterozygous p.R4810K of *RNF213* in the phenotype of Chinese moyamoya disease. *Neurology,* **2020**, *94*(7), e678-e686.
http://dx.doi.org/10.1212/WNL.0000000000008901 PMID: 31949090

[53] Liu, W.; Morito, D.; Takashima, S.; Mineharu, Y.; Kobayashi, H.; Hitomi, T.; Hashikata, H.; Matsuura, N.; Yamazaki, S.; Toyoda, A.; Kikuta, K.; Takagi, Y.; Harada, K.H.; Fujiyama, A.; Herzig, R.; Krischek, B.; Zou, L.; Kim, J.E.; Kitakaze, M.; Miyamoto, S.; Nagata, K.; Hashimoto, N.; Koizumi, A. Identification of RNF213 as a susceptibility gene for moyamoya disease and its possible role in vascular development. *PLoS One,* **2011**, *6*(7), e22542.
http://dx.doi.org/10.1371/journal.pone.0022542 PMID: 21799892

[54] Wu, Z.; Jiang, H.; Zhang, L.; Xu, X.; Zhang, X.; Kang, Z.; Song, D.; Zhang, J.; Guan, M.; Gu, Y. Molecular analysis of RNF213 gene for moyamoya disease in the Chinese Han population. *PLoS One,* **2012**, *7*(10), e48179.
http://dx.doi.org/10.1371/journal.pone.0048179 PMID: 23110205

[55] Masuda, J.; Ogata, J.; Yutani, C. Smooth muscle cell proliferation and localization of macrophages and T cells in the occlusive intracranial major arteries in moyamoya disease. *Stroke,* **1993**, *24*(12), 1960-1967.
http://dx.doi.org/10.1161/01.STR.24.12.1960 PMID: 7902623

[56] Mikami, T.; Suzuki, H.; Komatsu, K.; Mikuni, N. Influence of inflammatory disease on the pathophysiology of moyamoya disease and quasi-moyamoya disease. *Neurol. Med. Chir. (Tokyo),* **2019**, *59*(10), 361-370.
http://dx.doi.org/10.2176/nmc.ra.2019-0059 PMID: 31281171

[57] Huang, X.; Chen, M.; Wu, H.; Jiao, Y.; Zhou, C. Macrophage Polarization Mediated by Chitooligosaccharide (COS) and Associated Osteogenic and Angiogenic Activities. *ACS Biomater. Sci. Eng.,* **2020**, *6*(3), 1614-1629.
http://dx.doi.org/10.1021/acsbiomaterials.9b01550 PMID: 33455368

[58] Zhang, J.; Zhao, W.S.; Xu, L.; Wang, X.; Li, X.L.; Yang, X.C. Endothelium-specific endothelin-1 expression promotes pro-inflammatory macrophage activation by regulating miR-33/NR4A axis. *Exp. Cell Res.,* **2021**, *399*(1), 112443.
http://dx.doi.org/10.1016/j.yexcr.2020.112443 PMID: 33340492

[59] Han, L.; Zhang, Y.; Zhang, M.; Guo, L.; Wang, J.; Zeng, F.; Xu, D.; Yin, Z.; Xu, Y.; Wang, D.; Zhou, H. Interleukin-1β-Induced Senescence Promotes Osteoblastic Transition of Vascular Smooth Muscle Cells. *Kidney Blood Press. Res.,* **2020**, *45*(2), 314-330.
http://dx.doi.org/10.1159/000504298 PMID: 32126555

[60] Sharma, N.; Hans, C.P. Interleukin 12p40 Deficiency promotes abdominal aortic aneurysm by activating CCN2/MMP2 Pathways. *J. Am. Heart Assoc.,* **2021**, *10*(3), e017633.
http://dx.doi.org/10.1161/JAHA.120.017633 PMID: 33470127

[61] Icli, B.; Li, H.; Pérez-Cremades, D.; Wu, W.; Ozdemir, D.; Haemmig, S.; Guimaraes, R.B.; Manica, A.; Marchini, J.F.; Orgill, D.P.; Feinberg, M.W. MiR-4674 regulates angiogenesis in tissue injury by targeting p38K signaling in endothelial cells. *Am. J. Physiol. Cell Physiol.,* **2020**, *318*(3), C524-C535.
http://dx.doi.org/10.1152/ajpcell.00542.2019 PMID: 31913696

[62] Abarca-Buis, R.F.; Mandujano-Tinoco, E.A.; Cabrera-Wrooman, A.; Krötzsch, E. The complexity of TGFβ/activin signaling in regeneration. *J. Cell Commun. Signal.,* **2021**, *15*(1), 7-23.
http://dx.doi.org/10.1007/s12079-021-00605-7 PMID: 33481173

[63] Weng, L.; Cao, X.; Han, L.; Zhao, H.; Qiu, S.; Yan, Y.; Wang, X.; Chen, X.; Zheng, W.; Xu, X.; Gao, Y.; Chen, Y.; Li, J.; Yang, Y.; Xu, Y. Association of increased Treg and Th17 with pathogenesis of moyamoya disease. *Sci. Rep.,* **2017**, *7*(1), 3071.
http://dx.doi.org/10.1038/s41598-017-03278-8 PMID: 28596558

[64] Nabel, E.G.; Shum, L.; Pompili, V.J.; Yang, Z.Y.; San, H.; Shu, H.B.; Liptay, S.; Gold, L.; Gordon, D.; Derynck, R. Direct transfer of transforming growth factor beta 1 gene into arteries stimulates

fibrocellular hyperplasia. *Proc. Natl. Acad. Sci. USA,* **1993,** *90*(22), 10759-10763.
http://dx.doi.org/10.1073/pnas.90.22.10759 PMID: 8248168

[65]   Han, W.; Jin, F.; Zhang, H.; Yang, M.; Cui, C.; Wang, C.; Jiang, P. Association of brain-gut peptides with inflammatory cytokines in moyamoya disease. *Mediators Inflamm.,* **2020,** *2020,* 5847478.
http://dx.doi.org/10.1155/2020/5847478 PMID: 32410857

[66]   Sarkar, P.; Thirumurugan, K. New insights into TNFα/PTP1B and PPARγ pathway through RNF213- a link between inflammation, obesity, insulin resistance, and Moyamoya disease. *Gene,* **2021,** *771,* 145340.
http://dx.doi.org/10.1016/j.gene.2020.145340 PMID: 33333224

[67]   Chen, J.B.; Liu, Y.; Zhou, L.X.; Sun, H.; He, M.; You, C. Prevalence of autoimmune disease in moyamoya disease patients in Western Chinese population. *J. Neurol. Sci.,* **2015,** *351*(1-2), 184-186.
http://dx.doi.org/10.1016/j.jns.2015.02.037 PMID: 25743224

[68]   Hayashi, T.; Akioka, N.; Kashiwazaki, D.; Kuwayama, N.; Kuroda, S. Ischemic stroke in pediatric moyamoya disease associated with immune thrombocytopenia--a case report. *Childs Nerv. Syst.,* **2015,** *31*(6), 991-996.
http://dx.doi.org/10.1007/s00381-015-2619-4 PMID: 25663502

[69]   Yanagawa, Y.; Sugiura, T.; Suzuki, K.; Okada, Y. Moyamoya disease associated with positive findings for rheumatoid factor and myeloperoxidase-anti-neutrophil cytoplasmic antibody. *West Indian Med. J.,* **2007,** *56*(3), 282-284.
http://dx.doi.org/10.1590/S0043-31442007000300019 PMID: 18072414

[70]   Sigdel, T.K.; Shoemaker, L.D.; Chen, R.; Li, L.; Butte, A.J.; Sarwal, M.M.; Steinberg, G.K. Immune response profiling identifies autoantibodies specific to Moyamoya patients. *Orphanet J. Rare Dis.,* **2013,** *8,* 45.
http://dx.doi.org/10.1186/1750-1172-8-45 PMID: 23518061

[71]   Lin, R.; Xie, Z.; Zhang, J.; Xu, H.; Su, H.; Tan, X.; Tian, D.; Su, M. Clinical and immunopathological features of Moyamoya disease. *PLoS One,* **2012,** *7*(4), e36386.
http://dx.doi.org/10.1371/journal.pone.0036386 PMID: 22558457

[72]   Czabanka, M.; Petrilli, L.L.; Elvers-Hornung, S.; Bieback, K.; Albert Imhof, B.; Vajkoczy, P.; Vinci, M. Junctional adhesion molecule-c mediates the recruitment of embryonic-endothelial progenitor cells to the perivascular niche during tumor angiogenesis. *Int. J. Mol. Sci.,* **2020,** *21*(4), 1209.
http://dx.doi.org/10.3390/ijms21041209 PMID: 32054130

[73]   Crosby, C.O.; Hillsley, A.; Kumar, S.; Stern, B.; Parekh, S.H.; Rosales, A.; Zoldan, J. Phototunable interpenetrating polymer network hydrogels to stimulate the vasculogenesis of stem cell-derived endothelial progenitors. *Acta Biomater.,* **2021,** *122,* 133-144.
http://dx.doi.org/10.1016/j.actbio.2020.12.041 PMID: 33359297

[74]   Alwjwaj, M.; Kadir, R.R.A.; Bayraktutan, U. The secretome of endothelial progenitor cells: A potential therapeutic strategy for ischemic stroke. *Neural Regen. Res.,* **2021,** *16*(8), 1483-1489.
http://dx.doi.org/10.4103/1673-5374.303012 PMID: 33433461

[75]   Nouri Barkestani, M.; Shamdani, S.; Afshar Bakshloo, M.; Arouche, N.; Bambai, B.; Uzan, G.; Naserian, S. TNFα priming through its interaction with TNFR2 enhances endothelial progenitor cell immunosuppressive effect: New hope for their widespread clinical application. *Cell Commun. Signal.,* **2021,** *19*(1), 1.
http://dx.doi.org/10.1186/s12964-020-00683-x PMID: 33397378

[76]   Khakoo, A.Y.; Finkel, T. Endothelial progenitor cells. *Annu. Rev. Med.,* **2005,** *56,* 79-101.
http://dx.doi.org/10.1146/annurev.med.56.090203.104149 PMID: 15660503

[77]   Rafat, N.; Beck, G.Ch.; Peña-Tapia, P.G.; Schmiedek, P.; Vajkoczy, P. Increased levels of circulating endothelial progenitor cells in patients with Moyamoya disease. *Stroke,* **2009,** *40*(2), 432-438.
http://dx.doi.org/10.1161/STROKEAHA.108.529420 PMID: 19095988

[78]   Yoshihara, T.; Taguchi, A.; Matsuyama, T.; Shimizu, Y.; Kikuchi-Taura, A.; Soma, T.; Stern, D.M.; Yoshikawa, H.; Kasahara, Y.; Moriwaki, H.; Nagatsuka, K.; Naritomi, H. Increase in circulating CD34-positive cells in patients with angiographic evidence of moyamoya-like vessels. *J. Cereb. Blood Flow Metab.,* **2008,** *28*(6), 1086-1089.

http://dx.doi.org/10.1038/jcbfm.2008.1 PMID: 18231114

[79]   Wang, Q.N.; Zou, Z.X.; Wang, X.P.; Zhang, Q.; Zhao, Y.Q.; Duan, L.; Bao, X.Y. Endothelial progenitor cells induce angiogenesis: a potential mechanism underlying neovascularization in Encephaloduroarteriosynangiosis. *Transl. Stroke Res.,* **2021,** *12*(2), 357-365.
http://dx.doi.org/10.1007/s12975-020-00834-9 PMID: 32632776

[80]   Tinelli, F.; Nava, S.; Arioli, F.; Bedini, G.; Scelzo, E.; Lisini, D.; Faragò, G.; Gioppo, A.; Ciceri, E.F.; Acerbi, F.; Ferroli, P.; Vetrano, I.G.; Esposito, S.; Saletti, V.; Pantaleoni, C.; Zibordi, F.; Nardocci, N.; Zedde, M.L.; Pezzini, A.; Di Lazzaro, V.; Capone, F.; Dell'Acqua, M.L.; Vajkoczy, P.; Tournier-Lasserve, E.; Parati, E.A.; Bersano, A.; Gatti, L. Vascular remodeling in moyamoya angiopathy: from peripheral blood mononuclear cells to endothelial cells. *Int. J. Mol. Sci.,* **2020,** *21*(16), 5763.
http://dx.doi.org/10.3390/ijms21165763 PMID: 32796702

[81]   Kim, J.H.; Jung, J.H.; Phi, J.H.; Kang, H.S.; Kim, J.E.; Chae, J.H.; Kim, S.J.; Kim, Y.H.; Kim, Y.Y.; Cho, B.K.; Wang, K.C.; Kim, S.K. Decreased level and defective function of circulating endothelial progenitor cells in children with moyamoya disease. *J. Neurosci. Res.,* **2010,** *88*(3), 510-518.
http://dx.doi.org/10.1002/jnr.22228 PMID: 19774676

[82]   Yu, J.; Du, Q.; Hu, M.; Zhang, J.; Chen, J. Endothelial progenitor cells in moyamoya disease: current situation and controversial issues. *Cell Transplant.,* **2020,** *29,* 963689720913259.
http://dx.doi.org/10.1177/0963689720913259 PMID: 32193953

[83]   Beneventi, F.; De Maggio, I.; Cavagnoli, C.; Bellingeri, C.; Ruspini, B.; Riceputi, G.; Viarengo, G.; Ramoni, V.; Spinillo, A. Endothelial Progenitor Cell CD34$^+$ and CD133$^+$ Concentrations and Soluble HLA-G concentrations during pregnancy and in cord blood in undifferentiated connective tissue diseases compared to controls. *Reprod. Sci.,* **2021,** *28*(5), 1382-1389.
http://dx.doi.org/10.1007/s43032-020-00405-1 PMID: 33237511

[84]   Yu, M.; Feng, H.J.; Abdalla, A.M.E.; Teng, Y.F.; Li, Q. Apelin-13 promotes late endothelial progenitor cells differentiation by regulating Krüppel-like factor 4. *Eur. Rev. Med. Pharmacol. Sci.,* **2019,** *23*(16), 7098-7109.
http://dx.doi.org/10.26355/eurrev_201908_18755 PMID: 31486512

[85]   Petrova, O.N.; Lamarre, I.; Fasani, F.; Grillon, C.; Negrerie, M. Soluble guanylate cyclase inhibitors discovered among natural compounds. *J. Nat. Prod.,* **2020,** *83*(12), 3642-3651.
http://dx.doi.org/10.1021/acs.jnatprod.0c00854 PMID: 33290062

[86]   Costa, T.J.; Barros, P.R.; Arce, C.; Santos, J.D.; da Silva-Neto, J.; Egea, G.; Dantas, A.P.; Tostes, R.C.; Jiménez-Altayó, F. The homeostatic role of hydrogen peroxide, superoxide anion and nitric oxide in the vasculature. *Free Radic. Biol. Med.,* **2021,** *162,* 615-635.
http://dx.doi.org/10.1016/j.freeradbiomed.2020.11.021 PMID: 33248264

[87]   Gebauer, P.H.; Turzo, M.; Lasitschka, F.; Weigand, M.A.; Busch, C.J. Inhibition of ornithine decarboxylase restores hypoxic pulmonary vasoconstriction in endotoxemic mice. *Pulm. Circ.,* **2020,** *10*(4), 2045894020915831.
http://dx.doi.org/10.1177/2045894020915831 PMID: 33403098

[88]   Kolijn, D.; Kovács, Á.; Herwig, M.; Lódi, M.; Sieme, M.; Alhaj, A.; Sandner, P.; Papp, Z.; Reusch, P.H.; Haldenwang, P.; Falcão-Pires, I.; Linke, W.A.; Jaquet, K.; Van Linthout, S.; Mügge, A.; Tschöpe, C.; Hamdani, N. Enhanced cardiomyocyte function in hypertensive rats with diastolic dysfunction and human heart failure patients after acute treatment With soluble Guanylyl Cyclase (sGC) Activator. *Front. Physiol.,* **2020,** *11,* 345.
http://dx.doi.org/10.3389/fphys.2020.00345 PMID: 32523538

[89]   Takayasu, M.; Kajita, Y.; Suzuki, Y.; Shibuya, M.; Sugita, K.; Hidaka, H. A role of nitric oxide in vasomotor control of cerebral parenchymal arterioles in rats. *J. Auton. Nerv. Syst.,* **1994,** *49*(Suppl.), S63-S66.
http://dx.doi.org/10.1016/0165-1838(94)90089-2 PMID: 7836689

[90]   Hervé, D.; Philippi, A.; Belbouab, R.; Zerah, M.; Chabrier, S.; Collardeau-Frachon, S.; Bergametti, F.; Essongue, A.; Berrou, E.; Krivosic, V.; Sainte-Rose, C.; Houdart, E.; Adam, F.; Billiemaz, K.; Lebret, M.; Roman, S.; Passemard, S.; Boulday, G.; Delaforge, A.; Guey, S.; Dray, X.; Chabriat, H.; Brouckaert, P.; Bryckaert, M.; Tournier-Lasserve, E. Loss of α1β1 soluble guanylate cyclase, the

major nitric oxide receptor, leads to moyamoya and achalasia. *Am. J. Hum. Genet.,* **2014,** *94*(3), 385-394.
http://dx.doi.org/10.1016/j.ajhg.2014.01.018 PMID: 24581742

[91] Wallace, S.; Guo, D.C.; Regalado, E.; Mellor-Crummey, L.; Bamshad, M.; Nickerson, D.A.; Dauser, R.; Hanchard, N.; Marom, R.; Martin, E.; Berka, V.; Sharina, I.; Ganesan, V.; Saunders, D.; Morris, S.A.; Milewicz, D.M. Disrupted nitric oxide signaling due to GUCY1A3 mutations increases risk for moyamoya disease, achalasia and hypertension. *Clin. Genet.,* **2016,** *90*(4), 351-360.
http://dx.doi.org/10.1111/cge.12739 PMID: 26777256

[92] Kang, H.S.; Kim, J.H.; Phi, J.H.; Kim, Y.Y.; Kim, J.E.; Wang, K.C.; Cho, B.K.; Kim, S.K. Plasma matrix metalloproteinases, cytokines and angiogenic factors in moyamoya disease. *J. Neurol. Neurosurg. Psychiatry,* **2010,** *81*(6), 673-678.
http://dx.doi.org/10.1136/jnnp.2009.191817 PMID: 19965844

[93] Qing, Z.; Huang, H.; Yang, S.; Lin, J.; Zeng, Z.; Duan, J.; Yuan, B.; Ming, T. Hypoxia maintains the fenestration of liver sinusoidal endothelial cells and promotes their proliferation through the SENP1/HIF-1α/VEGF signaling axis. *Biochem. Biophys. Res. Commun.,* **2021,** *540*, 42-50.
http://dx.doi.org/10.1016/j.bbrc.2020.12.104 PMID: 33445109

[94] Bernaudin, M.; Nedelec, A.S.; Divoux, D.; MacKenzie, E.T.; Petit, E.; Schumann-Bard, P. Normobaric hypoxia induces tolerance to focal permanent cerebral ischemia in association with an increased expression of hypoxia-inducible factor-1 and its target genes, erythropoietin and VEGF, in the adult mouse brain. *J. Cereb. Blood Flow Metab.,* **2002,** *22*(4), 393-403.
http://dx.doi.org/10.1097/00004647-200204000-00003 PMID: 11919510

[95] Shao, W.; Li, X.; Peng, J.; Fan, S.; Liang, M.; Huang, K. Apatinib attenuates phenotypic switching of arterial smooth muscle cells in vascular remodelling by targeting the PDGF Receptor-β. *J. Cell. Mol. Med.,* **2020,** *24*(17), 10128-10139.
http://dx.doi.org/10.1111/jcmm.15623 PMID: 32697395

[96] Suzuki, J.; Takaku, A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. *Arch. Neurol.,* **1969,** *20*(3), 288-299.
http://dx.doi.org/10.1001/archneur.1969.00480090076012 PMID: 5775283

[97] Hwang, I.; Cho, W.S.; Yoo, R.E.; Kang, K.M.; Yoo, D.H.; Yun, T.J.; Choi, S.H.; Kim, J.H.; Kim, J.E.; Sohn, C.H. Revascularization evaluation in adult-onset moyamoya disease after bypass surgery: superselective arterial spin labeling perfusion mri compared with digital subtraction angiography. *Radiology,* **2020,** *297*(3), 630-637.
http://dx.doi.org/10.1148/radiol.2020201448 PMID: 32960727

[98] Robert, T.; Cicciò, G.; Sylvestre, P.; Chiappini, A.; Weil, A.G.; Smajda, S.; Chaalala, C.; Blanc, R.; Reinert, M.; Piotin, M.; Bojanowski, M.W. Anatomic and angiographic analyses of ophthalmic artery collaterals in moyamoya disease. *AJNR Am. J. Neuroradiol.,* **2018,** *39*(6), 1121-1126.
http://dx.doi.org/10.3174/ajnr.A5622 PMID: 29650781

[99] Ge, P.; Zhang, Q.; Ye, X.; Liu, X.; Deng, X.; Wang, J.; Wang, R.; Zhang, Y.; Zhang, D.; Zhao, J.Z. Digital subtraction angiographic characteristics of progression of moyamoya disease 6 months prior to surgical revascularisation. *Stroke Vasc. Neurol.,* **2020,** *5*(1), 97-102.
http://dx.doi.org/10.1136/svn-2019-000316 PMID: 32411414

[100] Bonasia, S.; Ciccio, G.; Smajda, S.; Weil, A.G.; Chaalala, C.; Blanc, R.; Reinert, M.; Piotin, M.; Bojanowski, M.; Robert, T. Angiographic analysis of natural anastomoses between the posterior and anterior cerebral arteries in moyamoya disease and syndrome. *AJNR Am. J. Neuroradiol.,* **2019,** *40*(12), 2066-2072.
http://dx.doi.org/10.3174/ajnr.A6291 PMID: 31672836

[101] Yeon, J.Y.; Shin, H.J.; Kong, D.S.; Seol, H.J.; Kim, J.S.; Hong, S.C.; Park, K. The prediction of contralateral progression in children and adolescents with unilateral moyamoya disease. *Stroke,* **2011,** *42*(10), 2973-2976.
http://dx.doi.org/10.1161/STROKEAHA.111.622522 PMID: 21836096

[102] Chen, Y.; Ma, L.; Lu, J.; Chen, X.; Ye, X.; Zhang, D.; Zhang, Y.; Wang, R.; Zhao, Y. Postoperative hemorrhage during the acute phase after direct or combined revascularization for moyamoya disease: Risk factors, prognosis, and literature review. *J. Neurosurg.,* **2019,** 1-10.
http://dx.doi.org/10.3171/2019.7.JNS19885 PMID: 31628285

[103] Hou, K.; Li, G.; Luan, T.; Xu, K.; Xu, B.; Yu, J. Anatomical study of anterior inferior cerebellar artery and its reciprocal relationship with posterior inferior cerebellar artery based on angiographic data. *World Neurosurg.,* **2020,** *133*, e459-e472.
http://dx.doi.org/10.1016/j.wneu.2019.09.047 PMID: 31526888

[104] Funaki, T.; Takahashi, J.C.; Houkin, K.; Kuroda, S.; Takeuchi, S.; Fujimura, M.; Tomata, Y.; Miyamoto, S. Angiographic features of hemorrhagic moyamoya disease with high recurrence risk: A supplementary analysis of the Japan Adult Moyamoya Trial. *J. Neurosurg.,* **2018,** *128*(3), 777-784.
http://dx.doi.org/10.3171/2016.11.JNS161650 PMID: 28409736

[105] Yamamoto, S.; Hori, S.; Kashiwazaki, D.; Akioka, N.; Kuwayama, N.; Kuroda, S. Longitudinal anterior-to-posterior shift of collateral channels in patients with moyamoya disease: An implication for its hemorrhagic onset. *J. Neurosurg.,* **2018,** *130*(3), 884-890.
http://dx.doi.org/10.3171/2017.9.JNS172231 PMID: 29570010

[106] Hori, S.; Kashiwazaki, D.; Yamamoto, S.; Acker, G.; Czabanka, M.; Akioka, N.; Kuwayama, N.; Vajkoczy, P.; Kuroda, S. Impact of interethnic difference of collateral angioarchitectures on prevalence of hemorrhagic stroke in moyamoya disease. *Neurosurgery,* **2019,** *85*(1), 134-146.
http://dx.doi.org/10.1093/neuros/nyy236 PMID: 29889273

[107] Zhang, J.; Li, S.; Fujimura, M.; Lau, T.Y.; Wu, X.; Hu, M.; Zheng, H.; Xu, H.; Zhao, W.; Li, X.; Chen, J. Hemodynamic analysis of the recipient parasylvian cortical arteries for predicting postoperative hyperperfusion during STA-MCA bypass in adult patients with moyamoya disease. *J. Neurosurg.,* **2019,** 1-8.
http://dx.doi.org/10.3171/2019.10.JNS191207 PMID: 31881540

[108] Liu, Z.W.; Han, C.; Wang, H.; Zhang, Q.; Li, S.J.; Bao, X.Y.; Zhang, Z.S.; Duan, L. Clinical characteristics and leptomeningeal collateral status in pediatric and adult patients with ischemic moyamoya disease. *CNS Neurosci. Ther.,* **2020,** *26*(1), 14-20.
http://dx.doi.org/10.1111/cns.13130 PMID: 31875482

[109] Karakama, J.; Nariai, T.; Hara, S.; Hayashi, S.; Sumita, K.; Inaji, M.; Tanaka, Y.; Wagatsuma, K.; Ishii, K.; Nemoto, S.; Maehara, T. Unique angiographic appearances of moyamoya disease detected with 3-dimensional rotational digital subtraction angiography imaging showing the hemodynamic status. *J. Stroke Cerebrovasc. Dis.,* **2018,** *27*(8), 2147-2157.
http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2018.03.006 PMID: 29653803

[110] Kashiwazaki, D.; Akioka, N.; Kuwayama, N.; Houkin, K.; Czabanka, M.; Vajkoczy, P.; Kuroda, S. Berlin grading system can stratify the onset and predict perioperative complications in adult moyamoya disease. *Neurosurgery,* **2017,** *81*(6), 986-991.
http://dx.doi.org/10.1093/neuros/nyx140 PMID: 28605471

[111] Liu, Z.W.; Han, C.; Zhao, F.; Qiao, P.G.; Wang, H.; Bao, X.Y.; Zhang, Z.S.; Yang, W.Z.; Li, D.S.; Duan, L. Collateral circulation in moyamoya disease: a new grading system. *Stroke,* **2019,** *50*(10), 2708-2715.
http://dx.doi.org/10.1161/STROKEAHA.119.024487 PMID: 31409266

[112] Li, Y.; Esene, I.; Mandel, M.; Bigder, M.; Steinberg, G.K. Incidental *De Novo* cerebral microhemorrhages are predictive of future symptomatic macrohemorrhages after surgical revascularization in moyamoya disease. *Neurosurgery,* **2020,** *88*(1), 74-81.
http://dx.doi.org/10.1093/neuros/nyaa319 PMID: 32717035

[113] Lehman, V.T.; Cogswell, P.M.; Rinaldo, L.; Brinjikji, W.; Huston, J.; Klaas, J.P.; Lanzino, G. Contemporary and emerging magnetic resonance imaging methods for evaluation of moyamoya disease. *Neurosurg. Focus,* **2019,** *47*(6), E6.
http://dx.doi.org/10.3171/2019.9.FOCUS19616 PMID: 31786551

[114] Liu, Z.; He, S.; Xu, Z.; Duan, R.; Yuan, L.; Xiao, C.; Yi, Z.; Wang, R. Association between white matter impairment and cognitive dysfunction in patients with ischemic Moyamoya disease. *BMC Neurol.,* **2020,** *20*(1), 302.
http://dx.doi.org/10.1186/s12883-020-01876-0 PMID: 32799829

[115] Hirano, Y.; Miyawaki, S.; Imai, H.; Hongo, H.; Ohara, K.; Dofuku, S.; Teranishi, Y.; Nakatomi, H.; Saito, N. Association between the onset pattern of adult moyamoya disease and risk factors for stroke. *Stroke,* **2020,** *51*(10), 3124-3128.

http://dx.doi.org/10.1161/STROKEAHA.120.030653 PMID: 32867597

[116]   Quon, J.L.; Kim, L.H.; MacEachern, S.J.; Maleki, M.; Steinberg, G.K.; Madhugiri, V.; Edwards, M.S.B.; Grant, G.A.; Yeom, K.W.; Forkert, N.D. Early diffusion magnetic resonance imaging changes in normal-appearing brain in pediatric moyamoya disease. *Neurosurgery,* **2020**, *86*(4), 530-537.
http://dx.doi.org/10.1093/neuros/nyaa265 PMID: 31245817

[117]   Su, J.B.; Xi, S.D.; Zhou, S.Y.; Zhang, X.; Jiang, S.H.; Xu, B.; Chen, L.; Lei, Y.; Gao, C.; Gu, Y.X. Microstructural damage pattern of vascular cognitive impairment: A comparison between moyamoya disease and cerebrovascular atherosclerotic disease. *Neural Regen. Res.,* **2019**, *14*(5), 858-867.
http://dx.doi.org/10.4103/1673-5374.249234 PMID: 30688272

[118]   Kazumata, K.; Tokairin, K.; Ito, M.; Uchino, H.; Sugiyama, T.; Kawabori, M.; Osanai, T.; Tha, K.K.; Houkin, K. Combined structural and diffusion tensor imaging detection of ischemic injury in moyamoya disease: Relation to disease advancement and cerebral hypoperfusion. *J. Neurosurg.,* **2020**, 1-10.
http://dx.doi.org/10.3171/2020.1.JNS193260 PMID: 32244209

[119]   Horie, N.; Morikawa, M.; Nozaki, A.; Hayashi, K.; Suyama, K.; Nagata, I. "Brush Sign" on susceptibility-weighted MR imaging indicates the severity of moyamoya disease. *AJNR Am. J. Neuroradiol.,* **2011**, *32*(9), 1697-1702.
http://dx.doi.org/10.3174/ajnr.A2568 PMID: 21799039

[120]   Miyakoshi, A.; Funaki, T.; Fushimi, Y.; Kikuchi, T.; Kataoka, H.; Yoshida, K.; Mineharu, Y.; Takahashi, J.C.; Miyamoto, S. Identification of the bleeding point in hemorrhagic moyamoya disease using fusion images of susceptibility-weighted imaging and time-of-flight mra. *AJNR Am. J. Neuroradiol.,* **2019**, *40*(10), 1674-1680.
http://dx.doi.org/10.3174/ajnr.A6207 PMID: 31515213

[121]   Ya, J.; Zhou, D.; Ding, J.; Ding, Y.; Ji, X.; Yang, Q.; Meng, R. High-resolution combined arterial spin labeling MR for identifying cerebral arterial stenosis induced by moyamoya disease or atherosclerosis. *Ann. Transl. Med.,* **2020**, *8*(4), 87.
http://dx.doi.org/10.21037/atm.2019.12.140 PMID: 32175380

[122]   Kathuveetil, A.; Sylaja, P.N.; Senthilvelan, S.; Kesavadas, C.; Banerjee, M.; Jayanand Sudhir, B. Vessel wall thickening and enhancement in high-resolution intracranial vessel wall imaging: a predictor of future ischemic events in moyamoya Disease. *AJNR Am. J. Neuroradiol.,* **2020**, *41*(1), 100-105.
http://dx.doi.org/10.3174/ajnr.A6360 PMID: 31896569

[123]   Lei, Y.; Su, J.; Jiang, H.; Guo, Q.; Ni, W.; Yang, H.; Gu, Y.; Mao, Y. Aberrant regional homogeneity of resting-state executive control, default mode, and salience networks in adult patients with moyamoya disease. *Brain Imaging Behav.,* **2017**, *11*(1), 176-184.
http://dx.doi.org/10.1007/s11682-016-9518-5 PMID: 26843005

[124]   Qiao, P.G.; Cheng, X.; Zuo, Z.W.; Han, C.; Yang, Z.H.; Li, G.J. Blood Oxygen Level-dependent response changes in the ipsilateral primary somatosensory cortex and thalamus of patients with moyamoya disease during median nerve electrical stimulation. *J. Comput. Assist. Tomogr.,* **2019**, *43*(4), 539-546.
http://dx.doi.org/10.1097/RCT.0000000000000891 PMID: 31268874

[125]   Taneja, K.; Lu, H.; Welch, B.G.; Thomas, B.P.; Pinho, M.; Lin, D.; Hillis, A.E.; Liu, P. Evaluation of cerebrovascular reserve in patients with cerebrovascular diseases using resting-state MRI: A feasibility study. *Magn. Reson. Imaging,* **2019**, *59*, 46-52.
http://dx.doi.org/10.1016/j.mri.2019.03.003 PMID: 30849484

[126]   Dlamini, N.; Shah-Basak, P.; Leung, J.; Kirkham, F.; Shroff, M.; Kassner, A.; Robertson, A.; Dirks, P.; Westmacott, R.; deVeber, G.; Logan, W. Breath-Hold Blood Oxygen Level-Dependent MRI: a tool for the assessment of cerebrovascular reserve in children with moyamoya disease. *AJNR Am. J. Neuroradiol.,* **2018**, *39*(9), 1717-1723.
http://dx.doi.org/10.3174/ajnr.A5739 PMID: 30139753

[127]   Hauser, T.K.; Seeger, A.; Bender, B.; Klose, U.; Thurow, J.; Ernemann, U.; Tatagiba, M.; Meyer, P.T.; Khan, N.; Roder, C. Hypercapnic BOLD MRI compared to $H_2^{15}O$ PET/CT for the hemodynamic evaluation of patients with Moyamoya Disease. *Neuroimage Clin.,* **2019**, *22*, 101713.
http://dx.doi.org/10.1016/j.nicl.2019.101713 PMID: 30743136

[128]   Sakamoto, Y.; Okamoto, S.; Maesawa, S.; Bagarinao, E.; Araki, Y.; Izumi, T.; Watanabe, H.; Sobue, G.; Wakabayashi, T. Default

mode network changes in moyamoya disease before and after bypass surgery: preliminary report. *World Neurosurg.,* **2018**, *112*, e652-e661.
http://dx.doi.org/10.1016/j.wneu.2018.01.117 PMID: 29374613

[129]   Lei, Y.; Chen, X.; Su, J.B.; Zhang, X.; Yang, H.; Gao, X.J.; Ni, W.; Chen, L.; Yu, J.H.; Gu, Y.X.; Mao, Y. Recognition of Cognitive Impairment in Adult Moyamoya Disease: A Classifier Based on High-Order Resting-State Functional Connectivity Network. *Front. Neural Circuits,* **2020**, *14*, 603208.
http://dx.doi.org/10.3389/fncir.2020.603208 PMID: 33408614

[130]   Lei, Y.; Song, B.; Chen, L.; Su, J.; Zhang, X.; Ni, W.; Yu, Y.; Xu, B.; Yu, L.; Gu, Y.; Mao, Y. Reconfigured functional network dynamics in adult moyamoya disease: A resting-state fMRI study. *Brain Imaging Behav.,* **2020**, *14*(3), 715-727.
http://dx.doi.org/10.1007/s11682-018-0009-8 PMID: 30511114

[131]   Togao, O.; Hiwatashi, A.; Obara, M.; Yamashita, K.; Kikuchi, K.; Kamei, R.; Nishimura, A.; Arimura, K.; Yoshimoto, K.; Iihara, K.; Van Cauteren, M.; Honda, H. Acceleration-selective arterial spin-labeling mr angiography used to visualize distal cerebral arteries and collateral vessels in moyamoya disease. *Radiology,* **2018**, *286*(2), 611-621.
http://dx.doi.org/10.1148/radiol.2017162279 PMID: 28915102

[132]   Quon, J.L.; Kim, L.H.; Lober, R.M.; Maleki, M.; Steinberg, G.K.; Yeom, K.W. Arterial spin-labeling cerebral perfusion changes after revascularization surgery in pediatric moyamoya disease and syndrome. *J. Neurosurg. Pediatr.,* **2019**, *23*(4), 486-492.
http://dx.doi.org/10.3171/2018.11.PEDS18498 PMID: 30738390

[133]   Lin, Y.H.; Kuo, M.F.; Lu, C.J.; Lee, C.W.; Yang, S.H.; Huang, Y.C.; Liu, H.M.; Chen, Y.F.; Standardized, M.R. Standardized MR perfusion scoring system for evaluation of sequential perfusion changes and surgical outcome of moyamoya disease. *AJNR Am. J. Neuroradiol.,* **2019**, *40*(2), 260-266.
http://dx.doi.org/10.3174/ajnr.A5945 PMID: 30655253

[134]   Kronenburg, A.; Bulder, M.M.M.; Bokkers, R.P.H.; Hartkamp, N.S.; Hendrikse, J.; Vonken, E.J.; Kappelle, L.J.; van der Zwan, A.; Klijn, C.J.M.; Braun, K.P.J. Cerebrovascular Reactivity Measured with ASL Perfusion MRI, ivy sign, and regional tissue vascularization in moyamoya. *World Neurosurg.,* **2019**, *125*, e639-e650.
http://dx.doi.org/10.1016/j.wneu.2019.01.140 PMID: 30716498

[135]   Lee, S.; Yun, T.J.; Yoo, R.E.; Yoon, B.W.; Kang, K.M.; Choi, S.H.; Kim, J.H.; Kim, J.E.; Sohn, C.H.; Han, M.H. Monitoring cerebral perfusion changes after revascularization in patients with moyamoya disease by using arterial spin-labeling MR Imaging. *Radiology,* **2018**, *288*(2), 565-572.
http://dx.doi.org/10.1148/radiol.2018170509 PMID: 29714677

[136]   Togao, O.; Hiwatashi, A.; Obara, M.; Yamashita, K.; Momosaka, D.; Nishimura, A.; Arimura, K.; Hata, N.; Yoshimoto, K.; Iihara, K.; Van Cauteren, M.; Honda, H. 4D ASL-based MR angiography for visualization of distal arteries and leptomeningeal collateral vessels in moyamoya disease: A comparison of techniques. *Eur. Radiol.,* **2018**, *28*(11), 4871-4881.
http://dx.doi.org/10.1007/s00330-018-5462-7 PMID: 29737389

[137]   Bolar, D.S.; Gagoski, B.; Orbach, D.B.; Smith, E.; Adalsteinsson, E.; Rosen, B.R.; Grant, P.E.; Robertson, R.L. Comparison of CBF measured with combined velocity-selective arterial spin-labeling and pulsed arterial spin-labeling to blood flow patterns assessed by conventional angiography in pediatric moyamoya. *AJNR Am. J. Neuroradiol.,* **2019**, *40*(11), 1842-1849.
http://dx.doi.org/10.3174/ajnr.A6262 PMID: 31694821

[138]   Yamasaki, M.; Yoshioka, H.; Kanemaru, K.; Yagi, T.; Hashimoto, K.; Senbokuya, N.; Kinouchi, H. Detection of transient increase of cerebral blood flow and reversible neuronal dysfunction by iodine-123-iomazenil single photon emission computed tomography after cerebral hyperperfusion syndrome after revascularization surgery for moyamoya disease. *World Neurosurg.,* **2020**, *141*, 335-338.
http://dx.doi.org/10.1016/j.wneu.2020.06.014 PMID: 32526363

[139]   Setta, K.; Kojima, D.; Shimada, Y.; Yoshida, J.; Oshida, S.; Fujimoto, K.; Tsutsui, S.; Chiba, T.; Fujiwara, S.; Terasaki, K.; Ogasawara, K. Accuracy of brain perfusion single-photon emission computed tomography for detecting misery perfusion in adult patients with symptomatic ischemic moyamoya disease. *Ann. Nucl. Med.,* **2018**, *32*(9), 611-619.
http://dx.doi.org/10.1007/s12149-018-1283-7 PMID: 30030783

[140]   Chen, D.Y.T.; Ishii, Y.; Fan, A.P.; Guo, J.; Zhao, M.Y.; Steinberg, G.K.; Zaharchuk, G. Predicting PET cerebrovascular reserve with deep learning by using Baseline MRI: a pilot investigation of a drug-free brain stress test. *Radiology,* **2020***, 296*(3), 627-637.
http://dx.doi.org/10.1148/radiol.2020192793 PMID: 32662761

[141]   Fan, A.P.; Khalighi, M.M.; Guo, J.; Ishii, Y.; Rosenberg, J.; Wardak, M.; Park, J.H.; Shen, B.; Holley, D.; Gandhi, H.; Haywood, T.; Singh, P.; Steinberg, G.K.; Chin, F.T.; Zaharchuk, G. Identifying hypoperfusion in moyamoya disease with arterial spin Labeling and an [^{15}O]-Water positron emission tomography/magnetic resonance Imaging normative database. *Stroke,* **2019***, 50*(2), 373-380.
http://dx.doi.org/10.1161/STROKEAHA.118.023426 PMID: 30636572

[142]   Roder, C.; Haas, P.; Fudali, M.; Milian, M.; Ernemann, U.; Meyer, P.T.; Tatagiba, M.; Khan, N. Neuropsychological impairment in adults with moyamoya angiopathy: Preoperative assessment and correlation to MRI and H$_2$^{15}O PET. *Neurosurg. Rev.,* **2020***, 43*(6), 1615-1622.
http://dx.doi.org/10.1007/s10143-019-01192-3 PMID: 31728848

[143]   Hara, S.; Hori, M.; Ueda, R.; Hayashi, S.; Inaji, M.; Tanaka, Y.; Maehara, T.; Ishii, K.; Aoki, S.; Nariai, T. Unraveling specific brain microstructural damage in moyamoya disease using diffusion magnetic resonance imaging and positron emission Tomography. *J. Stroke Cerebrovasc. Dis.,* **2019***, 28*(4), 1113-1125.
http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2018.12.038 PMID: 30679013

[144]   Lee, J.J.; Shimony, J.S.; Jafri, H.; Zazulia, A.R.; Dacey, R.G., Jr; Zipfel, G.R.; Derdeyn, C.P. Hemodynamic impairment measured by positron-emission tomography is regionally associated with decreased cortical thickness in moyamoya phenomenon. *AJNR Am. J. Neuroradiol.,* **2018***, 39*(11), 2037-2044.
http://dx.doi.org/10.3174/ajnr.A5812 PMID: 30361434

[145]   Miyoshi, K.; Chida, K.; Kobayashi, M.; Kubo, Y.; Yoshida, K.; Terasaki, K.; Ogasawara, K. Two-Year clinical, cerebral hemodynamic, and cognitive outcomes of adult patients undergoing medication alone for symptomatically ischemic moyamoya disease without cerebral misery perfusion: a prospective cohort study. *Neurosurgery,* **2019***, 84*(6), 1233-1241.
http://dx.doi.org/10.1093/neuros/nyy234 PMID: 29850833

[146]   Yanagihara, W.; Chida, K.; Kobayashi, M.; Kubo, Y.; Yoshida, K.; Terasaki, K.; Ogasawara, K. Impact of cerebral blood flow changes due to arterial bypass surgery on cognitive function in adult patients with symptomatic ischemic moyamoya disease. *J. Neurosurg.,* **2018***, 131*(6), 1716-1724.
http://dx.doi.org/10.3171/2018.7.JNS18149 PMID: 30554180

[147]   Hara, S.; Tanaka, Y.; Hayashi, S.; Inaji, M.; Maehara, T.; Hori, M.; Aoki, S.; Ishii, K.; Nariai, T. Bayesian Estimation of CBF Measured by DSC-MRI in patients with moyamoya disease: comparison with ^{15}o-gas pet and singular value decomposition. *AJNR Am. J. Neuroradiol.,* **2019***, 40*(11), 1894-1900.
http://dx.doi.org/10.3174/ajnr.A6248 PMID: 31601573

[148]   Cho, A.; Chae, J.H.; Kim, H.M.; Lim, B.C.; Hwang, H.; Hwang, Y.S.; Phi, J.H.; Kim, S.K.; Wang, K.C.; Cho, B.K.; Kim, K.J. Electroencephalography in pediatric moyamoya disease: Reappraisal of clinical value. *Childs Nerv. Syst.,* **2014***, 30*(3), 449-459.
http://dx.doi.org/10.1007/s00381-013-2215-4 PMID: 23943190

[149]   Al-Qazzaz, N.K.; Ali, S.H.B.M.; Ahmad, S.A.; Islam, M.S.; Escudero, J. Discrimination of stroke-related mild cognitive impairment and vascular dementia using EEG signal analysis. *Med. Biol. Eng. Comput.,* **2018***, 56*(1), 137-157.
http://dx.doi.org/10.1007/s11517-017-1734-7 PMID: 29119540

[150]   Frechette, E.S.; Bell-Stephens, T.E.; Steinberg, G.K.; Fisher, R.S. Electroencephalographic features of moyamoya in adults. *Clin. Neurophysiol.,* **2015***, 126*(3), 481-485.
http://dx.doi.org/10.1016/j.clinph.2014.06.033 PMID: 25065300

[151]   Matsuura, H.; Yoshitani, K.; Nakamori, Y.; Tsukinaga, A.; Takahashi, J.C.; Nakai, M.; Ohnishi, Y. Transient neurological events after surgery for pediatric moyamoya disease: a retrospective study of postoperative sedation practices. *J. Neurosurg. Anesthesiol.,* **2020***, 32*(2), 182-185.
http://dx.doi.org/10.1097/ANA.0000000000000593 PMID: 30882554

[152]   Phi, J.H.; Lee, S.J.; Kang, H.S.; Kim, J.E.; Kim, S.K.; Cho, W.S.; Lee, S.Y. Postoperative transient neurologic dysfunction: a proposal for pathophysiology. *J. Clin. Neurol.,* **2018***, 14*(3), 393-400.
http://dx.doi.org/10.3988/jcn.2018.14.3.393 PMID: 29971980

[153]   Silver, J.H.; Jaffe, R.A.; López, J.R. Plasma nitrite as an indicator of cerebral ischemia during extracranial/intracranial bypass surgery in moyamoya patients. *J. Stroke Cerebrovasc. Dis.,* **2020***, 29*(9), 104830.
http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2020.104830 PMID: 32807407

[154]   Ma, Y.; Zhao, M.; Zhang, Q.; Liu, X.; Zhang, D.; Wang, S.; Zhang, Y.; Li, M.; Zhao, J. Risk factors for epilepsy recurrence after revascularization in pediatric patients with Moyamoya Disease. *J. Stroke Cerebrovasc. Dis.,* **2018***, 27*(3), 740-746.
http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.10.012 PMID: 29128331

[155]   Noshiro, S.; Mikami, T.; Komatsu, K.; Kanno, A.; Enatsu, R.; Yazawa, S.; Nagamine, T.; Matsuhashi, M.; Mikuni, N. Neuromodulatory role of revascularization Surgery in Moyamoya Disease. *World Neurosurg.,* **2016***, 91*, 473-482.
http://dx.doi.org/10.1016/j.wneu.2016.04.087 PMID: 27150656

[156]   Vendrame, M.; Kaleyias, J.; Loddenkemper, T.; Smith, E.; McClain, C.; Rockoff, M.; Manganaro, S.; McKenzie, B.; Gao, L.; Scott, M.; Bourgeois, B.; Kothare, S.V. Electroencephalogram monitoring during intracranial surgery for moyamoya disease. *Pediatr. Neurol.,* **2011***, 44*(6), 427-432.
http://dx.doi.org/10.1016/j.pediatrneurol.2011.01.004 PMID: 21555053

[157]   Zhang, X.; Su, J.; Gao, C.; Ni, W.; Gao, X.; Li, Y.; Zhang, J.; Lei, Y.; Gu, Y. Progression in vascular cognitive impairment: pathogenesis, neuroimaging evaluation, and treatment. *Cell Transplant.,* **2019***, 28*(1), 18-25.
http://dx.doi.org/10.1177/0963689718815820 PMID: 30488737

[158]   Hara, S.; Hori, M.; Hagiwara, A.; Tsurushima, Y.; Tanaka, Y.; Maehara, T.; Aoki, S.; Nariai, T. Myelin and axonal damage in normal-appearing white matter in patients with moyamoya disease. *AJNR Am. J. Neuroradiol.,* **2020***, 41*(9), 1618-1624.
http://dx.doi.org/10.3174/ajnr.A6708 PMID: 32855183

[159]   Donahue, M.J.; Dlamini, N.; Bhatia, A.; Jordan, L.C. Neuroimaging advances in pediatric stroke. *Stroke,* **2019***, 50*(2), 240-248.
http://dx.doi.org/10.1161/STROKEAHA.118.020478 PMID: 30661496

[160]   Teo, M.; Furtado, S.; Kaneko, O.F.; Azad, T.D.; Madhugiri, V.; Do, H.M.; Steinberg, G.K. Validation and application for the berlin grading system of moyamoya disease in adult patients. *Neurosurgery,* **2020***, 86*(2), 203-212.
http://dx.doi.org/10.1093/neuros/nyz025 PMID: 30864668

[161]   Oki, K.; Katsumata, M.; Izawa, Y.; Takahashi, S.; Suzuki, N.; Houkin, K. Trends of antiplatelet therapy for the management of moyamoya disease in japan: results of a nationwide survey. *J. Stroke Cerebrovasc. Dis.,* **2018***, 27*(12), 3605-3612.
http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2018.08.030 PMID: 30220629

[162]   Sato, Y.; Kazumata, K.; Nakatani, E.; Houkin, K.; Kanatani, Y. Characteristics of moyamoya disease based on national registry data in japan. *Stroke,* **2019***, 50*(8), 1973-1980.
http://dx.doi.org/10.1161/STROKEAHA.119.024689 PMID: 31234758

[163]   Chiba, T.; Setta, K.; Shimada, Y.; Yoshida, J.; Fujimoto, K.; Tsutsui, S.; Yoshida, K.; Kobayashi, M.; Kubo, Y.; Fujiwara, S.; Terasaki, K.; Ogasawara, K. Comparison of Effects between clopidogrel and cilostazol on cerebral perfusion in nonsurgical adult patients with symptomatically ischemic moyamoya disease: subanalysis of a prospective Cohort. *J. Stroke Cerebrovasc. Dis.,* **2018***, 27*(11), 3373-3379.
http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2018.07.041 PMID: 30174225

[164]   Yamamoto, S.; Funaki, T.; Fujimura, M.; Takahashi, J.C.; Uchino, H.; Houkin, K.; Tominaga, T.; Miyamoto, S.; Kuroda, S. Development of hemorrhage-prone anastomoses in asymptomatic moyamoya disease-a comparative study with japan adult moyamoya trial. *J. Stroke Cerebrovasc. Dis.,* **2019***, 28*(11), 104328.
http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2019.104328 PMID: 31471213

[165]   Ando, S.; Tsutsui, S.; Miyoshi, K.; Sato, S.; Yanagihara, W.; Setta, K.; Chiba, T.; Fujiwara, S.; Kobayashi, M.; Yoshida, K.; Kubo, Y.; Ogasawara, K. Cilostazol may improve cognition better than clopidogrel in non-surgical adult patients with ischemic moyamoya disease: Subanalysis of a prospective cohort. *Neurol. Res.,* **2019**, *41*(5), 480-487.
http://dx.doi.org/10.1080/01616412.2019.1580455 PMID: 30774013

[166]   Farooq, M.U.; Min, J.; Goshgarian, C.; Gorelick, P.B. Pharmacotherapy for Vascular Cognitive Impairment. *CNS Drugs,* **2017**, *31*(9), 759-776.
http://dx.doi.org/10.1007/s40263-017-0459-3 PMID: 28786085

[167]   Li, Z.; Lu, J.; Ma, L.; Wu, C.; Xu, Z.; Chen, X.; Ye, X.; Wang, R.; Zhao, Y. dl-3-n-butylphthalide for alleviation of neurological deficit after combined extracranial-intracranial revascularization for moyamoya disease: A propensity score-matched analysis. *J. Neurosurg.,* **2019**, *132*(2), 421-433.
http://dx.doi.org/10.3171/2018.10.JNS182152 PMID: 30771781

[168]   Porras, J.L.; Yang, W.; Xu, R.; Garzon-Muvdi, T.; Caplan, J.M.; Colby, G.P.; Coon, A.L.; Ahn, E.S.; Tamargo, R.J.; Huang, J. Effectiveness of ipsilateral stroke prevention between conservative management and indirect revascularization for moyamoya disease in a north american cohort. *World Neurosurg.,* **2018**, *110*, e928-e936.
http://dx.doi.org/10.1016/j.wneu.2017.11.113 PMID: 29196251

[169]   Gao, B.; Kang, K.; Zhang, J.; Zhang, D.; Zhao, X. Clinical characteristics and long-term outcome of headaches associated with moyamoya disease in the chinese population-a cohort study. *Front. Neurol.,* **2020**, *11*, 605636.
http://dx.doi.org/10.3389/fneur.2020.605636 PMID: 33324340

[170]   Acker, G.; Fekonja, L.; Vajkoczy, P. Surgical management of moyamoya disease. *Stroke,* **2018**, *49*(2), 476-482.
http://dx.doi.org/10.1161/STROKEAHA.117.018563 PMID: 29343587

[171]   Morshed, R.A.; Abla, A.A.; Murph, D.; Dao, J.M.; Winkler, E.A.; Burkhardt, J.K.; Colao, K.; Hetts, S.W.; Fullerton, H.J.; Lawton, M.T.; Gupta, N.; Fox, C.K. Clinical outcomes after revascularization for pediatric moyamoya disease and syndrome: A single-center series. *J. Clin. Neurosci.,* **2020**, *79*, 137-143.
http://dx.doi.org/10.1016/j.jocn.2020.07.016 PMID: 33070883

[172]   Ni, W.; Jiang, H.; Xu, B.; Lei, Y.; Yang, H.; Su, J.; Gu, Y.; Mao, Y. Treatment of aneurysms in patients with moyamoya disease: A 10-year single-center experience. *J. Neurosurg.,* **2018**, *128*(6), 1813-1822.
http://dx.doi.org/10.3171/2017.3.JNS162290 PMID: 28841118

[173]   Fukuda, N.; Kanemaru, K.; Hashimoto, K.; Yoshioka, H.; Senbokuya, N.; Yagi, T.; Kinouchi, H. Embolization of a peripheral cerebral aneurysm associated with intracranial major artery occlusion through a transdural anastomotic artery: Case report. *Interv. Neuroradiol.,* **2019**, *25*(2), 172-176.
http://dx.doi.org/10.1177/1591019918801539 PMID: 30231796

[174]   Yamada, H.; Saga, I.; Kojima, A.; Horiguchi, T. Short-term spontaneous resolution of ruptured peripheral aneurysm in moyamoya disease. *World Neurosurg.,* **2019**, *126*, 247-251.
http://dx.doi.org/10.1016/j.wneu.2019.02.193 PMID: 30877003

[175]   Sayyahmelli, S.; Ozaydin, B.; Sahin, B.; Erginoglu, U.; Cikla, U.; Baskaya, M.K. Surgical strategies for cerebral revascularization in patients with limited bypass conduit options and unexpected intraoperative difficulties. *World Neurosurg.,* **2020**, *141*, e959-e970.
http://dx.doi.org/10.1016/j.wneu.2020.06.095 PMID: 32585374

[176]   Kolb, B.; Fadel, H.; Rajah, G.; Saber, H.; Luqman, A.; Rangel-Castilla, L. Effect of revascularization on cognitive outcomes in intracranial steno-occlusive disease: A systematic review. *Neurosurg. Focus,* **2019**, *46*(2), E14.
http://dx.doi.org/10.3171/2018.11.FOCUS18517 PMID: 30717064

[177]   Larson, A.; Rinaldo, L.; Brinjikji, W.; Meyer, F.; Lanzino, G. Intracranial Aneurysms in white patients with moyamoya disease: a u.s. single-center case series and review. *World Neurosurg.,* **2020**, *138*, e749-e758.
http://dx.doi.org/10.1016/j.wneu.2020.03.072 PMID: 32201292

[178]   Tashiro, R.; Fujimura, M.; Kameyama, M.; Mugikura, S.; Endo, H.; Takeuchi, Y.; Tomata, Y.; Niizuma, K.; Tominaga, T. Incidence and risk factors of the watershed shift phenomenon after superficial temporal artery-middle cerebral artery anastomosis for

adult moyamoya disease. *Cerebrovasc. Dis.,* **2019**, *47*(3-4), 178-187.
http://dx.doi.org/10.1159/000500802 PMID: 31121577

[179]   Arnone, G.D.; Hage, Z.A.; Charbel, F.T. Single vessel double anastomosis for flow augmentation - a novel technique for direct extracranial to intracranial bypass Surgery. *Oper. Neurosurg. (Hagerstown),* **2019**, *17*(4), 365-375.
http://dx.doi.org/10.1093/ons/opy396 PMID: 30690506

[180]   Li, Q.; Gao, Y.; Xin, W.; Zhou, Z.; Rong, H.; Qin, Y.; Li, K.; Zhou, Y.; Wang, J.; Xiong, J.; Dong, X.; Yang, M.; Liu, Y.; Shen, J.; Wang, G.; Song, A.; Zhang, J. Meta-analysis of prognosis of different treatments for symptomatic moyamoya disease. *World Neurosurg.,* **2019**, *127*, 354-361.
http://dx.doi.org/10.1016/j.wneu.2019.04.062 PMID: 30995556

[181]   Kurihara, H.; Yamaguchi, K.; Ishikawa, T.; Funatsu, T.; Matsuoka, G.; Omura, Y.; Okada, Y.; Kawamata, T. Direct double bypass using the posterior auricular artery as initial surgery for moyamoya disease: Technical note. *J. Neurosurg.,* **2019**, *1-4*, 1-4.
http://dx.doi.org/10.3171/2019.5.JNS19173 PMID: 31443070

[182]   Nielsen, T.H.; Abhinav, K.; Sussman, E.S.; Han, S.S.; Weng, Y.; Bell-Stephens, T.; Heit, J.J.; Steinberg, G.K. Direct *versus* indirect bypass procedure for the treatment of ischemic moyamoya disease: Results of an individualized selection strategy. *J. Neurosurg.,* **2020**, 1-12.
http://dx.doi.org/10.3171/2020.3.JNS192847 PMID: 32534489

[183]   Ong, J. A.; Low, S. Y.; Seow, W. T.; Goh, C. P.; Yeo, T. T.; Chou, N.; Low, D. C.; Nga, V. Revascularisation surgery for paediatric moyamoya disease: The Singapore experience. *J. Clin. Neurosci.,* **2020**, *82*(Pt B), 207-213.
http://dx.doi.org/10.1016/j.jocn.2020.11.008

[184]   Deng, X.; Gao, F.; Zhang, D.; Zhang, Y.; Wang, R.; Wang, S.; Cao, Y.; Zhao, Y.; Pan, Y.; Liu, X.; Zhang, Q.; Zhao, J. Direct *versus* indirect bypasses for adult ischemic-type moyamoya disease: A propensity score-matched analysis. *J. Neurosurg.,* **2018**, *128*(6), 1785-1791.
http://dx.doi.org/10.3171/2017.2.JNS162405 PMID: 28799875

[185]   Jeon, J.P.; Kim, J.E.; Cho, W.S.; Bang, J.S.; Son, Y.J.; Oh, C.W. Meta-analysis of the surgical outcomes of symptomatic moyamoya disease in adults. *J. Neurosurg.,* **2018**, *128*(3), 793-799.
http://dx.doi.org/10.3171/2016.11.JNS161688 PMID: 28474994

[186]   Choi, J.W.; Chong, S.; Phi, J.H.; Lee, J.Y.; Kim, H.S.; Chae, J.H.; Lee, J.; Kim, S.K. Postoperative symptomatic cerebral infarction in pediatric moyamoya disease: risk factors and clinical outcome. *World Neurosurg.,* **2020**, *136*, e158-e164.
http://dx.doi.org/10.1016/j.wneu.2019.12.072 PMID: 31870818

[187]   Hsu, Y.H.; Chen, Y.F.; Yang, S.H.; Yang, C.C.; Kuo, M.F. Postoperative change of neuropsychological function after indirect revascularization in childhood moyamoya disease: A correlation with cerebral perfusion study. *Childs Nerv. Syst.,* **2020**, *36*(6), 1245-1253.
http://dx.doi.org/10.1007/s00381-019-04432-5 PMID: 31797068

[188]   Ravindran, K.; Wellons, J.C.; Dewan, M.C. Surgical outcomes for pediatric moyamoya: A systematic review and meta-analysis. *J. Neurosurg. Pediatr.,* **2019**, 1-10.
http://dx.doi.org/10.3171/2019.6.PEDS19241 PMID: 31518973

[189]   Ha, E.J.; Kim, K.H.; Wang, K.C.; Phi, J.H.; Lee, J.Y.; Choi, J.W.; Cho, B.K.; Yang, J.; Byun, Y.H.; Kim, S.K. Long-term outcomes of indirect bypass for 629 children with moyamoya disease: longitudinal and cross-sectional analysis. *Stroke,* **2019**, *50*(11), 3177-3183.
http://dx.doi.org/10.1161/STROKEAHA.119.025609 PMID: 31551037

[190]   Park, S.E.; Kim, J.S.; Park, E.K.; Shim, K.W.; Kim, D.S. Direct *versus* indirect revascularization in the treatment of moyamoya disease. *J. Neurosurg.,* **2018**, *129*(2), 480-489.
http://dx.doi.org/10.3171/2017.5.JNS17353 PMID: 29076784

[191]   Mirone, G.; Cicala, D.; Meucci, C.; d'Amico, A.; Santoro, C.; Muto, M.; Cinalli, G. Multiple burr-hole surgery for the treatment of moyamoya disease and quasi-moyamoya disease in children: preliminary surgical and imaging results. *World Neurosurg.,* **2019**, *127*, e843-e855.
http://dx.doi.org/10.1016/j.wneu.2019.03.282 PMID: 30954732

[192]   Wang, Q.N.; Bao, X.Y.; Zhang, Y.; Zhang, Q.; Li, D.S.; Duan, L. Encephaloduroarteriosynangiosis for hemorrhagic moyamoya dis-

ease: Long-term outcome of a consecutive series of 95 adult patients from a single center. *J. Neurosurg.,* **2019**, *130*(6), 1898-1905.
http://dx.doi.org/10.3171/2017.12.JNS172246 PMID: 29999465

[193]   Zhao, Y.; Yu, S.; Lu, J.; Yu, L.; Li, J.; Zhang, Y.; Zhang, D.; Wang, R.; Zhao, Y. Direct bypass surgery *vs.* combined bypass surgery for hemorrhagic moyamoya disease: A comparison of angiographic outcomes. *Front. Neurol.,* **2018**, *9*, 1121.
http://dx.doi.org/10.3389/fneur.2018.01121 PMID: 30619072

[194]   Kuroda, S.; Nakayama, N.; Yamamoto, S.; Kashiwazaki, D.; Uchino, H.; Saito, H.; Hori, E.; Akioka, N.; Kuwayama, N.; Houkin, K. Late (5-20 years) outcomes after STA-MCA anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis in patients with moyamoya disease. *J. Neurosurg.,* **2020**, *134*(3),909-916.
http://dx.doi.org/10.3171/2019.12.JNS192938 PMID: 32168480

[195]   Jiang, H.; Yang, H.; Ni, W.; Lei, Y.; Su, J.; Gu, Y.; Xu, B.; Mao, Y. Long-Term Outcomes after combined revascularization surgery in adult hemorrhagic moyamoya disease. *World Neurosurg.,* **2018**, *116*, e1032-e1041.
http://dx.doi.org/10.1016/j.wneu.2018.05.153 PMID: 29859362

[196]   Kazumata, K.; Tha, K.K.; Tokairin, K.; Ito, M.; Uchino, H.; Kawabori, M.; Sugiyama, T. Brain structure, connectivity, and cognitive changes following revascularization surgery in adult moyamoya disease. *Neurosurgery,* **2019**, *85*(5), E943-E952.
http://dx.doi.org/10.1093/neuros/nyz176 PMID: 31157394

[197]   Kim, T.; Oh, C.W.; Bang, J.S.; Kim, J.E.; Cho, W.S. Moyamoya disease: treatment and outcomes. *J. Stroke,* **2016**, *18*(1), 21-30.
http://dx.doi.org/10.5853/jos.2015.01739 PMID: 26846757

[198]   Perng, C.H.; Chang, Y.C.; Tzang, R.F. The treatment of cognitive dysfunction in dementia: A multiple treatments meta-analysis. *Psychopharmacology (Berl.),* **2018**, *235*(5), 1571-1580.
http://dx.doi.org/10.1007/s00213-018-4867-y PMID: 29502274

[199]   Formica, C.; Corallo, F.; Morabito, R.; Allone, C.; De Salvo, S.; Micchia, K.; Corallo, F.; Todaro, A.; Marino, S. A multidiscipli-

nary approach to assess recovery of consciousness in a patient with moyamoya disease. *Brain Behav.,* **2019**, *9*(5), e01241.
http://dx.doi.org/10.1002/brb3.1241 PMID: 30953395

[200]   Kalra, N.; Bautista, M.; McCullagh, H.; Tyagi, A.; Peds, Q.L. PedsQL Score Post Encephalo-duro-arterio-myo-synangiosis procedure for moyamoya disease: a single center experience. *World Neurosurg.,* **2020**, *144*, e674-e678.
http://dx.doi.org/10.1016/j.wneu.2020.09.043 PMID: 32931995

[201]   Choi, E.S.; Lee, Y.S.; Park, B.S.; Kim, B.G.; Sohn, H.M.; Jeon, Y.T. Effects of combined remote ischemic pre-and post-conditioning on neurologic complications in moyamoya disease patients undergoing superficial temporal artery-middle cerebral artery anastomosis. *J. Clin. Med.,* **2019**, *8*(5), 638.
http://dx.doi.org/10.3390/jcm8050638 PMID: 31075871

[202]   Balea, M.; Muresanu, D.; Alvarez, A.; Homberg, V.; Bajenaru, O.; Guekht, A.; Heiss, W.D.; Popa, L.; Vester, J.; Muresanu, I.; Birle, C.; Slavoaca, D. VaD - An integrated framework for cognitive rehabilitation. *CNS Neurol. Disord. Drug Targets,* **2018**, *17*(1), 22-33.
http://dx.doi.org/10.2174/1871527317666180219164545 PMID: 29468984

[203]   Watchmaker, J.M.; Frederick, B.D.; Fusco, M.R.; Davis, L.T.; Juttukonda, M.R.; Lants, S.K.; Kirshner, H.S.; Donahue, M.J. Clinical use of cerebrovascular compliance imaging to evaluate revascularization in patients with moyamoya. *Neurosurgery,* **2019**, *84*(1), 261-271.
http://dx.doi.org/10.1093/neuros/nyx635 PMID: 29528447

[204]   Zhang, X.; Ni, W.; Feng, R.; Li, Y.; Lei, Y.; Xia, D.; Gao, P.; Yang, S.; Gu, Y. Evaluation of hemodynamic change by indocyanine green-flow 800 videoangiography mapping: prediction of hyperperfusion syndrome in patients with moyamoya disease. *Oxid. Med. Cell. Longev.,* **2020**, *2020*, 8561609.
http://dx.doi.org/10.1155/2020/8561609 PMID: 32850003