Macrohistory of Moyamoya Disease Analyzed Using Artificial Intelligence

Tomoyoshi Kuribara Yukinori Akiyama Takeshi Mikami Katsuya Komatsu
Yusuke Kimura Yasuhiro Takahashi Kyoya Sakashita Ryohei Chiba
Nobuhiro Mikuni

Department of Neurosurgery, Sapporo Medical University, Sapporo, Japan

Keywords

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Abstract

Introduction: Moyamoya disease is characterized by progressive stenotic changes in the terminal segment of the internal carotid artery and the development of abnormal vascular networks called moyamoya vessels. The objective of this review was to provide a holistic view of the epidemiology, etiology, clinical findings, treatment, and pathogenesis of moyamoya disease. A literature search was performed in PubMed using the term “moyamoya disease,” for articles published until 2021. **Results:** Artificial intelligence (AI) clustering was used to classify the articles into 5 clusters: (1) pathophysiology (23.5%); (2) clinical background (37.3%); (3) imaging (13.2%); (4) treatment (17.3%); and (5) genetics (8.7%). Many articles in the “clinical background” cluster were published from the 1970s. However, in the “treatment” and “genetics” clusters, the articles were published from the 2010s through 2021. In 2011, it was confirmed that a gene called Ringin protein 213 (*RNF213*) is a susceptibility gene for moyamoya disease. Since then, tremendous progress in genomic, transcriptomic, and epigenetic profiling (e.g., methylation profiling) has resulted in new concepts for classifying moyamoya disease. Our literature survey revealed that the

pathogenesis involves aberrations of multiple signaling pathways through genetic mutations and altered gene expression. **Conclusion:** We analyzed the content vectors in abstracts using AI, and reviewed the pathophysiology, clinical background, radiological features, treatments, and genetic peculiarity of moyamoya disease.

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Introduction

Moyamoya disease is a rare cerebrovascular disease that is characterized by progressive stenotic changes in the terminal portion of the internal carotid artery (ICA), and the development of abnormal vascular networks called moyamoya vessels around the base of the brain. This phenomenon was first described by Takeuchi and Shimizu [1] as “hypoplasia of the bilateral internal carotid arteries” in 1957 and was defined by Nishimoto and Takeuchi [2] as a “hemangiomatic malformation of bilateral internal carotid arteries at the base of the brain” in 1968. The term “moyamoya disease” was first introduced by Suzuki and Takaku [3] in 1969, to describe the smoky appearance of the vascular collateral network on angiography. A half century has passed since the naming of the disease, and many review articles and guidelines on moyamoya disease have been published. Essentially, this dis-

ease has 2 main characteristics: bilateral stenotic changes in the intracranial arteries and angiogenesis of collateral vessels. The overall view of moyamoya disease has been rapidly revealed by recent studies, especially those published in the last 10 years; however, the impetus for research has not been clear.

Artificial intelligence (AI) is a branch of computer science dealing with the simulation of intelligent behavior using computers and was first described by John McCarthy of Dartmouth College in 1956 [4, 5]. The application of this innovative technology in the clinical field has been rapidly progressing and has helped solve various real-world clinical problems [6, 7]. We believe that the current academic direction and unknown aspects of moyamoya disease could be shown by identifying changes in trends in previous studies depending on the period, through the use of AI. The aims of this study were to analyze the keywords of all articles about moyamoya disease in the Medline database using AI and to map academic clusters and track trends in the articles depending on the period through the last half century. Furthermore, this study aimed to reveal the impetus for the academic revolution by “connecting the dots” and to discuss future developments.

Materials and Methods

Data Processing with AI

We performed deep learning using an HP Z840 workstation (Hewlett-Packard Company) with a Core Xe-6700 K 4.00-GHz (Intel, Santa Clara, CA, USA) central processing unit, 64-GB random access memory, and a GeForce GTX 1080 (NVIDIA, Santa Clara, CA, USA) graphics processing unit. The datasets were processed using a code written in the programming language Python 3.7.4 (<http://www.python.org>). Clustering of the articles involved using an unsupervised learning algorithm to group data points based on similarities of article vectors, such that articles within the same cluster are similar to one another and articles from different clusters are dissimilar.

Several methods of grouping with a visualization technique are available. One of them is the t-distributed stochastic neighbor embedding (t-SNE) analysis technique with the use of AI. Several articles (document data), whose abstracts are publicly available, were classified according to the similarity of their contents and placed on a map according to the similarity of the classified contents. t-SNE is a technique published by van der Maaten and Hinton [8] in 2008 for investigating high-dimensional data. Our detailed code will be available on our homepage (<https://web.sapmed.ac.jp/nsurg/index.php>) after publication.

Mapping of Academic Clusters

Total 4,358 articles in the Medline database that contain keywords in abstract related to moyamoya disease were analyzed using AI (period 1968–2021). From the viewpoint of academic diver-

Fig. 1. Scatter diagram showing the distribution of the analyzed articles on moyamoya disease, grouped according to publication years using the t-SNE analysis technique with AI. Relatively old articles are located on the top left side, followed by a gradual spread of articles over time. Articles published around the year 2020 are particularly widely distributed on the lower right side. t-SNE, t-distributed stochastic neighbor embedding; AI, artificial intelligence.

gence, the articles were divided into the following 5 clusters: (1) pathophysiology; (2) clinical background; (3) imaging; (4) treatment; and (5) genetics. Mapping of small academic clusters (dense parts of categorically and chronologically similar articles) was also performed, and the trends of the clusters depending on the period and the interactions between each cluster were tracked and reviewed by referencing the key articles.

Results

Interpretation of the Overview Based on AI Analysis

From Figures 1 and 2, it is clear that the history of moyamoya disease began with pathophysiological studies, and genetic studies are the most recent. The clinical background cluster largely overlaps with other academic clusters, and the other academic clusters also partially overlap with each other; however, there is no overlap between treatment and genetics. Each academic cluster is not independent but reacts to each other. Therefore, establishing the basis of each academic cluster can be the key to the impetus for the recent progress in research. The development of each academic cluster and the interactions of the 5 academic clusters through the last half century are sum-

Fig. 2. Scatter diagram showing the distribution of the 5 clusters. **a** Summary of the 5 clusters: pathophysiology (**b**); clinical background (**c**); imaging (**d**); treatment (**e**), and genetics (**f**).

marized below. However, this is only an overview, and the details should be gleaned from the previous sections.

Moyamoya disease was first described in 1957 [1], and its pathophysiological characteristics were reported in the late 1960s based on cerebral angiography [2, 3]. Surgical treatment including superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis, and early indirect procedures, namely encephalo-myelo-synangiosis (EMS), and encephalo-duro-arterio-synangiosis (EDAS), have been reported since the late 1970s after the pathophysiology became understood to some extent about 10 years

after the early studies [9–12]. The clinical and histopathological characteristics have been described since the early 1980s after the accumulation of a certain number of cases [13, 14]. The natural history and treatment outcomes have been reported since the mid-1980s, several years after the introduction of surgical procedures [15–17]. With respect to hemodynamic evaluation, positron emission tomography (PET) studies have been applied to moyamoya disease from the late 1980s [18]. After a relatively large number of cases have accumulated in the early 1990s, epidemiological studies and long-term surgical outcomes, including a new

indirect bypass procedure (i.e., encephalo-duro-arterio-myo-synangiosis [EDAMS]), were reported [19–22]. At present, the effectiveness of surgical procedures in pediatric patients with moyamoya disease has been established to some extent based on these reports. At the same time, early immunohistochemical studies have been published [23–25]. In the mid-1990s, the hemodynamic features of moyamoya disease became clearer, and improved diagnostic techniques using computed tomography angiography (CTA), magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA) were reported [26–28]. In the late 1990s, the surgical outcomes for adult moyamoya disease were reported, although the evidence level was not sufficiently high [29–34]. In addition, more advanced epidemiological studies, including studies from other countries and early genetic studies, have been reported [35–40]. Furthermore, the Japanese guidelines for the diagnosis and treatment of moyamoya disease were introduced in 1997 and later revised in 2012 [41, 42]. In the early 2000s, the number of articles related to moyamoya disease rapidly increased. Evidence for surgical procedures, including from other countries, accumulated, and genetic studies progressed further [43–56]. Concerning etiology, congenital and acquired factors have been previously described [57, 58]; however, the number of associated articles increased in this period [59–65]. From the mid- to late 2000s, epidemiological and genetic studies became further advanced, and reports on surgical outcomes, including those from other countries, increased [66–79]. In addition, the concepts of unilateral moyamoya disease and its clinical features, cerebral hyperperfusion as a postoperative complication, and new imaging methods (e.g., fluorescence angiography with indocyanine green, blood-oxygen level-dependent MRI, and high-resolution arterial wall imaging using 3-T MRI) were reported [80–85]. To date, the standard hemodynamic evaluation is almost complete in its current form [86]. Since the 2010s, the number of associated articles has rapidly increased. In particular, genetic studies have rapidly progressed because of the identification of Ringin protein 213 (*RNF213*) as the first susceptibility gene for moyamoya disease in 2011 [87–95]. Furthermore, the preventive effect of direct bypass against hemorrhagic moyamoya disease was statistically confirmed in a multicenter, prospective, randomized, controlled trial conducted by 22 institutes in Japan in 2014 [96], and the evidence for surgical procedures was further established by various subsequent studies [97–105]. In addition, risk evaluations for hemorrhage based on morphological information have been reported [106–108], and more advanced imaging methods have been introduced [109–114].

Review of the 5 Academic Clusters Based on Key Articles

Pathophysiology

As previously mentioned, moyamoya disease was first described as “hypoplasia of the bilateral internal carotid arteries” in 1957 [1] and defined as a “hemangiomatic malformation of bilateral internal carotid arteries at the base of the brain” in 1968 [2]. The term “moyamoya disease” was first introduced by Suzuki and Takaku [3] in 1969. “Moyamoya” is a Japanese expression for something hazy, such as a puff of cigarette smoke drifting in the air. The disease was named on the basis of the appearance of abnormal net-like blood vessels at the base of the brain observed in patients with this disease. Accordingly, angiographical features such as bilateral stenotic changes in the intracranial arteries and angiogenesis of moyamoya arteries that function as collateral vessels were indicated as the 2 main characteristics of moyamoya disease in the late 1960s. Thereafter, Suzuki et al. [115] classified the variations in moyamoya vessels into the following 6 stages based on their angiographical follow-up studies in pediatric patients: stage 1, carotid fork stenosis; stage 2, progressive carotid stenosis with initial moyamoya collaterals and dilatation of cerebral arteries; stage 3, dilatation of moyamoya collaterals and disappearance of anterior cerebral arteries and MCAs; stage 4, thinning of moyamoya vessels; stage 5, contraction of moyamoya vessels and disappearance of posterior cerebral arteries; and stage 6, perfusion of intracerebral vessels from the external carotid and/or vertebrae. This is well known as the Suzuki staging system and is the first staging system for moyamoya disease. The vessels at the base of the brain that form as a result of bilateral stenotic changes in the ICA bifurcation are termed basal moyamoya, and 2 types of collateral pathways from the extracranial to the intracranial arteries have been identified (ethmoidal moyamoya and vault moyamoya) [116, 117]. Ethmoidal moyamoya is seen as net-like vessels in the orbit that are perfused from the ophthalmic artery, posterior and anterior ethmoidal arteries, and external carotid arteries. Vault moyamoya develops from transdural anastomoses derived from the middle meningeal arteries and STAs.

The differences between children and adults were described in a review of 100 cases in 1983 by Suzuki and Kodama [13]. Children typically present with recurrent episodes of sudden hemiplegia due to ischemic events, whereas adults often present with evidence of intracranial hemorrhage. They consider this difference to be based on the variation in the disease process. In children,

the disease seems to progressively develop with ample collateral flow, whereas the development is often arrested in adults, which may be related to altered circulatory dynamics. Further details of the differences are described in the “Clinical background” and “Treatment” sections.

In pathological studies, intimal thickening, excessive infolding, and thickening or deficiencies in the internal elastic lamina were described as prominent features of moyamoya disease in the late 1960s [118–122], and these findings were confirmed later [123, 124]. With respect to the mechanism of hemorrhagic moyamoya disease, Yamashita et al. [14] first described the pathological findings of the disease in a relatively large number of patients in 1983. They described that intracerebral perforating arteries show microaneurysm formation, focal fibrin deposits, and marked attenuation of the wall with diminution of the elastic lamina, and these vessels seem to be predisposed to rupture, thus offering some insights into the occurrence of intracerebral hemorrhage commonly seen in adults. The rate of intraventricular hemorrhage is higher than that of hypertensive hemorrhage in hemorrhagic moyamoya disease [39, 50]. The risk factors for hemorrhagic stroke have been reported from the viewpoint of morphology, including the collateral vessels, from the early 2000s. Morioka et al. [125] described that dilatation and abnormal branching of the anterior choroidal artery and/or posterior communicating artery are strong predictors of hemorrhagic events. Later, Funaki et al. [106] reported that choroidal anastomosis and posterior cerebral artery involvement are associated with posterior hemorrhage in adult hemorrhagic moyamoya disease, and choroidal anastomosis is also associated with rebleeding [108]. Furthermore, intracranial aneurysms associated with moyamoya disease have been reported, and surgical intervention is recommended to prevent rupture or rebleeding, especially for aneurysms around the circle of Willis [126].

In immunohistochemical studies, various mechanisms and associated cells, growth factors, enzymes, and peptides have been reported [23–25, 127–136]. In 1991, Hoshimaru et al. [23] indicated that the amount of basic fibroblast growth factor (FGF) is increased in the tissues of patients with moyamoya disease; therefore, basic FGF may play an important role in the pathogenesis of the disease. Later, Yoshimoto et al. [25] reported that the level of basic FGF in cerebrospinal fluid taken from patients with moyamoya disease is higher than that in patients with atherosclerotic occlusive disease, and apparently elevated in patients with well-developed neovascularization from indirect revascularization. Furthermore, Masuda et al. [24] described the proliferation of smooth

muscle cells, which may occur in occlusive lesions in intracranial arteries in moyamoya disease. They concluded that inflammatory stimuli may induce smooth muscle cell proliferation and contribute to the formation of intracranial occlusive lesions in moyamoya disease. Subsequently, FGF [127], transforming growth factor- β 1 [128, 129], hepatocyte growth factor [131], vascular endothelial growth factor [132], endothelial progenitor cells [133], autoantibodies [135], and retinaldehyde dehydrogenase 2 [136] were reported to be associated with moyamoya disease. Some of these are related to genetic factors and are discussed in the “Genetics” section.

Clinical Background

Moyamoya disease has been most frequently observed in Asia and in individuals of non-Caucasian origin, although it has been reported worldwide [19, 36, 38, 39]. The Research Committee on Spontaneous Occlusion of the Circle of Willis (moyamoya disease) of the Ministry of Health and Welfare, Japan, has studied the pathogenesis, clinical features, and treatment of the disease since 1977. Guidelines for the diagnosis and treatment of moyamoya disease in Japan were first described in 1997 and revised in 2012 [41, 42]; According to current guidelines, the diagnosis of moyamoya disease is largely based on imaging. Therefore, there are several problems, especially in adults, such as differentiation from non-moyamoya disease intracranial stenosis lesions, complications of other inflammatory diseases, and how to incorporate genetic diagnosis. In Japan, the estimated number of patients was 3,800–3,900 in 1994 and 7,700 in 2003, with prevalence and incidence rates of 3.16–10.5 and 0.35–0.94 per 100,000 population, respectively. Other reported findings include female predominance (male-to-female ratio 1:1.7–2.18), highest rate of onset in the age group <10 years or 10–14 years, second mild peak from 30 to 40 years or in the 40s, rate of familial cases approximately 10–15.4% (including identical twins), and normal activities of daily life or working ability even before treatment in approximately 75% of the patients [35, 37, 70, 72, 137]. In investigations in the Washington State and California, the ethnicity-specific incidence rate ratios relative to whites were 4.6 for Asian Americans, 2.2 for African-Americans, and 0.5 for Hispanics. In a study of 802 patients at a single institution in China, the male-to-female ratio was 1:1 and the rate of familial cases was 5.2% [138]. The Research Committee on Spontaneous Occlusion of the Circle of Willis (moyamoya disease) of the Ministry of Health and Welfare defines 4 types of moyamoya disease: ischemic, hemorrhagic, epileptic, and other [35].

The distribution of these presentations varies among ages and geographical regions; however, in general, adults show higher rates of the hemorrhagic type than children, whereas children show higher rates of the ischemic type than adults [46, 73]. In Japan, the disease patterns were reported as follows: ischemic in 78.4%, hemorrhagic in 2.7%, asymptomatic in 13.5%, and other in 5.4% of patients aged <10 years, and ischemic in 53.5%, hemorrhage in 24.3%, asymptomatic in 18.7%, and other in 3.5% of patients aged ≥10 years [70]. In Europe, the incidence was reported to be about one-tenth of that in Japan, and the rate of ischemia was higher [38, 71].

The natural history without surgery is reported to be poor, and surgical intervention is recommended, especially for ischemic moyamoya disease [16, 17, 30, 31, 43, 44, 68, 139]. Hemorrhagic moyamoya disease has a poor prognosis [50, 66], and the effectiveness of surgical intervention has been less reported for the hemorrhagic type than for the ischemic type [46, 73]. In a recent study on the natural course of hemorrhagic moyamoya disease, the cumulative risk of rebleeding was 7.8% at 5 years, 22.6% at 10 years, and 35.9% at 15 years [140], and 19.1% of patients with rebleeding died [140]. In addition, smoking is an independent risk factor for rebleeding, and rebleeding and hypertension are associated with increased mortality. Furthermore, even asymptomatic moyamoya disease has an annual stroke risk of 3.2% [69]. In children, lower age is correlated with a poor prognosis [20, 53]. In adults, female patients have a higher risk of disease progression than male patients [66]. In unilateral cases, 38.9% of patients are reported to progress to bilateral disease, and the presence of minor changes in the contralateral anterior cerebral artery, ICA, and MCA is an important predictor [81]. In addition, moyamoya vessels are also important in differentiating moyamoya disease from transient cerebral arteriopathy [84]. From the viewpoint of etiology, congenital and acquired factors have been considered. Congenital factors are discussed in the “Genetics” section. Concerning acquired factors, moyamoya disease is found in several acquired diseases including atherosclerosis [141], sickle cell anemia [57, 59, 142], tuberculous meningitis [143], leptospirosis [144], and hyperthyroidism [65], and after radiation therapy [58, 60, 145–147]; however, cases with these diseases or conditions are excluded in the 1997 and 2012 Japanese guidelines [41, 42], and are categorized as moyamoya syndrome [79].

Imaging

Cerebral angiography has been the only imaging modality used since the first report on moyamoya disease,

and diagnostic criteria have been developed on the basis of this method alone [1–3, 13, 15]. The findings of moyamoya disease on cerebral angiography are described in detail in the “Pathophysiology” section. In the 1980s, computed tomography (CT) and CT with contrast enhancement were performed in patients with moyamoya disease [15, 148]. The positive findings on CT are multiple low-density areas in the brain with atrophic change, and CT with contrast enhancement often reveals tortuous, curvilinear vessels in the basal ganglia, corresponding to findings of extensive parenchymal and leptomeningeal collaterals on cerebral angiography; however, these methods cannot be an alternative to cerebral angiography. In the mid-1990s, MRI, MRA, and CTA were introduced as alternative diagnostic modalities to cerebral angiography [27, 28]. Katz et al. [27] reported similarly high sensitivities for CTA (88.5%) and MRA (85.5%), and no significant differences were found between the 2 modalities and conventional angiography in detecting the absence of arteries of the circle of Willis. Yamada et al. [28] reported high sensitivities of MRA (73%), MRI (92%), and MRA combined with MRI (92%), and concluded that MRA and MRI offer the most thorough assessment of moyamoya disease. In diagnostic guidelines established in 1997 and 2012, cerebral angiography is not mandatory when MRI and MRA clearly demonstrate typical findings of moyamoya disease [41, 42]. From the viewpoint of differentiating moyamoya disease from atherosclerotic disease, high-resolution arterial wall imaging using 3-T MRI has been described to be useful from the late 2000s. Concentric enhancement of the distal ICA and MCA is seen in patients with moyamoya disease, whereas focal eccentric enhancement is observed in patients with atherosclerotic disease, and 3-T MRI is useful for the differentiation [110, 112, 123, 149]. For staging, Houkin et al. [150] proposed a classification based on MRA findings, in addition to the conventional Suzuki grading system. MRA findings can be noninvasively obtained, and the classification reflects the Suzuki grading system. Therefore, the system is widely used today.

Various cerebral hemodynamic studies have been reported [86]. Since the 1980s, PET has been performed and later applied to moyamoya disease [18, 26, 151, 152]. Ikezaki et al. [26] reported the typical perioperative cerebral hemodynamics in moyamoya disease using PET evaluation in 1994. In moyamoya disease, the regional cerebral blood flow (CBF) and mean transit time are decreased and increased, respectively. Further, regional cerebral blood volume and regional oxygen extraction fraction increase to compensate for the reduced regional CBF and perfusion

pressure, and to maintain the regional cerebral metabolic rate of oxygen. These parameters improve postoperatively. In addition, the authors indicated that angiographical findings are not always compatible with clinical results, whereas PET evaluation correlates with the disappearance of transient ischemic attacks. The main disadvantage of PET evaluation is the requirement for cyclotrons to produce PET tracers, which are expensive. Later, hemodynamic evaluation using single-photon emission CT [32, 153, 154] and xenon-enhanced CT [155–157] were reported in the mid-1990s. Single-photon emission CT evaluation is more easily available and more frequently used; however, it is not strictly quantitative and has a poor spatial resolution. Xenon-enhanced CT is also widely used, but has main disadvantages of relatively long acquisition time, motion artifacts, and inhalation of xenon through a face mask. CT perfusion is a relatively new method and has been reported since the late 2000s [158–160]. This method can evaluate various parameters, such as CBF, cerebral blood volume, mean transit time, and time to peak, with relatively short acquisition time and high resolution. The disadvantages are delay and dispersion of the contrast medium, and the possibility of underestimation of hemodynamic parameters. Despite these disadvantages, this method is expected to be widely used in the future because CT equipment is available in many institutions worldwide. However, these methods are often used with acetazolamide to evaluate cerebrovascular reactivity, and the use of acetazolamide has been restricted since the mid-2010s owing to associated complications [161, 162]. Doppler ultrasonography [163], arterial spin labeling [109, 164, 165], and blood-oxygen level-dependent MRI [83, 166] have been reported as noninvasive hemodynamic evaluation methods. In addition, arterial spin labeling based on magnetic resonance fingerprinting is a relatively recent approach that can provide noncontrast and multiparametric estimation of hemodynamics, and its effectiveness has also been reported in moyamoya disease [111, 113, 114]. Fluorescence angiography with indocyanine green as a tracer was introduced as an intraoperative imaging technique to confirm successful revascularization in 2005 and is widely used today [80].

Treatment

With respect to the treatment of moyamoya disease, Suzuki et al. [115] employed vasodilators, steroid hormones, antibiotics, stellate ganglion blocks, and other agents for their early cases; however, improvement of symptoms was not observed. Subsequently, they described cervical perivascular sympathectomy and superior cervical ganglionectomy for moyamoya disease in

1975 [115]. Although these procedures can prevent the progression of the disease, their effects are short term. As the basis of current treatment, STA-MCA anastomosis was described in the late 1970s [10, 167, 168]. It is an effective procedure for improving cerebral circulation in moyamoya disease; however, it is not easily applicable in children because of the size of the cerebral arteries and STAs. Therefore, EMS, in which temporal muscle is placed on the surface of the brain, was developed for patients who lack an arterial branch suitable for anastomosis. It was first reported by Henschen [169] in 1950. Karasawa et al. [9, 10] later applied the method to moyamoya disease and described the clinical results of STA-MCA anastomosis and EMS in the late 1970s. Twenty-three STA-MCA anastomoses and 7 EMS were performed in 13 cases of moyamoya disease and in 4 additional atypical cases. The results were excellent in 9 patients, good in 5 patients, no change in 2 patients, and fair in 1 patient, during the follow-up period ranging from 1 year and 4 months to 4 years and 1 month postoperatively. The authors concluded that these anastomotic procedures were most effective for ischemic moyamoya disease. However, EMS has some concerns related to muscle flap placement, such as possible unfavorable effects produced by electrical activity potentials, movement of the muscle directly adherent to the brain surface, and compression of the brain. Therefore, Matsushima et al. [12] developed EDAS, in which a scalp artery with a strip of galea is taken, leaving the distal and proximal arteries intact and transplanted to a narrow linear dural opening made under an osteoplastic craniotomy. EDAS does not have the concerns of EMS, and Matsushima et al. [12] described excellent results in 34 hemispheres in 21 pediatric patients [15]. Furthermore, Olds et al. [17] also recommended the EDAS procedure, including opening of the arachnoid, for treating younger children, and reported favorable results in their retrospective study in 23 pediatric cases of moyamoya disease in 1987. However, Matsushima et al. [21] compared the results of EDAS and STA-MCA anastomosis combined with EMS in 1992 and found that STA-MCA anastomosis combined with EMS is superior to EDAS in terms of both the development of collateral circulation and postoperative clinical improvement. They concluded that EDAS can be easily and safely performed in small children with moyamoya disease, but STA-MCA anastomosis with EMS is appropriate and should be selected whenever possible. Subsequently, Kinugasa et al. [22] developed EDAMS because they observed that some patients lack an arterial branch suitable for anastomosis or require more abundant CBF to avoid persistent ische-

mic attacks even after STA-MCA anastomosis or EDAS. They performed this procedure in 28 hemispheric sides in 17 patients, with favorable results, and concluded that EDAMS seems to be one of the more effective treatments for moyamoya disease [22]. As other indirect bypass procedures, intracranial transplantation of the omentum and multiple burr-hole operations were reported to have favorable outcomes [11, 170], although only a small number of patients were included in the studies. Furthermore, Scott et al. [55] reported the effectiveness of pial synangiosis, in which intact STA is transposed and affixed to the brain surface after the dura mater and arachnoid have been widely opened, in their study on a relatively large number of pediatric patients. In addition, Kim et al. [171] reported the favorable outcomes of bilateral EDAS augmented by bifrontal encephalogaleo-/periosteal synangiosis without direct bypass in 410 pediatric patients. With respect to a combined procedure (direct bypass combined with indirect bypass), Ishikawa et al. [172] reported that STA-MCA bypass combined with EDAMS is more effective in reducing the risk of postoperative ischemic events than EDAMS alone in pediatric patients. Thereafter, similar reports indicating the importance of a combined procedure in children were also published.

The effectiveness of revascularization surgery has been confirmed in children; however, its effectiveness in adults has not been reported thus far. Houkin et al. performed STA-MCA anastomosis combined with EDAS in 35 patients with moyamoya disease in 1996. They concluded that revascularization surgery decreases moyamoya vessels, which are considered to be responsible for hemorrhage, and may reduce the risk of hemorrhage more effectively than conservative treatment, although 5 of their 35 patients (14.3%) had postoperative hemorrhage. Furthermore, they suggested that direct bypass is particularly important in adults, as indirect bypass was not as useful as in children in their postoperative angiographical evaluation, and similar later reports confirmed these findings [47]. Thereafter, the effectiveness of direct bypass for adult hemorrhagic moyamoya disease was also indicated in other reports, although the evidence levels of the studies were not sufficiently high [32, 34, 49]. In the 1997 and 2012 Japanese guidelines, the efficacy of bypass surgery was still unclear in terms of preventing rebleeding in hemorrhagic moyamoya disease [41, 42]. However, in 2014, the preventive effect of direct bypass against hemorrhagic moyamoya disease was statistically confirmed in a multicenter, prospective, randomized, controlled trial conducted by 22 institutes in Japan [96]. As a result, revascularization surgery became the gold standard therapy

for both ischemic and hemorrhagic moyamoya disease. Jeon et al. [101] reported that bypass surgery significantly decreased the risk of future stroke events compared with conservative treatments in both hemorrhagic and ischemic moyamoya disease in a total of 771 patients in their meta-analysis of 6 studies.

Concerning the optimal surgical procedures, a combined procedure for children and direct bypass for adults is recommended. Recently, Deng et al. [100] reported that both direct bypass and a combined procedure provided a longer ischemia-free time than indirect bypass, although there was no significant difference in the hemorrhage-free time. This result may support the effectiveness of direct bypass as the main surgical procedure for moyamoya disease in patients of any age. Conversely, Macyszyn et al. [97] indicated that direct bypass is inferior in terms of quality-adjusted life years in both adults at 4 years postoperatively and in children at 5 and 10 years postoperatively. They recommended indirect and combined procedures as the optimal surgical procedures for long-term outcomes [97]. Therefore, the optimal surgical procedures are still unclear, and further clinical studies are needed to clarify this issue. With respect to antithrombotic treatments, antiplatelets are widely used in patients whose ischemic symptoms seem to arise from emboli from microthrombus formation at sites of arterial stenosis and routinely for all patients in many operative reports; however, the evidence is not sufficiently high [55, 173, 174].

Concerning postoperative complications, in a report on 450 revascularization procedures in the USA, the postoperative morbidity rate and mortality rate were 3.5 and 0.7%, respectively, and the ischemic stroke and hemorrhagic stroke rates were 1.7 and 1.8%, respectively [78]. Furthermore, in a report on 610 hemispheric sides in 500 adult patients in China, postoperative complications were observed in 12.1% of the procedures, including ischemic stroke (4.9%), hyperperfusion (4.4%), impaired wound healing (2.0%), and subdural effusion (1.0%), and the risk factors for postoperative ischemic stroke were advanced Suzuki stage and preoperative ischemic presentation [103]. Concerning cerebral hyperperfusion, Fujimura et al. [82, 85] reported an incidence rate of 21.5–27.5%, and the risk factors were adult status, hemorrhagic presentation, and preoperative decreased CBF [103]. In addition, the rate of this complication was higher in patients with moyamoya disease than in those without [85, 175].

Genetics

Evidence for a hereditary factor in moyamoya disease has been reported [176–178], and the rate of familial cases

was reported to be approximately 10–15.4% (including identical twins) [35, 37, 70]. Moyamoya disease has been reported to be related to congenital diseases including Down syndrome [63, 179], neurofibromatosis [58, 64, 180], abnormal connective tissue [181], Alagille syndrome [62], and microcephalic osteodysplastic primordial dwarfism type 2 [182], although cases with these basic diseases or conditions as acquired factors are excluded in the 1997 and 2012 Japanese guidelines [41, 42], and are categorized as moyamoya syndrome [79]. Genetic factors are considered to play an important role in moyamoya disease, and associations with loci on chromosomes 3, 6, 8, and 17; specific human leukocyte antigen; and smooth muscle cell-specific isoform of α -actin have been reported [40, 45, 48, 51, 54, 74, 77, 183, 184]. In particular, *RNF213* is the first identified susceptibility gene for moyamoya disease, and a variant of p.R4810K in *RNF213* has been demonstrated to have a strong association with moyamoya disease in East Asian populations [87, 88]. Furthermore, the homozygous c.14576G>A variant of *RNF213* was reported, in 2012, to be a potential biomarker for predicting the severity of moyamoya disease [89]. Thereafter, various variants of *RNF213* have been detected in different ethnicities [90, 91, 93, 95]. In a meta-analysis of 13,000 individuals in 24 studies, the fixed-effect odds ratios of *RNF213* rs112735431 in the allelic model were 39.74 in China, 74.65 in Japan, and 50.04 in Korea [185]. Furthermore, *RNF213* rs112735431 and rs148731719 were positively associated, and tissue inhibitor of metalloproteinase (*MMP*) 2 rs8179090, matrix MPP 2 rs243865, and *MMP*-3 rs3025058 were inversely associated with moyamoya disease [185–189]. Several studies have been performed to understand the mechanism of *RNF213* in moyamoya disease. In 2019, depletion of *RNF213* was reported to be associated with protection from lipotoxicity [94]. This finding is expected to lead to novel therapeutic strategies for moyamoya disease in the future.

Discussion

Clustering is an unsupervised machine learning task that involves automatically discovering natural grouping in datasets. Clustering with k-means was performed in this study. Visualization of the distributed representation of text vectors is difficult because text vectors are multidimensional, considerably beyond the usual 2- or 3-dimensional vector plots that humans can understand and interpret. To enable human understanding, these high-dimensional datasets need to be easily mapped into a 2- or 3-dimensional space. The use of AI algorithms, such as

t-SNE, might be a way to reduce the dimensionality of high-dimensional datasets. The distribution of the analysis of all articles collected in keyword “moyamoya disease” was visualized with heatmap according to published period were shown by a scatter plot using the t-SNE analysis technique with the use of AI (Fig. 1). Relatively old articles were located in the top left side, and it gradually spreads toward the lower right. Recent articles, around 2020 in particular, were distributed over the lower right widely. However, the use of t-SNE has some limitations in that the algorithm returns slightly different results for the same dataset every time it is run. This is because t-SNE uses a randomized technique to select the first 2 articles that are used to compare the similarities among all articles.

In this study, we set 5 clusters for the analysis with t-SNE, as follows: pathophysiology, clinical background, imaging, treatment, and genetics (Fig. 2). We described the development of each cluster and the interactions of the clusters through the last half century. Once the basis of 1 academic cluster was established, academic spread was promoted and other clusters were established through the interactions of already established clusters. At present, the 5 main academic clusters are almost completely established, and this can be the impetus for the recent progress in research. Non-overlapping areas, such as the area between treatment and genetics, are expected to be a new research focus. The establishment of a new research focus will promote further academic spread and will lead to further advanced research. However, the trends do not always correspond to the clinical questions. In the future, we would like to examine which direction the trends in the articles are pointing to clinical questions. As a result, better outcomes are expected in the future. We hope that the visualization of these academic clusters and their interactions through the last half century provides a better understanding of this rare disease.

Statement of Ethics

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest Statement

There is no conflict of interest to declare.

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Author Contributions

Y.A. and T.M. designed the study. T.K. and Y.A. wrote the study protocol and the manuscript. T.M. contributed to interpretation of data. K.K., Y.K., K.S., and N.M. collected the data and other variables. All coauthors read the manuscript, revised it critically, and made important comments and final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Our detailed code will be available in our homepage after publication (<https://web.sapmed.ac.jp/nsurg/index.php>). Further inquiries can be directed to the corresponding author.

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