Cite as: Lipska J: Moyamoya disease and moyamoya syndrome.
Aktualn Neurol 2025; 25 (1): 33–38

Received: : 24.02.2025
Accepted: 23.07.2025
Published: 29.08.2025

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Moyamoya disease and moyamoya syndrome

Choroba i zespół moyamoya

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https://doi.org/10.15557/AN.2025.0006

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Abstract

Moyamoya disease is a rare, progressive cerebrovascular disorder caused by narrowed or blocked arteries supplying the brain. The name refers to the appearance of net-like collateral blood vessels that develop in response. Its incidence is significantly higher in East Asian countries and primarily affects children in the first decade of life, although it can also occur in older individuals. The disease may cause ischaemic or haemorrhagic strokes that are considered the two main types of moyamoya disease presentation, varying in prevalence in the population of children and adults. Other symptoms include headache, epilepsy, and transient ischaemic attack. Treatment remains mainly surgical, as no medication has yet been found to cure or slow down the progression of the disease. The pathogenesis remains unclear, although it is most likely multifactorial, including modifiable risk factors such as obesity, but also unmodifiable risk factors, like genetic predisposition. At the same time, moyamoya syndrome, also known as quasi-moyamoya disease, is a moyamoya-like vasculopathy associated with various systemic diseases or conditions, such as atherosclerosis or brain tumours. However, many studies do not distinguish moyamoya disease from moyamoya syndrome. Still, both conditions present with the same symptoms, and the management approach is generally the same.

Keywords: vasculopathy, moyamoya disease, moyamoya syndrome

Streszczenie

Choroba moyamoya (*moyamoya disease*, MMD) jest rzadkim i postępującym schorzeniem naczyniowo-mózgowym, spowodowanym przez zwężenie lub zablokowanie tętnic zaopatrujących mózg. Pochodząca z języka japońskiego nazwa odnosi się do wyglądu drobnych, przypominających sieć naczyń krwionośnych widocznych w obrazie tej choroby. Częstość jej występowania jest zdecydowanie wyższa w krajach wschodniej Azji. MMD dotyka głównie dzieci w pierwszej dekadzie życia, jednak może pojawić się również u osób starszych. Choroba może prowadzić do udaru niedokrwiennego lub krwotocznego, które są jej głównymi postaciami. Częstość ich występowania różni się w populacji dzieci i dorosłych. Innymi objawami MMD mogą być bóle głowy, padaczka lub przemijające ataki niedokrwienne. MMD leczy się głównie chirurgicznie, ponieważ do dziś nie znaleziono leku, który mógłby ją całkowicie wyleczyć czy nawet spowolnić jej postęp. Patogeneza tego schorzenia pozostaje niejasna, chociaż prawdopodobnie jest wieloczynnikowa i obejmuje zarówno modyfikowalne czynniki ryzyka, takie jak otyłość, jak i niemodyfikowalne, na przykład czynniki genetyczne. Jednocześnie możemy wyróżnić zespół moyamoya (*moyamoya syndrome*, MMS), zwany również chorobą quasi-moyamoya. Jest to waskulopatia objawiająca się tak samo jak MMD, jednak związana z różnymi chorobami lub stanami ogólnoustrojowymi, takimi jak miażdżyca czy guzy mózgu. Wiele analizowanych prac nie rozróżnia MMD od MMS. Niemniej jednak obie jednostki chorobowe charakteryzują się tymi samymi objawami, a ich leczenie nie różni się.

Słowa kluczowe: waskulopatia, choroba moyamoya, zespół moyamoya

INTRODUCTION

Moyamoya disease (MMD) is an uncommon disorder with a significant mortality rate (Gonzalez et al., 2023). It is a chronic, isolated cerebrovascular disease characterised by progressive stenosis of the arteries forming the circle of Willis, with the development of collateral vascular networks at the base of the brain (Zhang et al., 2022). More specifically, the affected vessels include the internal carotid artery (ICA), middle cerebral artery (MCA) and/or proximal anterior cerebral artery (ACA). This phenomenon is accompanied by the formation of smoke-like abnormal blood vessels at the base of the skull in digital subtraction angiography (DSA) (Zhang et al., 2019). The condition was first described in Japan (Ott et al., 2023) in 1957 (Rupareliya and Lui, 2018). The term "moyamoya" means "puff of smoke" in Japanese (Berry et al., 2020), referring to the tangled appearance of tiny vessels compensating for the blockage (Uchiyama and Fujimura, 2024). The name was first used in 1969 by Suzuki and Takaku (Rupareliya and Lui, 2018). MMD usually occurs bilaterally, and its aetiology remains undetermined (Rupareliya and Lui, 2018). In contrast, moyamoya syndrome (MMS), also known as "quasi-moyamoya disease", is a vasculopathy associated with various systemic diseases. It tends to be unilateral, and the most common underlying causes include atherosclerosis, autoimmune diseases, head trauma, brain tumour, radiation exposure, and meningitis (Mikami et al., 2019; Uchiyama and Fujimura, 2024), although there is no agreement among authors as to which disorders should be included in this list. Clear phenotypic differences between those two variants of disease (MMD and MMS) remain elusive, though both are characterised by the same stroke hazard and require the same method of treatment (Feghali et al., 2019).
The aim of this paper is to analyse the available literature with the objective of:

1. increasing awareness of this rare condition;
2. highlighting potentially modifiable risk factors for moyamoya vasculopathy.

MATERIALS AND METHODS

A literature search was conducted for this systematic review, using the PubMed and Google Scholar electronic databases. Only these two databases were used, as the aim was to focus on the most accessible journals and search engines. No article types were excluded. Initially, no particular language was set, but ultimately only English-language publications were chosen. Subsequently, the language was set as Polish, and additional two articles written in Polish were selected. A time filter was applied to search for studies published within the last five years. The keywords used were: "moyamoya disease + risk factors" OR "moyamoya disease + obesity" OR "moyamoya disease + symptoms" OR "moyamoya disease + treatment" OR "moyamoya syndrome + risk factors" OR "moyamoya syndrome + symptoms" OR "moyamoya syndrome + treatment" OR "moyamoya disease vs. moyamoya syndrome" OR "quasi moyamoya disease" OR "moyamoya prevalence" OR "moyamoya + EEG" OR "moyamoya + antiplatelets" OR "moyamoya + cilostazol". On Google Scholar, no particular language was chosen, the results were sorted by relevance, and no specific type of publication was selected. The keywords used were the same as in the PubMed database. The studies were published between 2018 and 2025. No restrictions for age, sex, ethnicity etc. of individuals described in the papers were set. Results are summarised in Fig. 1.
Inclusion criteria:

1. publications on MMD and/or MMS/quasi-moyamoya disease.

Exclusion criteria:

1. studies focused solely on stroke without reference to MMD or MMS.

To meet the review's limit of no more than 30 references, a total of 30 articles were identified and synthesised in this

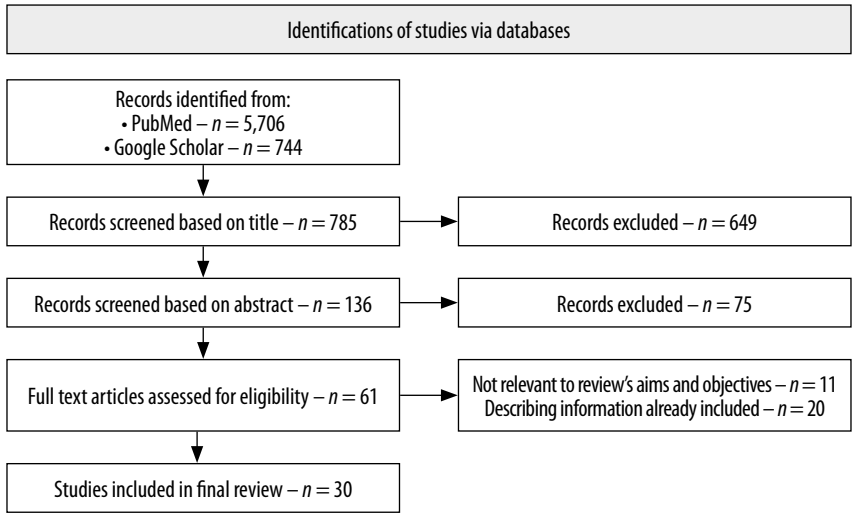

Fig. 1. PRISMA flow diagram

DOI: 10.15557/AN.2025.0006

review, including 17 review papers, two of which were also meta-analyses, 10 cohort studies, and 3 case reports.

EPIDEMIOLOGY

MMD is most commonly seen in East Asian countries (mainly Japan and Korea) (Uchiyama and Fujimura, 2024), but Western countries have also noted an increase in the incidence of MMD in recent years (Gonzalez et al., 2023; Rupareliya and Lui, 2018). MMD prevalence is estimated to be approximately 1 in 280,000 in Japan, 1 in 89,000 in China, and 1 in 1,100,000 in the United States, with around 5,000 individuals affected by moyamoya in the US as of June 2024 (Cottrell and Haley, 2024). However, there remains a general lack of comprehensive global epidemiological data. Overall, most authors agree that two peaks of MMD occurrence can be distinguished. In the paediatric population, the diagnosis most frequently comes at the age of five, or, as other authors claim, between the ages of 5 to 9. In the adult population, individuals are most often diagnosed in the fourth decade of life, specifically between the ages of 45 to 49 (Rupareliya and Lui, 2018). The disease tends to occur more commonly in women, as MMD has an almost 2:1 female-to-male ratio in the adult population (Gonzalez et al., 2023). Interestingly, this ratio seems to be 1:1 in China (Zheng et al., 2019). Also, a higher stroke risk seems to be observed in females (Birkeland et al., 2024).

As mentioned above, despite MMD occurring predominantly in Asian patients, rare cases have been described in other populations. Interestingly, cerebral ischaemia and transient ischaemic attack (TIA) are more common in North American and European patients, while Asian patients more often suffer from intracranial haemorrhage. At the same time, according to some authors, in China MMD is mainly ischaemic (Zhang et al., 2019). All in all, despite both MMD and MMS being rare disorders, they are characterised by a significant morbidity and mortality (Gonzalez et al., 2023).

RISK FACTORS

Although the direct cause of MMD remains unknown (Zhang et al., 2019), several risk factors have been proposed. It is most likely a multifactorial disease (Mertens et al., 2022). According to Ge et al. (2020), modifiable factors presumably associated with a higher risk of MMD are increased body mass index (BMI) and homocysteine levels. At the same time, they pointed out that elevated albumin and HDL cholesterol levels correlated with a lower risk of MMD. It is worth noting that the aforementioned factors are associated with hypertension, current smoking, diabetes mellitus, and alcohol use, which makes them modifiable risk factors, as they may be controlled (Hirano et al., 2020; Ott et al., 2023). Overall, obesity and metabolic syndrome, especially when combined, are considered to significantly increase the odds for the development of MMS in young adults (Lee et al., 2023).

It is also possible that environmental risk factors for MMD include radiation exposure, bacterial infections, varicella zoster virus (VZV), Epstein–Barr virus (EBV), cytomegalovirus (CMV) (Mertens et al., 2022), as well as leptospirosis and HIV (Gonzalez et al., 2023). Non-modifiable risk factors may include older age, as well as possible genetic and immune components (Ge et al., 2020), as up to 12% of patients have a positive family history (Gonzalez et al., 2023), and because type 1 diabetes, autoimmune thyroid disorders, and other autoimmune disorders are often found in individuals with MMD (Rupareliya and Lui, 2018). Interestingly, Lee et al. (2023) concluded that at all BMI stages the risk of MMS tends to be higher among females than males. They noted the same correlation in individuals with metabolic syndrome. Undoubtedly, Asian ethnicity is associated with a much greater risk of developing MMD compared to other populations, as white individuals carry less common non-Arg4810Lys variants of the *RNF213* gene on chromosome 17 (presumably inherited in an autosomal dominant manner), which is the major susceptibility gene for MMD (Ihara et al., 2022; Ott et al., 2023).

Additionally, predisposing conditions for moyamoya vasculopathy include neurofibromatosis type I, sickle cell disease, and Down syndrome (Berry et al., 2020). However, some authors consider them as underlying cause of MMS, while others treat them as common comorbidities of MMD. Interestingly, moyamoya occurs in 2% of individuals suffering from neurofibromatosis type I (Marjańska et al., 2024).

SYMPTOMS

Usually, the first symptom of MMD in children is progressive cerebral ischaemia, which includes stroke or recurrent TIAs, also known as "mini-strokes" (Zhang et al., 2019). Frequently, they are accompanied by muscular weakness or paralysis affecting one side of the body. Adults may also experience these symptoms due to blocked arteries, but, on the other hand, more often experience a haemorrhagic stroke due to bleeding into the brain (Zhang et al., 2019). Other symptoms may include headaches, seizures, altered consciousness, involuntary movements, vision problems, as well as cognitive and/or sensory impairment (Berry et al., 2020; Rupareliya and Lui, 2018). At the same time, some authors claim that mental decline or seizures may be the first symptom in children. Headaches are reported in 20% of paediatric patients with MMD (Zhang et al., 2019). Ott et al. (2023) in their case report of a Hispanic woman with MMD highlighted confusion, hyperglycaemia, hypertension, paraesthesia, and weakness as the individual's presenting symptoms.

DIAGNOSIS

The diagnosis of MMD is based mainly on cerebral angiography (Ott et al., 2023), which is considered obligatory for making a definitive diagnosis (Uchiyama and Fujimura,

 DOI: 10.15557/AN.2025.0006

2024). The first test to perform in the diagnostic algorithm is usually magnetic resonance imagining (MRI), but other tests include magnetic resonance angiography (MRA), conventional cerebral angiography, transcranial Doppler (TCD), and cerebral perfusion measurement (Rupareliya and Lui, 2018). Non-contrast computed tomography (CT) of the head is also used to rule out acute haemorrhage in the presence of a progressive neurological deficit (Berry et al., 2020). Zhang et al. (2019) highlight that, according to guidelines, in order to diagnose MMD, the following underlying cerebrovascular conditions should be excluded: atherosclerosis, autoimmune diseases, meningitis, brain tumours, Down syndrome, Recklinghausen disease, head injury, and cerebrovascular damage after cranial irradiation, as these may indicate the presence of MMS (Uchiyama and Fujimura, 2024). On the other hand, Kuroda et al. (2022), in their diagnostic criteria, proposed excluding atherosclerosis, hyperthyroidism, head trauma, and some other conditions from the underlying comorbidities of quasi-moyamoya disease. Still, according to some authors, unified diagnostic criteria for both MMD and MMS are lacking (Gonzalez et al., 2023).

Although electroencephalogram (EEG) is not used to diagnose moyamoya, multiple studies point to it as a non-invasive and useful tool for preoperative and intraoperative, as well as postoperative evaluation of patients with moyamoya vasculopathy (Giacomini, 2022; Huguenard et al., 2021). Huguenard et al. (2021) underline that the most common use of EEG is intraoperative monitoring for cerebral changes that may indicate ischaemia; if such changes occur in EEG activity, anaesthetic techniques are adjusted, including increasing mean arterial blood pressure. Interestingly, a few minutes after hyperventilation, moyamoya patients usually present a characteristic pattern called the "rebuild up phenomenon" – high-voltage slow waves on EEG – which disappears after successful revascularisation surgery. This phenomenon is seen in about half of all patients with moyamoya and is not found in any other conditions (Mkwambe et al., 2024). This implies that EEG can be reliably compared with perfusion data to evaluate the results of surgery and monitor patients during follow-up (Giacomini, 2022).

TREATMENT

These days, the main treatment for MMD focuses on neuroprotection, cerebral blood flow reconstruction, as well as neurological rehabilitation, including pharmacological treatment, surgical revascularisation, and cognitive rehabilitation (Zhang et al., 2022). It is worth noting that antiplatelet drugs, such as aspirin (50 mg to 325 mg per day) or clopidogrel (75 mg once daily), are commonly used in the management of MMD to reduce the risk of thrombus formation as cerebral vessels progressively become occluded (Berry et al., 2020; Ott et al., 2023; Uchiyama and Fujimura, 2024; Zhang et al., 2019). However, the optimal regimen and duration of antiplatelet treatment remain uncertain. Abedi et al. (2023) concluded that preoperative aspirin use had a beneficial effect regardless of whether it was stopped three days prior to surgery, the day of surgery, or continued postoperatively. Also, cilostazol, a selective phosphodiesterase III inhibitor with antiplatelet, antithrombotic, and vasodilatory effects, is increasingly being used as a potential therapy for MMD management. It is administered orally in tablet form, with available dosages of 50 mg and 100 mg, and the recommended dosage in adults is 100 mg every 12 hours. Compared to clopidogrel, patients receiving cilostazol show significantly greater improvement in cognitive function at two-year follow-up (Abedi et al., 2023).

Furthermore, some studies have highlighted that cilostazol is comparable or even superior to aspirin for long-term secondary stroke prevention, and may be associated with improved neurological outcomes after ischaemic stroke, especially in patients who receive both aspirin and cilostazol in the first 14 days after ischaemic stroke (Abedi et al., 2023).

However, the main treatment is generally surgical, involving either direct or indirect cerebrovascular bypass. According to Paluch et al. (2021), indirect bypass is regarded as easier to perform and safer than direct bypass. This relation is particularly seen in younger patients or those with comorbidities. Overall, this method includes relocation of vascularised tissue onto the brain's surface to promote angiogenesis, utilising several procedures such as burr holes, pial synangiosis, dural inversion, or omental transposition. The augmentation of cerebral blood flow may take several months to a year (Nguyen et al., 2022).

In contrast, despite the greater risk of complications, such as transient cerebral hyperperfusion or stroke, direct bypass provides immediate restoration of normal blood flow in narrowed vessels (Paluch et al., 2021). It is often preferred in adults because it is believed that indirect revascularisation may be associated with insufficient neoangiogenesis in adults, as opposed to children. Direct bypass involves a direct anastomosis between donor and recipient arteries, that is typically the superficial temporal artery and the middle cerebral artery (Nguyen et al., 2022). In recent years, combined methods – direct and indirect – seem to predominate (Paluch et al., 2021). There have been failed attempts at stenting stenosed vessels, as well as unsuccessful attempts at medical treatment to halt disease progression; consequently, all medical therapies are proposed mainly with the aim of preventing secondary complications of MMD (Berry et al., 2020). Overall, revascularisation surgery for haemorrhagic MMD is performed to prevent rebleeding, but there is no evidence that bypass surgery prevents de novo haemorrhage in patients with asymptomatic MMD. Revascularisation surgery also leads to the regression of periventricular anastomosis and peripheral aneurysm (Hirano et al., 2024). It is worth mentioning that in Birkeland et al. (2024) cohort study, patients who underwent bypass surgery had fewer stroke events than those treated conservatively. Also, symptomatic treatment may be introduced; for example, headaches and seizures

DOI: 10.15557/AN.2025.0006 AKTUALN NEUROL 2025, 25 (1), p. 33–38

are usually managed by using analgesics and antiepileptic medications, respectively (Rupareliya and Lui, 2018).

RISK FACTORS FOR ISCHAEMIC STROKE AND FOR POSTOPERATIVE ISCHAEMIC COMPLICATIONS

Asymptomatic MMD may carry a 1.0% annual stroke risk during the first five years, the majority of which are haemorrhagic strokes. At the same time, long-term prognoses remain uncertain (Kuroda et al., 2023), and it is worth noting that the risk varies depending on moyamoya aetiology (Gatti et al., 2021). The main risk factors for postoperative stroke in MMD patients include preoperative ischaemic events, posterior cortical atrophy (PCA) involvement, and diabetes (Liu et al., 2023; Wei et al., 2019). At the same time, gender, age of onset, and surgery type seem to be statistically insignificant (Wei et al., 2019). In the cohort study by Feghali et al. (2019), the overall rate of surgical complications was 33% in patients with MMD and 16% in patients with MMS. However, the difference was not statistically significant, though it was highlighted that stroke-free survival rates were similar between MMD and MMS patients. The authors also mentioned haemorrhagic or ischaemic stroke, TIA, hyperperfusion syndrome, postoperative seizure, skin flap ischaemia, and surgical site infection as the most common postoperative complications. Ischaemic complications after revascularisation surgery for MMD occur in 4.7–22.2% of cases, mostly on the surgical side. Occlusion of the contralateral ICA in the acute phase after revascularisation surgery is an extremely rare complication, but with potentially serious consequences (Ogawa et al., 2021).

CONCLUSIONS

Both MMD and MMS are rare, progressive conditions that can cause stroke. The understanding of their pathophysiology and effective methods of management remains limited. However, a strong association between obesity and moyamoya vasculopathy has been established, which means some modifiable risk factors can be considered in terms of prevention. Its first symptom, unfortunately, may be stroke, either ischaemic or haemorrhagic.

Overall, the imagining of the circle of Wills to detect stenosis is the golden standard for diagnosing both MMD and MMS, which are distinguished primarily by the presence of underlying diseases that can cause this vasculopathy. Still, there are no unified diagnostic criteria. Despite the attempts made in the past to halt moyamoya pharmacologically, currently, the only effective treatment remains early surgical revascularisation (Berry et al., 2020). It is worth noting that no method currently exists that could stop MMD progression or reverse it (Paluch et al., 2021). Although this vasculopathy is most prevalent in East Asia, growing awareness is essential, as its incidence is increasing in Europe and North America – possibly due to migration.

Conflict of interest

The author does not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript; critical review of manuscript; final approval of manuscript: JL.

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DOI: 10.15557/AN.2025.0006