Chapter

Introductory Chapter: Moyamoya Disease, Silent Killer

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1. Introduction

Moyamoya disease is a cerebrovascular ailment that entails a progressive steno-occlusive process of the terminal internal carotid artery and its main branches. Secondarily it induces the development of an extensive network of unusual reticular collateral vessels at the skull base, mainly at the lenticulostriate and choroidal arteries [1–4]. These abnormal vessels create a hazy picture on cerebral angiogram that looks like a "puff of cigarette smoke drifting in the air" [5], which is the meaning of moyamoya in the Japanese language. These abnormal collateral vessels undergo pathological changes that lead to the appearance of haemorrhages [6].

Moyamoya disease leads to ischemic and haemorrhagic brain strokes and induces cognitive impairment [2, 7–9], partly due to the cerebrovascular insults [8], chronic brain hypoperfusion and white matter involvement [10]. The cognitive decline seems to be more severe in the haemorrhagic than in the ischemic type [11]. Disease progression is typical if left untreated [12].

Moyamoya disease aetiology is mostly unknown [13, 14], and without precise knowledge in this area, it is challenging to devise an effective treatment that prevents and cures this disease.

2. Disease incidence and prevalence

It is more prevalent in East Asian countries [15–17], namely Japan (10.3/100,000 people in 2006) [5], Korea (9.1/100,000 in 2008) [18] and China (3.92/100,000 in 2010) [19] than in the USA [20] and Europe [21].

Moyamoya incidence and prevalence have been increasing steadily over the years. In Japan the reported incidence rose from 0.35/100,00 in 1995 [16] to 0.54/100,000 in 2003 [5] and 0.94/100,000 in 2006 and the prevalence from 3.16/100,000 in 1995 [16], to 6.03/100,000 in 2003 [5] and 10.4/100,000 in 2006 [5], with a 1.8:1 female to male ratio [22] and a 10%-15% [5, 22, 23] familial cases. Another important aspect is that while the affected parents presented moyamoya related clinical symptoms at 22-36 years of age, their siblings showed the first symptoms when they were 5-11 years old [24]. In the USA [25] and Europe [21], the incidence in 10 times smaller, and the female to male ratio 2.2:1 [21]. In 2005 in the USA, the incidence was 0.086 cases/100,000 inhabitants [20].

Moyamoya disease has two peaks in incidence. The first in children before 18 years of age (maximum at 5-9 years old) and the second in adults in the fourth and fifth decades of life (highest rate from 35 to 45 years of age) [5, 17, 22, 26, 27]. In 47.8% of the patients, symptoms start before ten years of age [14].

In Japan, the paediatric prevalence is the highest worldwide, with 3 cases per 100,000 children [5, 22, 28].

3. Asymptomatic moyamoya disease

It has been described as moyamoya features in the absence of any ischemic or haemorrhagic stroke [12]. The number of these patients has increased progressively over the years with improved diagnostic capacities [5, 24, 29–32] and the introduction of regular medical brain check-ups [12, 33]. In the Japan brain check-ups, the percentage of positive asymptomatic moyamoya patients was 0.07% (0.05% for males and 0.10% for females) with a female to male ratio of 3.3:1, mean age of 54 years [33]. Most of these asymptomatic patients were adults [34–37]. In children, the diagnosis can be unduly delayed due to their inability to communicate adequately, particularly at a very young ages [38].

But clinically asymptomatic patients do not mean that they have no pathological findings. In Japan, 20-30% of them harboured a cerebral infarction in watershed brain areas [24, 31] while the incidence of asymptomatic brain infarction in the general Japanese population in their fifth decade of life was 4.4% [39]. Additionally, 15-44% of adult moyamoya asymptomatic patients have clinically silent microbleeds [40–42] in the basal ganglia, thalamus and periventricular areas [43]. In a multicenter study in Japan, 34.3% of asymptomatic moyamoya patients with a normal cerebral blood flow had reduced cerebral vascular reserve [43]. In the follow-up, 12.5% [30] to 30% [12] of these patients suffered transitory ischemic attacks, ischemic or haemorrhagic stroke [12, 24, 31, 32], with a 3.2% annual stroke risk [12, 30, 31]. The female gender was associated with a greater risk of disease progression [31].

In Korea, the symptomatic progression in asymptomatic moyamoya patients was radiological in 12% and clinical in 5.3% with a reduced cerebral reserve capacity in 9.3% [30]. Clinical progression has been the rule worldwide for paediatric asymptomatic moyamoya patients [44]. As asymptomatic moyamoya disease is not a stable situation [12, 45, 46] close surveillance is mandatory, notably if there is a reduced cerebral vascular reserve [12, 30], ivy sign on MRI flair imaging [47, 48] or smoking habit [12]. The ivy sign is associated with an impaired cerebrovascular hemodynamic status [47]. It has been reported in 31.3% of asymptomatic moyamoya patients [47] that rises to 66% in those that already have ischemic stroke-related symptoms [48–50].

Moreover, these patients are not entirely asymptomatic but suffer from a steady cognitive decline in intelligence, spatial imagination, working memory, working memory-backwards digit span, computational ability, complex subtraction, complex arithmetic and word short-term memory [8, 51], particularly in children [45, 52, 53]. This cognitive decay precedes the onset of clinical symptoms due to brain infarction, or haemorrhage [8] and inevitable worsens when these cerebrovascular insults happen [51, 54]. Additionally, asymptomatic moyamoya patients can suffer from ischemic or haemorrhagic strokes [31]. Another critical aspect is that 20% of moyamoya children who undergo ischemic strokes are handicapped to undergo an independent social life [45, 53, 55].

Some have recommended performing surgical revascularization on asymptomatic moyamoya patients, particularly children, to prevent this unpleasant progressive neurological and cognitive deterioration [30, 44, 54]. Some have suggested undertaking surgical treatment if the ivy sign is seen in MRI flair imaging [47]. In any case, symptomatic progression in previously asymptomatic patients should be addressed with aggressive surgical revascularization in adults and children [30] as it halts disease progression [31].

4. Treatment modalities

Medical treatment with antithrombotic drugs (aspirin [56], cilostazol [57], clopidogrel [58, 59], low molecular-weight heparin, argatroban) [60] or calcium channel blockers [61] is used for mild asymptomatic cases, although their effectiveness has never been proven convincingly [15, 62]. Cilostazol is preferred over aspirin and clopidogrel because of its lower hemorrhagic risk [60], and clopidogrel recommended when aspirin is not tolerated [60]. These antithrombotic agents are advised for the ischemic-type moyamoya disease [15]. In any case, they are not very useful [63] as some researchers have reported an almost 3-fold chance of future neurological deterioration in the patients treated conservatively compared to those treated surgically [54, 64].

Direct, indirect or combined revascularization provides much better long-term results than conservative treatment, minimising the risk of ischemic and haemorrhagic strokes [54, 65, 66]. Early surgical intervention, particularly in paediatric patients, reduces cerebrovascular events and should be considered in asymptomatic children [44, 67]. Specific hospital perioperative morbidity and mortality have to be considered when recommending surgical treatment to these patients [12]. Thus, surgical treatment should be advised a soon as there is any sign of clinical or subclinical deterioration.

5. Conclusions

Moyamoya disease is more prevalent than previously thought because many patients go undiagnosed. Once diagnosed, asymptomatic patients may already harbour a cognitive decline long before cerebrovascular events take place. The only effective treatment is surgical revascularization, which should be undertaken as soon as any clinical deterioration sign occurs. Many posit that preventive surgical treatment should be recommended to asymptomatic patients, particularly in the paediatric age group.

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References

[1] Suzuki, J. & Takaku, A. Cerebrovascular 'moyamoya' disease. Disease showing abnormal net-like vessels in base of brain. Arch. Neurol. **20**, 288-299 (1969).

[2] Kuroda, S. & Houkin, K. Moyamoya disease: current concepts and future perspectives. Lancet Neurol. **7**, 1056-1066 (2008).

[3] Suzuki, J. & Kodama, N. Moyamoya disease--a review. Stroke **14**, 104-109 (1983).

[4] Scott, R. M. & Smith, E. R. Moyamoya disease and moyamoya syndrome. N. Engl. J. Med. **360**, 1226-1237 (2009).

[5] Baba, T., Houkin, K. & Kuroda, S. Novel epidemiological features of moyamoya disease. J. Neurol. Neurosurg. Psychiatry **79**, 900-904 (2008).

[6] Funaki, T. *et al.* Effect of choroidal collateral vessels on de novo hemorrhage in moyamoya disease: analysis of nonhemorrhagic hemispheres in the Japan Adult Moyamoya Trial. J. Neurosurg. **132**, 408-414 (2019).

[7] Fang, L. *et al.* Different aspects of dysexecutive syndrome in patients with moyamoya disease and its clinical subtypes. J. Neurosurg. **125**, 299-307 (2016).

[8] He, S. *et al.* Characteristics of cognitive impairment in adult asymptomatic moyamoya disease. BMC Neurol. **20**, 322 (2020).

[9] Festa, J. R. *et al.* Neurocognitive dysfunction in adult moyamoya disease. J. Neurol. **257**, 806-815 (2010).

[10] Liu, Z. *et al.* Association between white matter impairment and cognitive dysfunction in patients with ischemic Moyamoya disease. BMC Neurol. **20**, 302 (2020).

[11] Su, S.-H., Hai, J., Zhang, L., Yu, F. & Wu, Y.-F. Assessment of cognitive function in adult patients with hemorrhagic moyamoya disease who received no surgical revascularization. Eur. J. Neurol. **20**, 1081-1087 (2013).

[12] Jo, K.-I., Yeon, J. Y., Hong, S.-C. & Kim, J.-S. Clinical course of asymptomatic adult moyamoya disease. Cerebrovasc. Dis. Basel Switz. **37**, 94-101 (2014).

[13] 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) **59**, 361-370 (2019).

[14] Huang, S., Guo, Z.-N., Shi, M., Yang, Y. & Rao, M. Etiology and pathogenesis of Moyamoya Disease: An update on disease prevalence. Int. J. Stroke Off. J. Int. Stroke Soc. **12**, 246-253 (2017).

[15] Shang, S. *et al.* Progress in moyamoya disease. Neurosurg. Rev. **43**, 371-382 (2020).

[16] Ikezaki, K., Inamura, T., Kawano, T. & Fukui, M. Clinical features of probable moyamoya disease in Japan. Clin. Neurol. Neurosurg. **99 Suppl 2**, S173-S177 (1997).

[17] Bao, X.-Y. *et al.* Epidemiology of Moyamoya Disease in China: Single-Center, Population-Based Study. World Neurosurg. **122**, e917–e923 (2019).

[18] Im, S. H. *et al.* Prevalence and epidemiological features of moyamoya disease in Korea. J. Cerebrovasc. Endovasc. Neurosurg. **14**, 75-78 (2012).

[19] Miao, W. *et al.* Epidemiological and clinical features of Moyamoya disease in

Nanjing, China. *Clin. Neurol. Neurosurg.* **112**, 199-203 (2010).

[20] Uchino, K., Johnston, S. C., Becker, K. J. & Tirschwell, D. L. Moyamoya disease in Washington State and California. Neurology **65**, 956-958 (2005).

[21] Yonekawa, Y., Ogata, N., Kaku, Y., Taub, E. & Imhof, H. G. Moyamoya disease in Europe, past and present status. *Clin. Neurol. Neurosurg.* **99 Suppl 2**, S58-S60 (1997).

[22] Wakai, K. *et al.* Epidemiological features of moyamoya disease in Japan: findings from a nationwide survey. Clin. Neurol. Neurosurg. **99 Suppl 2**, S1-S5 (1997).

[23] Yamauchi, T., Houkin, K., Tada, M. & Abe, H. Familial occurrence of moyamoya disease. Clin. Neurol. Neurosurg. **99 Suppl 2**, S162-S167 (1997).

[24] Nanba, R. *et al.* [Clinical features and outcomes of 10 asymptomatic adult patients with moyamoya disease]. No Shinkei Geka. **31**, 1291-1295 (2003).

[25] Numaguchi, Y. *et al.* Moyamoya disease in the United States. Clin. Neurol. Neurosurg. **99 Suppl 2**, S26-S30 (1997).

[26] Fujimura, M., Bang, O. Y. & Kim, J. S. Moyamoya Disease. Front. Neurol. Neurosci. **40**, 204-220 (2016).

[27] Han, D. H. *et al.* A co-operative study: clinical characteristics of 334 Korean patients with moyamoya disease treated at neurosurgical institutes (1976-1994). The Korean Society for Cerebrovascular Disease. *Acta Neurochir. (Wien)* **142**, 1263-1273; discussion 1273-1274 (2000).

[28] Nagaraja, D., Verma, A., Taly, A. B., Kumar, M. V. & Jayakumar, P. N. Cerebrovascular disease in children. Acta Neurol. Scand. **90**, 251-255 (1994).

[29] Ahn, I. M. *et al.* Incidence, prevalence, and survival of moyamoya disease in Korea: a nationwide, population-based study. Stroke **45**, 1090-1095 (2014).

[30] Yang, J. *et al.* Clinicoepidemiological features of asymptomatic moyamoya disease in adult patients. J. Cerebrovasc. Endovasc. Neurosurg. **16**, 241-246 (2014).

[31] Kuroda, S., Hashimoto, N., Yoshimoto, T., Iwasaki, Y., & Research Committee on Moyamoya Disease in Japan. Radiological findings, clinical course, and outcome in asymptomatic moyamoya disease: results of multicenter survey in Japan. Stroke **38**, 1430-1435 (2007).

[32] Yamada, M., Fujii, K. & Fukui, M. [Clinical features and outcomes in patients with asymptomatic moyamoya disease--from the results of nation-wide questionnaire survey]. No Shinkei Geka. **33**, 337-342 (2005).

[33] Ikeda, K. *et al.* Adult moyamoya disease in the asymptomatic Japanese population. J. Clin. Neurosci. Off. J. Neurosurg. Soc. Australas. **13**, 334-338 (2006).

[34] Ryu, G. W., Yang, Y. S., Choi, M. & Shim, K. W. Lived experiences of adult patients with moyamoya disease: A qualitative case study. Jpn. J. Nurs. Sci. JJNS **17**, e12332 (2020).

[35] Luo, R., Gao, F., Deng, X., Zhang, D. & Zhang, Y. Results of Conservative Follow-up or Surgical Treatment of Moyamoya Patients Who Present without Hemorrhage, Transient Ischemic Attack, or Stroke. World Neurosurg. **108**, 683-689 (2017).

[36] Kleinloog, R., Regli, L., Rinkel, G. J. E. & Klijn, C. J. M. Regional differences

in incidence and patient characteristics of moyamoya disease: a systematic review. J. Neurol. Neurosurg. Psychiatry **83**, 531-536 (2012).

[37] Nariai, T. *et al.* Severe haemodynamic stress in selected subtypes of patients with moyamoya disease: a positron emission tomography study. J. Neurol. Neurosurg. Psychiatry **76**, 663-669 (2005).

[38] Jea, A., Smith, E. R., Robertson, R. & Scott, R. M. Moyamoya syndrome associated with Down syndrome: outcome after surgical revascularization. Pediatrics **116**, e694-e701 (2005).

[39] Shinkawa, A. *et al.* Silent cerebral infarction in a community-based autopsy series in Japan. The Hisayama Study. Stroke **26**, 380-385 (1995).

[40] Kuroda, S. & AMORE Study Group. Asymptomatic moyamoya disease: literature review and ongoing AMORE study. Neurol. Med. Chir. (Tokyo) **55**, 194-198 (2015).

[41] Ishikawa, T. *et al.* Prevalence of asymptomatic microbleeds in patients with moyamoya disease. *Neurol. Med. Chir. (Tokyo)* **45**, 495-500; discussion 500 (2005).

[42] Kikuta, K.-I. *et al.* Asymptomatic microbleeds in moyamoya disease: T2*-weighted gradient-echo magnetic resonance imaging study. J. Neurosurg. **102**, 470-475 (2005).

[43] Kuroda, S., Kashiwazaki, D., Ishikawa, T., Nakayama, N. & Houkin, K. Incidence, locations, and longitudinal course of silent microbleeds in moyamoya disease: a prospective T2*-weighted MRI study. Stroke **44**, 516-518 (2013).

[44] Lin, N. *et al.* Discovery of asymptomatic moyamoya arteriopathy in pediatric syndromic populations: radiographic and clinical progression. *Neurosurg.* Focus **31**, E6 (2011).

[45] Imaizumi, T., Hayashi, K., Saito, K., Osawa, M. & Fukuyama, Y. Long-term outcomes of pediatric moyamoya disease monitored to adulthood. Pediatr. Neurol. **18**, 321-325 (1998).

[46] Kuroda, S. *et al.* Incidence and clinical features of disease progression in adult moyamoya disease. Stroke **36**, 2148-2153 (2005).

[47] Vuignier, S. *et al.* Ivy sign, misery perfusion, and asymptomatic moyamoya disease: FLAIR imaging and (15)O-gas positron emission tomography. Acta Neurochir. (Wien) **155**, 2097-2104 (2013).

[48] Kawashima, M. *et al.* Unilateral hemispheric proliferation of ivy sign on fluid-attenuated inversion recovery images in moyamoya disease correlates highly with ipsilateral hemispheric decrease of cerebrovascular reserve. AJNR Am. J. Neuroradiol. **30**, 1709-1716 (2009).

[49] Fujiwara, H., Momoshima, S. & Kuribayashi, S. Leptomeningeal high signal intensity (ivy sign) on fluid-attenuated inversion-recovery (FLAIR) MR images in moyamoya disease. Eur. J. Radiol. **55**, 224-230 (2005).

[50] Yoon, H.-K., Shin, H.-J. & Chang, Y. W.' Ivy sign' in childhood moyamoya disease: depiction on FLAIR and contrast-enhanced T1-weighted MR images. Radiology **223**, 384-389 (2002).

[51] Karzmark, P., Zeifert, P. D., Bell-Stephens, T. E., Steinberg, G. K. & Dorfman, L. J. Neurocognitive impairment in adults with moyamoya disease without stroke. Neurosurgery **70**, 634-638 (2012).

[52] Kurokawa, T. *et al.* Prognosis of occlusive disease of the circle of Willis (moyamoya disease) in children. Pediatr. Neurol. **1**, 274-277 (1985).

[53] Imaizumi, C., Imaizumi, T., Osawa, M., Fukuyama, Y. & Takeshita, M. Serial intelligence test scores in pediatric moyamoya disease. Neuropediatrics **30**, 294-299 (1999).

[54] Zeng, H. *et al.* Comparison of Operative and Conservative Treatment for Asymptomatic Moyamoya Disease: Preliminary Experience in Small Retrospective Series. World Neurosurg. **146**, e955–e960 (2021).

[55] Matsushima, Y., Aoyagi, M., Masaoka, H., Suzuki, R. & Ohno, K. Mental outcome following encephaloduroarteriosynangiosis in children with moyamoya disease with the onset earlier than 5 years of age. Childs Nerv. Syst. ChNS Off. J. Int. Soc. Pediatr. Neurosurg. **6**, 440-443 (1990).

[56] Aihara, Y. *et al.* Aspirin use and platelet aggregation in ischemic onset-type pediatric moyamoya patients with intractable headaches (moya-ache). *Childs Nerv. Syst. ChNS Off. J. Int. Soc. Pediatr. Neurosurg.* (2021) doi:10.1007/s00381-020-04991-y.

[57] Ando, S. *et al.* Cilostazol may improve cognition better than clopidogrel in non-surgical adult patients with ischemic moyamoya disease: subanalysis of a prospective cohort. Neurol. Res. **41**, 480-487 (2019).

[58] Chiba, T. *et al.* 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. Off. J. Natl. Stroke Assoc. **27**, 3373-3379 (2018).

[59] Soman, T. *et al.* The risks and safety of clopidogrel in pediatric arterial ischemic stroke. Stroke **37**, 1120-1122 (2006).

[60] Oki, K. *et al.* Trends of Antiplatelet Therapy for the Management of Moyamoya Disease in Japan: Results of a Nationwide Survey. J. Stroke Cerebrovasc. Dis. Off. J. Natl. Stroke Assoc. **27**, 3605-3612 (2018).

[61] Hosain, S. A., Hughes, J. T., Forem, S. L., Wisoff, J. & Fish, I. Use of a calcium channel blocker (nicardipine HCl) in the treatment of childhood moyamoya disease. J. Child Neurol. **9**, 378-380 (1994).

[62] Ge, P. *et al.* Long-Term Outcome After Conservative Treatment and Direct Bypass Surgery of Moyamoya Disease at Late Suzuki Stage. World Neurosurg. **103**, 283-290 (2017).

[63] Choi, J. U., Kim, D. S., Kim, E. Y. & Lee, K. C. Natural history of moyamoya disease: comparison of activity of daily living in surgery and non surgery groups. Clin. Neurol. Neurosurg. **99 Suppl 2**, S11-S18 (1997).

[64] Jang, D.-K. *et al.* Bypass surgery versus medical treatment for symptomatic moyamoya disease in adults. J. Neurosurg. **127**, 492-502 (2017).

[65] Kawaguchi, S., Okuno, S. & Sakaki, T. Effect of direct arterial bypass on the prevention of future stroke in patients with the hemorrhagic variety of moyamoya disease. J. Neurosurg. **93**, 397-401 (2000).

[66] Kuroda, S., Houkin, K., Ishikawa, T., Nakayama, N. & Iwasaki, Y. Novel bypass surgery for moyamoya disease using pericranial flap: its impacts on cerebral hemodynamics and long-term outcome. *Neurosurgery* **66**, 1093-1101; discussion 1101 (2010).

[67] Kim, S.-K. *et al.* Moyamoya disease among young patients: its aggressive clinical course and the role of active surgical treatment. *Neurosurgery* **54**, 840-844; discussion 844-846 (2004).