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Introductory Chapter: Moyamoya Disease, Silent Killer

Vicente Vanaclocha, Nieves Saiz-Sapena and Leyre Vanaclocha

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. Secondly 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 0.35/100,000 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 is 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 as 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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