Abstract

Background and purpose: Originally described and extensively studied in Japan, Moyamoya disease (MMD) is assumed to be a very rare cause of stroke elsewhere, possibly with distinct clinical features. Using nationwide registers we conducted a population based study of the incidence and clinical features of MMD in Denmark

Methods: Eligible patients were identified in The Danish National Patient Register from 1994 to 2017. Additional cases from one referral centre not yet listed in the register were also included. We collected clinical data from individual patient records. The diagnosis was validated according to established criteria. We also extracted basic demographic data on the cohort from the Danish Civil Registration system.

Results: 52 patients fulfilled the criteria for probable or definite MMD. Until 2008 the incidence was 0.02 per 100 000 person years and from 2009 and onwards the incidence rose to 0.07 per 100 000 person years. The ratio of female to male patients was 1.8, and the incidence had two peaks: one in childhood and another in middle age. The most common mode of presentation was ischaemic stroke with 33% followed by brain haemorrhage with 23%. Eight patients (15%) suffered a subsequent stroke.

Conclusions: Moyamoya disease remains a rare cause of stroke in Denmark. We assume the increased incidence seen recently can be attributed to a higher detection rate. The clinical presentation does not differ significantly to that from Japan. MMD should in particular be considered in the work up for stroke in children as well as middle-aged adults as treatment differs significantly compared to stroke of other origin.

Introduction

Moyamoya disease (MMD) is an idiopathic cerebrovascular disease characterised by progressive stenosis and occlusion of the distal intracranial internal carotid arteries and its proximal branches[1]. As the disease progresses small collaterals so-called moyamoya vessels develop at the base of the brain. Affected patients carry an increased risk of stroke: Ischaemic lesions are a result of the narrowed vessels whereas rupture of fragile collaterals may cause haemorrhage. No known causal treatment exists. Current management aims to reduce the risk of stroke and unlike stroke of other origin surgical revascularisation may play a crucial role in preventing future stroke. MMD was first reported in Japan[2] where it remains a well-known cause of stroke in children as well as adults with a reported overall incidence of 0.94 per 100 000 person-years[3]. The disease occurs less frequently in other parts of the world: Population based data are available from the U.S[4], however the epidemiology of MMD in Europe is not well described due to a paucity of population based data[5]. Being a rare disease in Europe, affected patients are at risk of going undiagnosed thus delaying appropriate treatment. Also, observations from Japan are not necessarily directly applicable to a European practice as MMD may have distinct clinical features in a European population[6]. For example, a surgical series from Germany indicated that a haemorhagic presentation was considerably less common than in Japan[7].

Using nation wide registers the present study aims to shed light on this rare disease and describe its epidemiology and clinical features in Denmark. In our preliminary paper[8] we reported an overall incidence of 0.047 per 100 000 person-years between 1994 and 2015 with an upward trend. However, it was exclusively based on anonymous register data, which neither allowed us to validate the register diagnosis nor provided us with useful information on the clinical presentation of the disease. For the present paper we applied for permission to access individual patient charts and radiology reports to address these shortcomings. The study period was also extended to cover the period from 1994 to 2017. To our knowledge this is the first population based study of MMD in Europe.

Methods

We identified cases from two sources: The Danish National Patient Register and cases not yet listed in the register from a referral centre were also included (figure 1). First, patients with a diagnosis of MMD (I67.5) between 1994 and 2017 were identified in the Danish National Patient Register. Discharge diagnoses and date of discharges from all Danish hospitals have been recorded in the register since 1977 and from 1994 information on visits to outpatient clinics has been included as well[9].

Different referral and treatment pathways for moyamoya disease have existed during the study period. Whereas there is no specific reference to moyamoya disease in the current guidelines, the Danish Health Authority recommends that patients with cerebral hypoperfusion are referred to Aarhus University Hospital or Rigshospitalet in Copenhagen for further workup. Patients are generally managed medically in collaboration with local neurological or paediatric departments. If surgical revascularisation is contemplated the procedure is usually carried out at an international center. In the past bypass surgery for moyamoya disease was regularly carried out at Aalborg University Hospital. However, regardless of the referral and treatment pathway all patients with a diagnosis of moyamoya disease are picked up as the Danish National Patient Register covers all hospital contacts in Denmark.

1994 was chosen as the diagnosis first appeared in the Danish disease classification, when *the International Classification of Diseases version 10* (ICD-10) was introduced that year[9]. Furthermore, patients are registered with their unique person identification number, which allowed us to extract information on all admissions and outpatient visits to Danish hospitals for this patient population. Among all hospital contacts we identified the neurological, neurosurgical and/or paediatric department in which the diagnosis of moyamoya disease was first made. Whenever a

patient had been under the care of a referral center for further workup we selected the referral center for record review as only referral centers (i.e. university hospital) have a neuroradiological service with access to catheter angiography. We also assumed that any further clinical events would be evaluated at the referral center. From the Civil Registration System we extracted basic demographic data (including sex, date and place of birth) as well as information on whether a person is native, immigrant or descendant and in the latter cases country of origin. Adopted children are recorded under their adoptive parents. Of note, the register does not contain data on race and ethnicity. Second, records from additional patients from one referral center, who have had work-up for MMD, but not yet registered with the diagnosis I67.5 in the Danish National Patient Register were also reviewed. One author (VT) visited key hospital departments and reviewed all clinical notes, clinic letters and radiology reports. Data were collected on data sheets using the EpiData Entry Software (www.epidata.dk). Items included date of angiography as well as changes in vessel caliber for individual artery segments in both the anterior and posterior cerebral circulation as well as presence of moyamoya collaterals if any. Next, the mode of presentation of MMD was established. We also looked at if patients had revascularisation surgery done. Subsequent strokes, if any, were also recorded. Based on the clinical notes patients were assigned a modified Rankin score (mRS) at the time of the last clinic visit. Two authors (PB, consultant neurosurgeon with a subspecialty interest in vascular neurosurgery and PvW-M, consultant neurologist with a subspecialty interest in vascular neurology) independently reviewed the data sheets. We used the definition of MMD as stated by the Research Committee on Spontaneous Occlusion of the circle of Willis (Moyamoya Disease) in Japan[10]. In accordance with this definition patients were classified as having definite MMD (MMD) probable MMD (pMMD), i.e. unilateral vascular changes or moyamoya syndrome (MMS, i.e. the characteristic vascular pathology in association with an underlying condition). In accordance with clinical practice we also included patients with bilateral stenoses without moyamoya vessels (i.e. Suzuki grade I) reflecting that moyamoya disease likely is a continuum. Those cases were classified as pMMD. In children, we also classified bilateral stenoses with unilateral moyamoya vessels as MMD. When feasible we reviewed the radiographic films before making a definite diagnosis. If the

register diagnosis could not be confirmed patients were excluded from further analysis. Disagreement was resolved in a consensus meeting. A case was defined as incident at the date of the first angiography suggestive of moyamoya disease. For the calculation of incidence, person-years were approximated by the number of persons at 1 January at any given calendar year. These data are accessible on Statistics Denmark (www.statistikbanken.dk). The prevalence at 1 Jan 2018 was also calculated. We did a pooled analysis of pMMD and MMD.

Analyses were performed using Epidata Analysis software (www.epidata.dk) and the OpenEpi software (www.openepi.com). For statistics, we used the Fisher exact test and χ^2 - test. The study was approved by the Danish Data Protection Agency and The Danish Patient Safely Authority.

Results

Case validation

80 eligible patients were identified (76 in The Danish National Patient Register and 4 from a referral center). Register data from 2121 admissions or outpatient visits (including 340 contacts with a primary or secondary diagnosis of moyamoya disease) to Danish hospitals were reviewed. Subsequently, 13 clinical departments in 6 different hospitals were visited. Two patients were excluded as the patient records could not be retrieved. Thus, charts and radiology reports from 78 patients were available for review. In 10 cases a diagnosis of moyamoya disease could not be confirmed. Two were known with an ACTA2 gene mutation[11], two cases were investigated due to affected first degree relatives, but the diagnosis was eventually ruled out; one case presented with TIA and had unilateral stenosis that did not meet the diagnostic criteria, one case with Fanconi anaemia had an isolated stenosis of the left middle cerebral artery; the remaining cases were probably coding errors as there were no clinical features whatsoever suggestive of moyamoya disease). Further 16 patients had findings consistent with MMS with neurofibromatosis as the most common associated conditions followed by Down's syndrome, atherosclerosis, multiple sclerosis, Grange syndrome and Noonan syndrome. The remaining 52

patients fulfilled the diagnostic criteria: 27 patients and 25 patients were classified as having MMD and pMMD respectively (see figure 1).

Angiographic features

Of the 52 patients with confirmed moyamoya disease 36 patients had catheter angiography either at diagnosis or at followup. In the remaining patients the diagnosis was based on magnetic resonance angiography or computed tomography angiography (1 case). 13 cases (25%) had unilateral stenosis and moyamoya vessels, 7 cases (13%) had bilateral stenoses without moyamoya vessels, 8 cases (15%) bilateral stenoses and unilateral moyamoya vessels, while the remaining 24 patients (46%) had bilateral stenoses and bilateral moyamoya vessels. In 11 cases posterior involvement was reported. 3 patients had associated intracranial aneurysms.

Demographic characteristics

There were 34 females and 18 males (see figure 2). Record review revealed that four of the patients were diagnosed with moyamoya disease before the study period. These patients were excluded from the calculation of incidence, but were included in the other analyses. 40 patients were native Danes, while 12 patients originated from other countries. Six of those were descendants from Korea or registered as born in Korea to native Danish parents, i.e. likely adopted from Korea. One additional patient also originated from East Asia. The age at diagnosis showed a bimodal distribution with a peak in childhood and another in the age group 30 - 40 years (see figure 2). 18 patients (35%) were younger than 18 years at diagnosis.

Incidence and prevalence

50% of the cases were diagnosed after 2010. Until 2008, 0 - 3 cases were diagnosed annually and from 2009 this number rose to 2 - 6 cases (see figure 3), where it remains stable. Correspondingly, the incidence rate was 0.02 per 100 000 person years (95% confidence interval

0.01 - 0.03 per 100 000 person years) and 0.07 per 100 000 person years (95% confidence interval 0.05 - 0.09 per 100 000 person years) for the two time periods respectively. The difference between the two incidence rates was statistically significant ($p<0.01$). Five cases had died as of 31 December 2017. Thus, the prevalence at 1 Jan 2018 was 0.8 per 100 000.

Clinical presentation

The most common mode of presentation was ischaemic stroke (33%) followed by haemorrhage (23%), headache (17%) and transitory ischaemic attack, TIA (14%). Only one patient was asymptomatic at diagnosis. There was no significant difference in the mode of presentation between males and females. In patients younger than 18 years more than half had TIA (11%) or ischaemic stroke (39%) at presentation, while 11% had haemorrhage. Among patients 18 years or older, 29% and 15% presented with ischaemic stroke and TIA respectively, while 29% presented with haemorrhage (see figure 4). However, the difference in clinical presentation between the two age groups was not statistically significant.

Clinical course and outcome

Patients were followed up for a median of 1026 days (range, 1 to 10609) at a referral center. Eight patients (seven adults and one child) experienced stroke during followup. Six patients of those had bilateral stenoses and moyamoya vessels, one patient had unilateral stenosis with moyamoya vessels and one patient had bilateral stenoses without moyamoya vessels. A total of 37 patients had revascularisation surgery performed. Four of those experienced a new stroke after surgery. All but one patient could be assigned a mRS at last followup visit: 42 patients (82%) had a mRS<3. Of the five deaths we retrieved two death certificates. In one case cardiac arrest was listed as the immediate cause of death, whereas the underlying cause of death was attributed to moyamoya disease. In the other case the cause of death was cerebral haemorrhage. From The Danish National Patient Register we learned that the remaining three patients were hospitalised

shortly before their deaths. One with a diagnosis of cerebral haemorrhage, the other two with unrelated diagnoses.

Discussion

We identified and validated a national cohort of 52 patients, who received a diagnosis with pMMD or MMD from 1994 to 2017. During the study period we observed a significant increase in incidence to 0.07 per 100 000 person years from 2009 with peaks in two age groups: childhood and middle age. There were almost twice as many female compared to male patients and 13% of patients had an East Asian background. Overall, the most common mode of presentation was ischaemic stroke followed by haemorrhage. During a median of 2.8 y follow up after diagnosis 15% of patients had a(nother) stroke. At last visit 82% had a good outcome (mRS<3). Of five deaths, 3 could be attributed to moyamoya disease.

Due to comprehensive nation wide registers we were able to show that immigration from East Asia only has a minor impact on the incidence and prevalence of moyamoya disease in Denmark. Then, the increase in incidence most likely reflects an increased detection rate due to improved imaging rather than a real increase. Accessibility to and quality of MR imaging has also improved tremendously during the study period. Thus, the incidence of 0.07 per 100 000 person years is our best estimate of the true incidence. Compared to other population based studies the incidence in Denmark was less than one-tenth of an incidence of 0.94 per 100 000 person years in Japan[3], but comparable to an incidence of 0.086 per 100 000 person years reported in Washington State and California (U.S.A.)[4]. Like in Japan we found a bimodal age distribution and a higher proportion of patients with haemorrhagic presentation among adults. Thus, our data does not suggest that MMD has different clinical presentation features in Denmark compared to Japan.

Previous studies in Europe have mostly been hospital based surgical series[7, 12]. Such studies may be subjected to a selection bias. For example, observed variations in proportion of paediatric

patients may reflect different referral patterns rather than true differences. Likewise, a reported lower proportion of cases with a haemorrhagic presentation[7] may simply reflect that some of those patients have been in a poor clinical state precluding them from referral to a large tertiary centre. Finally, observed differences should not be overinterpreted: the patient sample sizes in most studies are small and the differences may be simply be due to chance.

During short term follow up stroke occurred in only 15% of cases overall and only in one of 18 paediatric cases (6%) and almost exclusively in patients with severe disease. This stroke rate is much lower than observed in a UK paediatric cohort[13]. A longer and more comprehensive follow up is needed to analyse risk factors for subsequent stroke and/or poor outcome. In the UK paediatric cohort presentation with ischaemic stroke and posterior circulation involvement were risk factors for a poor outcome[13]. The low stroke rate observed in our study may also reflect that some of the cases in our cohort had less severe disease. Our study was not designed to evaluate the effect of medical and surgical treatment.

This work is the first population based study on MMD in Europe. Including the use of comprehensive nation wide registers as well as validation of the diagnosis and time of onset by reviewing individual patient charts the incidence estimate given here is more precise than in our previous paper and should by all means include virtually all patients in Denmark diagnosed with moyamoya disease.

There are still a couple of limitations. First, we primarily based the classification on radiology reports, i.e. the radiologists interpretation of the images rather than the images themselves. Of note, radiological films are only kept for a maximum of ten years and thus this study could not have been conducted if the diagnosis should have rested on review of the original films. This may introduce an uncertainty onto the diagnosis. However, we reviewed the original films whenever feasible. Second, the sub classification into the entities pMMD, MMD and MMS will always to a certain degree be investigator dependent. In order to get a precise estimation two authors independently assessed each case before a decision was made. Third, some patients may still go undetected (false negatives). This includes asymptomatic cases of which we saw only one. In Japan, asymptomatic cases comprised 17.8% of patients[3]. Screening of individuals with

increased risk (e.g. in neurofibromatosis) may help to identify asymptomatic cases. Fourth, further studies are needed to establish the clinical course and outcome of the disease. The follow up time was limited (most cases were diagnosed in recent years) and we may have missed cases of recurrent stroke, i.e. not all cases of further clinical events may have been evaluated in a referral center. A more comprehensive review of all case notes of all patients including all local hospitals as well as interviewing individual patients may have revealed more events and given a more accurate estimate of outcome, however the study was neither funded nor designed for that purpose.

In conclusion, this study confirms that moyamoya disease is much less frequent in Denmark than in Japan. No difference in the clinical features could be detected. Despite its rarity among Caucasians moyamoya disease should be considered in the work up for stroke in children as well as middle-aged adults as treatment differs significantly compared to stroke of other origin.

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Bibliografi

1. Scott, R.M. and E.R. Smith, Moyamoya disease and moyamoya syndrome. N Engl J Med, 2009. **360**(12): p. 1226-37.
2. Suzuki, J. and A. Takaku, Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol, 1969. **20**(3): p. 288-99.
3. Baba, T., K. Houkin, and S. Kuroda, Novel epidemiological features of moyamoya disease. J Neurol Neurosurg Psychiatry, 2008. **79**(8): p. 900-4.
4. Uchino, K., et al., Moyamoya disease in Washington State and California. Neurology, 2005. **65**(6): p. 956-8.
5. Kleinloog, R., et al., Regional differences in incidence and patient characteristics of moyamoya disease: a systematic review. J Neurol Neurosurg Psychiatry, 2012. **83**(5): p. 531-6.
6. Hever, P., A. Alamri, and C. Tolias, Moyamoya angiopathy - Is there a Western phenotype? Br J Neurosurg, 2015. **29**(6): p. 765-71.
7. Acker, G., et al., Distinct clinical and radiographic characteristics of moyamoya disease amongst European Caucasians. Eur J Neurol, 2015. **22**(6): p. 1012-7.
8. Birkeland, P. and J. Lauritsen, Incidence of Moyamoya Disease in Denmark: A Population-Based Register Study. Acta Neurochir Suppl, 2018. **129**: p. 91-93.
9. Schmidt, M., et al., The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol, 2015. **7**: p. 449-90.
10. Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). Neurol Med Chir (Tokyo), 2012. **52**(5): p. 245-66.
11. Munot, P., et al., A novel distinctive cerebrovascular phenotype is associated with heterozygous Arg179 ACTA2 mutations. Brain, 2012. **135**(Pt 8): p. 2506-14.
12. Saarela, M., et al., Moyamoya vasculopathy - Patient demographics and characteristics in the Finnish population. Int J Stroke, 2017. **12**(1): p. 90-95.
13. Tho-Calvi, S.C., et al., Clinical features, course, and outcomes of a UK cohort of pediatric moyamoya. Neurology, 2018. **90**(9): p. e763-e770.