Characteristics of Moyamoya Disease Based on National Registry Data in Japan

Yoko Sato, DDS, PhD; Ken Kazumata, MD, PhD; Eiji Nakatani, PhD; Kiyohiro Houkin, MD, PhD; Yasuhiro Kanatani, MD, PhD

Background and Purpose—A public registration system for intractable diseases was started in Japan in 1972 to investigate the etiology and pathogenesis of intractable diseases while reducing out-of-pocket medical expenses on patients. The goal of this study was to investigate the epidemiology and clinical characteristics of Moyamoya disease using data from applications submitted to this system between 2004 and 2008.

Methods—In addition to demographic factors such as onset age and family history, we evaluated clinical presentation type, imaging findings, clinical symptoms, and functioning in activities of daily living (ADL).

Results—Of 3859 cases for which applications were submitted, 2545 were confirmed to meet the diagnostic criteria after data cleansing. Onset age showed a bimodal distribution, and Moyamoya disease had a higher incidence in women than in men. The presence of occlusion and infarction in the proximal region of the anterior cerebral artery was more frequent in pediatric cases than adult cases. Our findings also indicated that 23% of patients required assistance with ADL. Cerebral infarction (odds ratio [OR], 12.5; 95% CI, 3.55–44.66), seizure (OR, 7.44; 95% CI, 1.29–42.96), and sensory disorders (OR, 5.23; 95% CI, 1.15–23.75) were identified as significant predictors of impaired ADL in pediatric cases 3 years after the initial application. Moderate ADL function (OR, 11.59; 95% CI, 5.29–25.39) and intellectual disabilities (OR, 4.38; 95% CI, 1.58–12.17) at the time of the application were identified as significant prognostic factors in adults.

Conclusions—The results of this study indicated that characteristics of Moyamoya disease such as onset type, symptoms, and imaging abnormalities differ with onset age. Prognostic analyses suggested that pediatric cases with good ADL but with infarct type onset, seizure, or sensory disorders might have a subsequent decline in ADL. **(*Stroke*. 2019;50:1973-1980. DOI: 10.1161/STROKEAHA.119.024689.)**

Key Words: adults ■ Moyamoya disease ■ pediatrics ■ prognosis

Moyamoya disease (MMD) is a cerebrovascular disease of unknown pathogenesis that causes stenosis and occlusion of the internal carotid artery, which results in the development of compensatory collateral circulation paths called moyamoya blood vessels. There are various patterns of disease onset, ranging from asymptomatic to cerebral ischemic attack. Most studies of MMD have focused on the prognosis after surgery, cerebral circulatory insufficiency in surgically treated cases, or surgical complications,[1–3] and have been performed as multicenter collaborative studies in hospitals specializing in diagnosis and treatment of MMD or other cerebrovascular diseases.[4] These studies use appropriate approaches, but clinical features, epidemiological data, and quality of life (QOL) at these hospitals may not reflect the overall characteristics of MMD. An analysis of data from a national survey database for MMD may be more effective in this respect.

In this study, we examined data from a large number of cases of mild-to-severe MMD. These data were derived from a database of applications for medical subsidies submitted to the government of Japan.[5] This nationwide database may provide more accurate data for QOL in cases of MMD. We used the database to examine the characteristics of MMD, including functioning during activities of daily living (ADL)—an indicator of QOL; incidence by sex and onset age; comparison of background factors by onset age, including relationships of onset age with clinical presentation type, imaging findings, clinical symptoms, and ADL function; associations between clinical symptoms and imaging findings; and prognostic factors.

Methods

Data supporting the findings of this study are available from the corresponding author on reasonable request.

Received January 29, 2019; final revision received April 24, 2019; accepted May 14, 2019.

From the Division of Biomedical Engineering, National Defense Medical Research Institute, National Defense Medical College, Saitama, Japan (Y.S.); Department of Neurosurgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan (K.K., K.H.); Division of Medical Statistics, Translational Research Center for Medical Innovation, Foundation for Biomedical Research and Innovation at Kobe, Hyogo, Japan (E.N.); Division of Statistical Analysis, Research Support Center, Shizuoka General Hospital, Japan (E.N.); and Department of Clinical Pharmacology, Tokai University School of Medicine, Japan (Y.K.).

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.119.024689.

Correspondence to Yasuhiro Kanatani, MD, PhD, Department of Clinical Pharmacology, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259–1193, Japan. Email kanatani.yasuhiro.f@tokai.ac.jp

Ethics

This study fulfills the ethical guidelines for epidemiological research of the Ministry of Health, Labour and Welfare (MHLW) and the Ministry of Education, Culture, Sports, Science, and Technology of Japan. Patients diagnosed with MMD could participate in the specified disease treatment research program, which began in Japan in 1972 as a national registry that aimed to investigate the etiology and pathology of several intractable diseases and reduce the burden of medical expenses on patients. Patients submitted a consent form for registration of data and utilization of these data in research, in addition to an application form including their medical information when applying for medical expenses subsidies. Patients who received certification needed to reapply and updated their information annually. Consent for minors was provided by their guardian. After approval of a review committee, including neurologists and the respective prefectural governors, personal information for each patient was anonymized and registered in the MHLW database. The anonymized data were made available to us for analysis (Notification of Health Service Bureau, MHLW; No. 0708-1; July 8, 2010). The Ethics Committee of the National Institute of Public Health approved the study (No. 218; June 10, 2010).

Data and Diagnosis

Data were analyzed from application forms submitted to and digitized by the MHLW between 2004 and 2008. Duplicate cases and those without essential demographic data, such as onset age, were excluded. Cases included in data analysis fulfilled the diagnostic criteria for MMD established by the Research Committee on MMD of the MHLW.[6]

Variables

The following demographic and clinical factors were obtained from application forms submitted by patients with MMD: sex, date of birth, onset age, date of first clinical visit, family history, clinical presentation, imaging findings, clinical symptoms, ADL function, and treatment (Table I in the online-only Data Supplement).

Onset age was evaluated based on 2 classification schemes: in the first analysis, cases were divided into 5-year age groups; and in the second analysis, cases were categorized into pediatric (<20 years of age) and adult (≥20 years of age) groups. Cases were also categorized into 2 groups based on the time from date of onset to the first clinical visit (<6 and ≥6 months). Family history was analyzed based on the presence (yes) or absence (no or unknown) of MMD.

Clinical presentation was categorized into hemorrhagic, epileptic, infarction, transient ischemic attack (TIA), asymptomatic, and other types. Cases that fell into >1 category were reclassified into 1 category using the following types listed from higher to lower priority: hemorrhagic, epileptic, infarction, TIA, and asymptomatic. An exception was made for cases involving hemorrhage and infarction, which were classified as hemorrhagic infarct type. The following 11 clinical symptoms were rated as absent, mild, or severe: motor disorders, disturbance of consciousness, headache, seizure, psychological symptoms, speech disorder, sensory disorder, involuntary movements, intellectual disability, visual disturbance, and visual field disturbance. Clinical symptoms were analyzed based on the presence (mild or severe) or absence.

The presence of stenosis/occlusion was evaluated in 6 locations (left and right sides of 3 areas) using cerebral angiography and brain magnetic resonance angiography images: internal carotid artery terminal, proximal region of the anterior cerebral artery, and proximal region of the middle cerebral artery (MCA). Imaging abnormalities were analyzed based on the presence or absence of vascular stenosis and occlusion in the left and right internal carotid artery, anterior cerebral artery, and MCA.

The level of functioning during ADL was defined as follows: no disability/no assistance required, good; disability/no assistance required, moderate; assistance required, poor. Treatment approaches during the previous year were classified as no treatment, oral treatment only, surgical treatment only, or both oral and surgical treatment.

Statistical Analysis

Age distributions were drawn by Kernel density estimation. Comparison of continuous variables between groups was performed by Wilcoxon rank-sum test. χ^2 tests were used to compare categorical variables. When significant bias was observed in the χ^2 test ($P<0.05$), residual analysis was performed to determine which cell numbers in the cross-table were numerous or few ($P<0.05$). A Poisson regression model was used to identify factors associated with disease incidence; the offset, however, was not used, as we could not observe the denominator for incidence. The relative risk, 95% CI, and P values were calculated using a Wald test, and the global P for each variable was calculated using the likelihood ratio test. Univariate and multivariate logistic regression analyses were performed to evaluate associations between factors of interest. The odds ratio (OR), 95% CI, and P values were calculated by Wald test. Adjustment was performed for sex, onset age (pediatric or adult), time from onset to first clinical visit, family history, and ADL function.

Prognostic factors predicting cases that would require assistance with ADL after 3 years (poor outcome) were investigated. The candidate prognostic variables were sex, onset age (pediatric or adult), time from onset to first clinical visit, family history, clinical presentation type, imaging abnormalities, clinical symptoms, ADL function at initial application, and treatment approaches over the previous 3 years. Multivariate logistic regression analysis of prognostic factors was performed for each age of onset by selecting variables with $P<0.05$ in univariate analysis. Variable selection was performed using the backward method with $P<0.05$. All analyses were performed using R, version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Data Availability

All relevant data are contained in the article and the online-only Data Supplement.

Results

Patient Characteristics

Of the 3859 first-time applications submitted between 2004 and 2008, 2545 cases were confirmed to meet the diagnostic criteria after data cleansing. The ratio of men to women was 1:1.9 (Table 1). The median onset age was 35.0 years (interquartile range, 15.0–49.0). Pediatric and adult cases accounted for 28.8% and 71.2%, respectively. A family history of MMD was present in 11.1% of cases. The time from onset to first clinical visit was <6 months in 70.1% of cases. Clinical presentation was most commonly categorized as infarction (29.4%), followed by TIA (29.1%) and hemorrhagic (25.3%). ADL function was good in 49.6% of cases, moderate in 27.4%, and poor in 23.0%.

Comparison of Annual Incidences

The numbers of new applications received annually from 2004 to 2008 were 464, 588, 477, 474, and 542, respectively. The incidence of pediatric MMD increased from 2004 to 2005 ($P=0.043$; Table II in the online-only Data Supplement). Increases in adult MMD cases occurred from 2004 to 2005 ($P=0.001$) and 2004 to 2008 ($P=0.015$).

Variation of Onset Age and Sex in Each Clinical Presentation Type

The distributions of onset age in men and women were bimodal (Figure 1A). Compared with the MMD incidence in

Table 1. Characteristics of Moyamoya Disease According to Onset Age

Variable	Category	Overall	Pediatric	Adult	*P* Value
		2545	733 (28.8)	1812 (71.2)	
Women/men, n (%)	…	1.9	1.71	1.98	0.133
Family history, n (%)	…	282 (11.1)	102 (13.9)	180 (9.9)	0.005
Time from onset to first clinical visit, n (%)	<6 mo	1785 (70.1)	334 (45.6)	1451 (80.1)	<0.001
Clinical presentation, n (%)					
Hemorrhagic type		644 (25.3)	56 (7.64)*	588 (32.45)†	<0.001
Infarction type		748 (29.4)	195 (26.6)	553 (30.5)	
Hemorrhagic infarct type		37 (1.5)	4 (0.55)*	33 (1.82)†	
Epileptic type		63 (2.5)	39 (5.32)†	24 (1.32)*	
Transient ischemic attack type		740 (29.1)	382 (52.11)†	358 (19.76)*	
Asymptomatic type		195 (7.7)	19 (2.59)*	176 (9.71)†	
Other/unknown		118 (4.6)	38 (5.2)	80 (4.4)	
Abnormal imaging findings, n (%)					
Left					
Internal carotid artery terminal	Yes	2227 (87.5)	649 (88.5)	1578 (87.1)	0.348
Anterior cerebral artery proximal part	Yes	2120 (83.3)	636 (86.8)	1484 (81.9)	0.003
MCA proximal part	Yes	2187 (85.9)	636 (86.8)	1551 (85.6)	0.480
Right					
Internal carotid artery terminal	Yes	2264 (89.0)	664 (90.6)	1600 (88.3)	0.110
Anterior cerebral artery proximal part	Yes	2145 (84.3)	642 (87.6)	1503 (83.0)	0.004
MCA proximal part	Yes	2232 (87.7)	651 (88.8)	1581 (87.3)	0.308
Clinical symptoms, n (%)					
Motor disorders	Yes	949 (38.1)	236 (32.8)	713 (40.2)	<0.001
Disturbance of consciousness	Yes	403 (16.2)	38 (5.3)	365 (20.6)	<0.001
Headache	Yes	870 (35.6)	287 (40.0)	583 (33.7)	0.004
Seizure	Yes	136 (5.5)	63 (8.8)	73 (4.1)	<0.001
Psychological symptoms	Yes	295 (12.0)	38 (5.3)	257 (14.8)	<0.001
Speech disorder	Yes	575 (23.3)	91 (12.7)	484 (27.7)	<0.001
Sensory disorder	Yes	623 (25.6)	108 (15.2)	515 (29.9)	<0.001
Involuntary movements	Yes	85 (3.4)	28 (3.9)	57 (3.3)	0.485
Intellectual disability	Yes	360 (14.9)	65 (9.2)	295 (17.3)	<0.001
Visual disturbance	Yes	115 (4.8)	23 (3.3)	92 (5.5)	0.030
Visual field disturbance	Yes	250 (10.5)	49 (6.9)	201 (12.0)	<0.001
ADL, n (%)	Good	1255 (49.6)	465 (63.61)†	790 (43.86)*	<0.001
	Moderate	695 (27.5)	204 (27.9)	491 (27.3)	
	Poor	582 (23.0)	62 (8.48)*	520 (28.87)†	

ADL indicates activities of daily living; and MCA, middle cerebral artery.
*Significantly smaller ($P<0.05$) in residual analysis.
†Significantly larger ($P<0.05$) in residual analysis.

pediatric boys, the incidences in pediatric girls, adult men, and adult women were 1.71 (95% CI, 1.48–1.99), 2.26 (95% CI, 1.95–2.60), and 4.46 (95% CI, 3.90–5.08) times higher, respectively (Table 2). The incidence in women was 2.60 (95% CI, 2.33–2.89) times higher than that in girls. There was no apparent difference of onset age between women and men ($P=0.133$). Distributions of onset age in men and women according to clinical presentation types are shown Figures 1B, 1D, and 2A through 2D. Clear bimodal peaks were found for pediatric and adult cases of infarction-type MMD (Figure 1C), while a single peak was present for pediatric girls with the epileptic type (Figure 2A).

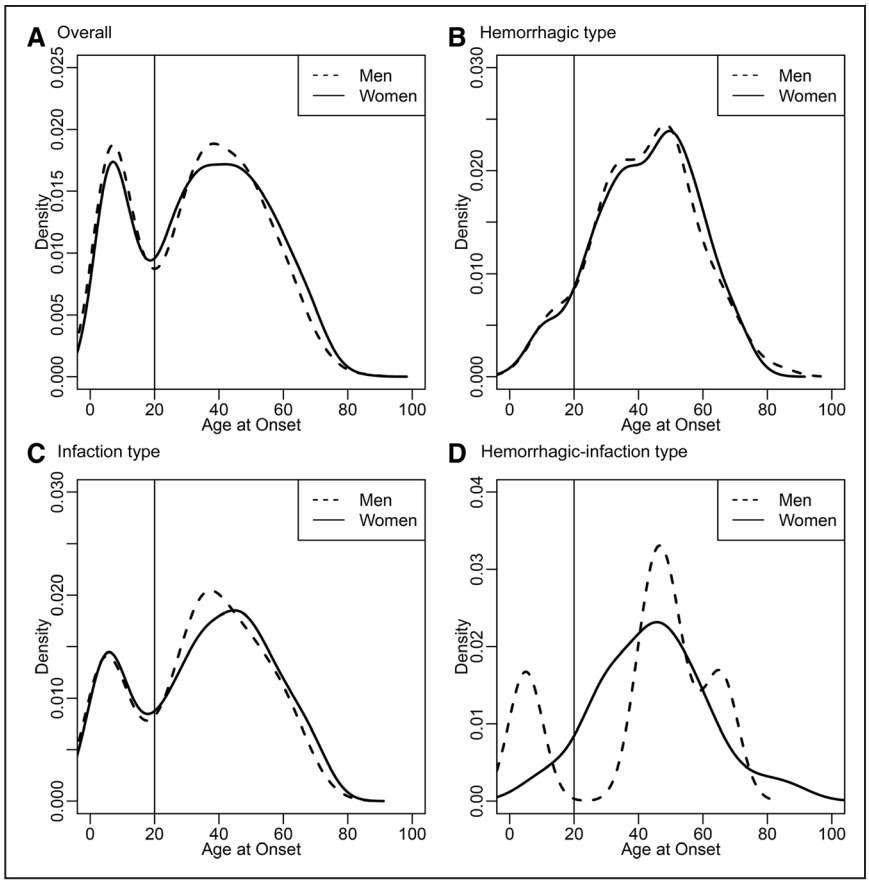

Figure 1. Distribution of onset age in patients with Moyamoya disease according to sex. The bimodalities of age distributions for all cases (**A**) and hemorrhagic (**B**), infarction (**C**), and hemorrhagic infarction (**D**) types were obtained by Kernel density estimation.

Differences in incidence according to sex between onset age categories (adult and pediatric) and between each clinical presentation type are shown in the left side of Table III in the online-only Data Supplement. Most subgroups had a higher incidence in women than men (relative risk >1.00), regardless of onset age, particularly for the hemorrhagic (pediatric, P=0.004; adults, P<0.001), infarction (pediatric, P<0.001; adults, P<0.001), and TIA (pediatric, P<0.001; adults, P<0.001) types.

Background Characteristics in Pediatric and Adult Cases

The male:female ratios in pediatric and adult cases were 1:1.71 and 1:1.98, respectively (Table IV in the online-only Data Supplement. More cases had a family history of relevant diseases in pediatric cases (P=0.005), and a relevant family history was more frequent in girls than in boys (15.98% versus 10.37%; P=0.045; Table IV in the online-only Data Supplement). The number of cases in which the time from onset to first clinical visit was <6 months was higher in adults than in pediatric cases (P<0.001; Table 1).

Associations Between Onset Age and Clinical Presentation Type

Epileptic and TIA types were more frequent in pediatric cases, while hemorrhagic, hemorrhagic infarct, and asymptomatic types were more frequent in adults (all P<0.001; Table 1). Adjusted analyses had the same trends, except for the hemorrhagic infarct type (Table V in the online-only Data Supplement). The right side of Table III in the online-only Data Supplement shows differences in incidence according to onset age between the sexes and each clinical presentation type. While there were more adult cases for almost all clinical types, the numbers of girls and boys presenting with the epileptic type and the TIA type were higher than adults of the same sex in those categories (relative risk, 0.44 [P=0.057] and 0.79 [P<0.001]).

Abnormal Imaging, Clinical Symptoms, and ADL in Pediatric and Adult Cases

The rates of imaging abnormalities in the right and left anterior cerebral artery were less frequent in adults than pediatric

Table 2. Univariate Poisson Regression Analysis of the Incidence of Moyamoya Disease

Category		n	Relative Risk	95% CI	*P* Value	Relative Risk	95% CI	*P* Value
Pediatric	Boys	270	1.00					
	Girls	463	1.71	1.48–1.99	<0.001	1.00		
Adult	Men	609	2.26	1.95–2.60	<0.001			
	Women	1203	4.46	3.90–5.08	<0.001	2.60	2.33–2.89	<0.001

cases (left, P=0.003; right, P=0.004; Table 1). Adjusted analyses had the same trends (Table VI in the online-only Data Supplement).

Motor disorders, disturbances of consciousness, seizure, psychological symptoms, speech disorders, sensory disorders, intellectual disability, visual disturbance, and visual field disturbance were more common in adults (all $P \leq 0.030$; Table 1), whereas headache was significantly more common in pediatric cases (P=0.004). In adjusted analyses, sensory disorders were more common in adults (OR, 1.69; 95% CI, 1.23–2.30; Table VII in the online-only Data Supplement), whereas motor disorders (OR, 0.46; 95% CI, 0.33–0.63), headache (OR, 0.55; 95% CI, 0.44–0.70), seizure (OR, 0.31; 95% CI, 0.19–0.51), and involuntary movements (OR, 0.52; 95% CI, 0.27–0.99) were more common in pediatric cases. Headache was more frequent in women in pediatric (P=0.018) and adult (P<0.001) cases (Table IV in the online-only Data Supplement).

Good ADL function was more frequent in pediatric cases, whereas poor ADL function was more common in adults (P<0.001; Table 1). Adjusted analyses had the same trends (Table VIII in the online-only Data Supplement).

Association Between Clinical Symptoms and Abnormal Imaging Findings

An association was found between disturbance of consciousness and imaging abnormalities in the left MCA (OR, 0.54; 95% CI, 0.33–0.89; P=0.016) and right MCA (OR, 0.55; 95% CI, 0.33–0.94; P=0.029; Table IX in the online-only Data Supplement). There were also associations of headache with imaging abnormalities in the right anterior cerebral artery (OR, 1.64; 95% CI, 1.02–2.64; P=0.041), speech disorders with imaging abnormalities in the left internal carotid artery (OR, 1.80; 95% CI, 1.15–2.83; P=0.010), and intellectual disability with imaging abnormalities in the left internal carotid artery (OR, 1.85; 95% CI, 1.08–3.17; P=0.026) and right MCA (OR, 0.48; 95% CI, 0.28–0.84; P=0.010).

Prognostic Factors for Poor ADL Function at 3 Years After Application

We obtained data from 308 cases that were updated 3 years after initial applications, in which data for 1052 cases were submitted between 2004 and 2005. Of these cases, 145 (47.0%) had poor ADL function 3 years after the original application. The rate of poor ADL function was significantly higher in adults (51.1%) than in pediatric cases (35.4%; P=0.019). Among the 82 pediatric cases, univariate analysis showed that the level of ADL function at the time of application, infarction type, TIA type, motor disorders, seizure, speech disorders, sensory disorders, and intellectual disability were significant predictors of ADL function 3 years after initial application (Table X in the online-only Data Supplement). Multivariate analysis of these variables identified infarction type (OR, 12.58; 95% CI, 3.55–44.66; P<0.001), seizure (OR, 7.44; 95% CI, 1.29–42.96; P=0.025), and sensory disorders (OR, 5.23; 95% CI, 1.15–23.75; P=0.028) as significant prognostic factors (Table 3). In the 266 adult cases, univariate analysis revealed that level of ADL function at the time

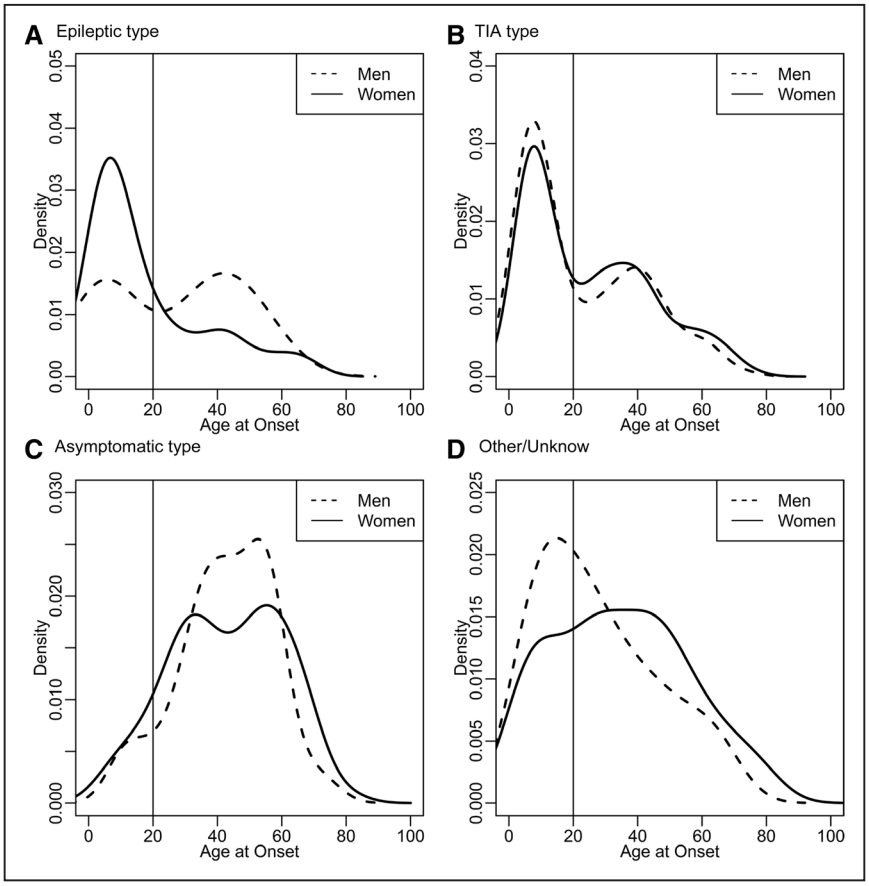

Figure 2. Distribution of onset age in patients with Moyamoya disease according to sex. The bimodalities of the overall age distribution and the age distributions for epileptic (**A**), transient ischemic attack (TIA; **B**), asymptomatic (**C**), and other/unknown (**D**) types were obtained by Kernel density estimation.

Table 3. Multivariate Analysis of Prognostic Factors for Poor Function in ADL in Patients With Moyamoya Disease 3 Years After the Initial Application

Variable		Category (Reference)	Pediatric			Adult		
			Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
ADL in the initial year		Moderate (vs good)				11.59	5.29–25.39	<0.001
		Poor (vs good)				2.20	0.84–5.79	0.109
Clinical type in the initial year	Infarction type	Yes (vs no)	12.58	3.55–44.66	<0.001			
Clinical symptoms in the initial year	Seizure	Present (vs absent)	7.44	1.29–42.96	0.025			
	Sensory disorders	Present (vs absent)	5.23	1.15–23.75	0.028			
	Intellectual disability	Present (vs absent)				4.38	1.58–12.17	0.005

ADL indicates activities of daily living.

of application, infarction type, TIA type, asymptomatic type, movement disorders, speech disorders, sensory disorders, intellectual disability, and visual field disturbance were significant predictors of ADL function 3 years later (Table XI in the online-only Data Supplement). Multivariate analysis identified moderate ADL function at the time of application (OR, 11.60; 95% CI, 5.29–25.39; *P*<0.001) and intellectual disability (OR, 4.38; 95% CI, 1.58–12.17; *P*=0.005) as significant prognostic factors (Table 3).

Discussion

In this study, we investigated associations among patient characteristics, QOL, and clinical variables in a large number of cases with MMD based on data acquired from applications for medical subsidies submitted to the MHLW. This system was originally run by the Specified Disease Treatment Research Program, which began in 1972[7] as a national registry in Japan that aimed to investigate the etiology and pathology of intractable diseases and reduce the burden of medical expenses on patients. The program was extended to include MMD in 1982. Patients with intractable diseases are required to send an application signed by their doctor to their local prefecture. A review committee including neurologists and the respective prefectural governors investigates application forms, decides whether patients are eligible for a subsidy, and sends them claimant certifications. Personal information for each patient is then anonymized and registered in the MHLW database.

Data on the application forms may be useful for epidemiological analysis of intractable diseases at the national level, as well as for examining the pathology of intractable diseases and the efficacy of treatment. We used these data to investigate the epidemiology and characteristics of MMD using application forms submitted to the MHLW. Anonymized and digitized data are available in the database from 2001 to 2014. We used data after 2004 because registration items on application forms were changed in 2004. Additionally, in considering the impact of the Great East Japan Earthquake that occurred at the end of 2010, we decided to use data for the 5 years from 2004 to 2008 as a stable period.

A total of 2545 cases were available for statistical analysis (65.9%), which is the largest series of Japanese cases with MMD analyzed to date. Our findings indicated that the incidence of MMD was higher among women than men and that 23% of cases had poor ADL function. Furthermore, we identified cerebral infarction, seizure, and sensory disorders as significant predictors of poor ADL function in pediatric cases 3 years after the initial application. In adult cases, moderate ADL function at the time of application and intellectual disability were similarly identified as prognostic factors.

An analysis of the change in the number of new registrants between 2004 and 2008 showed an increase in MMD prevalence among adults. This finding may be explained by recent advances in noninvasive imaging methods that enable diagnosis of MMD, even in the absence of symptoms.[2] We found a family history of MMD in 11.8% of cases, which agrees with previous findings of rates of 9.9% in 1989, 10.0% in 1995, and 12.1% in 2003.[8] Some areas of Japan, however, have reported a slightly higher rate of 15.4%.[9] One study in the United States found a family history in only 6% of cases[10]; however, the frequency of the 4810 polymorphism of RNF 213 (p.R4810K) on chromosome 17—a potent genetic factor for MMD—is low among whites compared with its prevalence in East Asian populations.[11] Furthermore, similarly to previous findings, we found an age difference in the frequency of family history,[9] and a sex difference in the pediatric group, with a family history being more frequent in girls than in boys. Results for the association of p.R4810K with sex have been inconsistent,[11,12] and further studies are required to clarify this issue.

Two peaks at 10 and 40 years of age were observed in the age distribution at MMD onset, consistent with previous studies.[6,9] The incidence in adulthood was about twice that in childhood, and this difference in onset age has previously been found to be more pronounced in women.[9,13] These findings suggest that secondary sex characteristics such as pregnancy, childbirth, and dysmenorrhea contribute to onset of MMD. However, we were unable to confirm a predominance in women in the present study; the within-sex incidence difference between pediatric and adult cases was similar for male and female patients.

Identifying the rate of cases with poor QOL is critical for establishing optimal treatment strategies for rare and intractable diseases. However, such information has been lacking for MMD[14] because most studies have involved surgical candidates or postoperative cases treated at tertiary hospitals. QOL at these facilities does not necessarily reflect the overall characteristics of MMD. The nationwide database used in the present study may provide more accurate data for QOL in cases with MMD. Our evaluation of function in ADL as an indicator

of QOL showed that 50.4% of patients were clinically unstable (moderate and poor function in ADL) and required ongoing surveillance and periodic neuroimaging examinations. Furthermore, 23% of cases were unable to live independently because of poor QOL and required advanced care.

We also identified predictors of poor ADL in cases with MMD. In additional analysis, we confirmed that the average number of clinical symptoms increased as ADL function worsened: good, 0.61; moderate, 2.02; poor, 4.48 ($P<0.001$ for comparisons of all pairs by Mann-Whitney U test adjusted by the Bonferroni method). Several predictors, such as hemodynamic compromise and the pattern of carotid artery collaterals, have been found in elaborate neuroimaging studies.[15–18] In contrast, we focused on clinical data that can easily be obtained in daily practice and determined whether items on the application form for medical subsidies were associated with a poor prognosis. At the time of application, significant predictors of poor ADL function in pediatric cases 3 years after the initial application included infarction type, seizure, and sensory disorders. These findings suggest that cases with these features require ongoing rehabilitation treatment, as well as mental health support.[19] Relative to other clinical presentation types, the OR for infarction-type cases was 12.58 (95% CI, 3.55–44.66). Regarding prognosis after surgery, patients with infarcts before surgery are more likely to have poor outcomes,[20] and a study of neurocognitive profiles before and after surgery found more severe symptoms in cases with infarction.[21] While the prognosis is expected to be poor for hemorrhagic cases,[22] only 5% of pediatric cases of the hemorrhagic type in our study had poor ADL function after 3 years. For other clinical types, we divided the ischemic type into infarction and TIA subtypes, instead of comparing only hemorrhagic and ischemic types, as performed in previous studies. TIAs may predict subsequent stroke in individuals with MMD,[23] and surgery in these cases may lead to a good prognosis; however, we found no association between surgery and outcome. Surgery may have effects on patients with MMD,[24] but we were unable to perform an analysis because treatment details were not available in our data.

Among the adult cases, intellectual disability was identified as a significant predictor of poor ADL function 3 years after the initial application. Associations of neurocognitive dysfunction and cerebral blood flow reduction have been identified in previous studies.[25] However, such studies have also suggested that the association of cognitive dysfunction with the ischemic state of the brain microstructure cannot be detected using conventional imaging.[17]

Our findings also showed that unstable ADL function at the time of registration was associated with a loss of independence 3 years later, which indicates that evaluation of ADL function is critical for planning the appropriate course of treatment. Thus, the MHLW application should include a more elaborate rating system for ADL function (eg, the modified Rankin Scale and the Barthel Index).

Given the association between intellectual disability and poor prognosis, objective assessments of neurocognitive function are also required. MMD was originally recognized as a typical disease affecting the anterior circulation, but the posterior circulation may also be involved in disease progression and cognitive deterioration.[26] Thus, a more detailed analysis of prognostic factors is needed in future studies, particularly with regard to abnormal findings in the posterior cerebral artery. Bleeding events have also been identified as a significant prognostic factor,[27] and the details require investigation. Also, as the prognostic analyses in this study were based on ADL function, the results primarily reflect deterioration of motor function. To determine the cause and pathology of MMD and to make it possible to stratify risks that contribute to treatment choice,[28] outcomes such as progression of ischemia and changes in cognitive function should be examined.

There are some limitations in the study. First, it was difficult to evaluate data bias. One of the significant biases is the possibility that physicians declared heavier symptoms in the application form than were actually present because this registration system is also used for medical expenses subsidies. During 2004 to 2008, more than 90% of MMD patients who had applied for this research program were approved and eligible for a subsidy; however, it was difficult to check bias of the registration data because we could not access the 10% of cases had been not approved. We were unable to control data management, and our results may be limited by poor data accuracy and a low digitization rate. Indeed, ≈40% of cases were unavailable for analysis. In addition to the missing data, information was excluded because of a mismatch of items and data duplication, and other patients were excluded from subsequent subsidies because of improvements in their health. Based on the number of medical certificates issued (Table XII in the online-only Data Supplement), the digitization rate was ≈50%. Although patients must submit an application form every year to update the certificate, the digitization rate of updated application forms is much lower. Thus, the proportion of digitized data at the 3-year mark in this study was 12.1%. Nonetheless, the low digitization rate was clear from a clinical perspective. These issues can be resolved by checking for missing data and inconsistencies at the time of input into the electronic system by the attending physician.[7,29] In 2015, the Intractable Disease Health Care Act was implemented to secure a budget for maintaining medical expense subsidies for patients with intractable diseases and to promote research on pathogenesis and development of drugs and medical devices. The number of designated intractable diseases was expanded from 56 to 306 in 2015 and to 330 in 2017. Because of this, more clinical information on intractable diseases will be obtained in the near future. Therefore, it is vital to create a systematic electronic system to solve the above problems.

To conclude, we examined the overall epidemiology and clinical characteristics of MMD in Japan using clinical data obtained from a public registration system between 2004 and 2008. Our findings indicated that 23% of cases exhibited poor ADL function. Cerebral infarction, seizure, and sensory disorders were identified as significant predictors of poor ADL function in pediatric cases 3 years after the initial application. Moderate ADL function at the time of the application and intellectual disability were identified as significant prognostic factors in adults. These results suggest that the registration system for intractable diseases in Japan should be updated to improve patient care and to advance clinical research on the pathogenesis of MMD and on therapeutic strategies.

Acknowledgments

We are grateful to Eiji Nakatani (Osaka University Graduate School of Medicine) for assistance with statistical analysis.

Sources of Funding

The costs for publication were borne by a research grant from the Ministry of Health, Labour and Welfare (MHLW) of Japan (Research on Measures for Intractable Diseases). This study was supported by grants for Health and Labour Sciences Research from the MHLW: Research on Medical ICT and Artificial Intelligence (201803011A), and Research on Measures for Intractable Disease (Moyamoya Disease).

Disclosures

None.

References

1. Fujimura M, Tominaga T. Diagnosis of moyamoya disease: international standard and regional differences. *Neurol Med Chir (Tokyo)*. 2015;55:189–193. doi: 10.2176/nmc.ra.2014-0307
2. Kuroda S; AMORE Study Group. Asymptomatic moyamoya disease: literature review and ongoing AMORE Study. *Neurol Med Chir (Tokyo)*. 2015;55:194–198. doi: 10.2176/nmc.ra.2014-0305
3. Miyamoto S, Yoshimoto T, Hashimoto N, Okada Y, Tsuji I, Tominaga T, et al; JAM Trial Investigators. Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan Adult Moyamoya Trial. *Stroke*. 2014;45:1415–1421. doi: 10.1161/STROKEAHA.113.004386
4. Takagi Y, Miyamoto S; COSMO-Japan Study Group. Cognitive dysfunction survey of the Japanese patients with moyamoya disease (COSMO-JAPAN study): study protocol. *Neurol Med Chir (Tokyo)*. 2015;55:199–203. doi: 10.2176/nmc.ra.2014-0326
5. Hayashi S, Umeda T. 35 years of Japanese policy on rare diseases. *Lancet*. 2008;372:889–890. doi: 10.1016/S0140-6736(08)61393-8
6. Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis; Health Labour Sciences Research Grant for Research on Measures for Intractable Diseases. Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). *Neurol Med Chir (Tokyo)*. 2012;52:245–266.
7. Kanatani Y, Tomita N, Sato Y, Eto A, Omoe H, Mizushima H. National registry of designated intractable diseases in Japan: present status and future prospects. *Neurol Med Chir (Tokyo)*. 2017;57:1–7. doi: 10.2176/nmc.st.2016-0135
8. Kuriyama S, Kusaka Y, Fujimura M, Wakai K, Tamakoshi A, Hashimoto S, et al. Prevalence and clinicoepidemiological features of moyamoya disease in Japan: findings from a nationwide epidemiological survey. *Stroke*. 2008;39:42–47. doi: 10.1161/STROKEAHA.107.490714
9. Baba T, Houkin K, Kuroda S. Novel epidemiological features of moyamoya disease. *J Neurol Neurosurg Psychiatry*. 2008;79:900–904. doi: 10.1136/jnnp.2007.130666
10. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. *N Engl J Med.* 2009;360:1226–1237. doi: 10.1056/NEJMra0804622
11. Moteki Y, Onda H, Kasuya H, Yoneyama T, Okada Y, Hirota K, et al. Systematic validation of RNF213 coding variants in Japanese patients with moyamoya disease. *J Am Heart Assoc*. 2015;4:e001862.
12. Morimoto T, Mineharu Y, Ono K, Nakatochi M, Ichihara S, Kabata R, et al. Significant association of RNF213 p.R4810K, a moyamoya susceptibility variant, with coronary artery disease. *PLoS One*. 2017;12:e0175649. doi: 10.1371/journal.pone.0175649
13. Chen PC, Yang SH, Chien KL, Tsai IJ, Kuo MF. Epidemiology of moyamoya disease in Taiwan: a nationwide population-based study. *Stroke*. 2014;45:1258–1263. doi: 10.1161/STROKEAHA.113.004160
14. Weinberg DG, Rahme RJ, Aoun SG, Batjer HH, Bendok BR. Moyamoya disease: functional and neurocognitive outcomes in the pediatric and adult populations. *Neurosurg Focus*. 2011;30:E21. doi: 10.3171/2011.3.FOCUS1150
15. Tatlı B, Ekici B, Sencer A, Sencer S, Aydın K, Aydınlı N, et al. Clinical features, prothrombotic risk factors, and long-term follow-up of eight pediatric moyamoya patients. *J Clin Neurol*. 2012;8:100–103. doi: 10.3988/jcn.2012.8.2.100
16. So Y, Lee HY, Kim SK, Lee JS, Wang KC, Cho BK, et al. Prediction of the clinical outcome of pediatric moyamoya disease with postoperative basal/acetazolamide stress brain perfusion SPECT after revascularization surgery. *Stroke*. 2005;36:1485–1489. doi: 10.1161/01.STR.0000170709.95185.b1
17. Kazumata K, Tha KK, Narita H, Kusumi I, Shichinohe H, Ito M, et al. Chronic ischemia alters brain microstructural integrity and cognitive performance in adult moyamoya disease. *Stroke*. 2015;46:354–360. doi: 10.1161/STROKEAHA.114.007407
18. Zhao M, Zhang D, Wang S, Zhang Y, Deng X, Zhao J. The collateral circulation in moyamoya disease: a single-center experience in 140 pediatric patients. *Pediatr Neurol*. 2017;77:78–83. doi: 10.1016/j.pediatrneurol.2017.08.016
19. Ball AJ, Steinberg GK, Elbers J. Quality of life in pediatric moyamoya disease. *Pediatr Neurol*. 2016;63:60–65. doi: 10.1016/j.pediatrneurol.2016.06.012
20. Kim SK, Cho BK, Phi JH, Lee JY, Chae JH, Kim KJ, et al. Pediatric moyamoya disease: an analysis of 410 consecutive cases. *Ann Neurol*. 2010;68:92–101. doi: 10.1002/ana.21981
21. Lee JY, Phi JH, Wang KC, Cho BK, Shin MS, Kim SK. Neurocognitive profiles of children with moyamoya disease before and after surgical intervention. *Cerebrovasc Dis*. 2011;31:230–237. doi: 10.1159/000321901
22. Liu P, Han C, Li DS, Lv XL, Li YX, Duan L. Hemorrhagic moyamoya disease in children: clinical, angiographic features, and long-term surgical outcome. *Stroke*. 2016;47:240–243. doi: 10.1161/STROKEAHA.115.010512
23. Zhao M, Zhang D, Wang S, Zhang Y, Wang R, Zhao J. Transient ischemic attack in pediatric patients with moyamoya disease: clinical features, natural history, and predictors of stroke. *Pediatr Neurol*. 2017;75:48–54. doi: 10.1016/j.pediatrneurol.2017.06.020
24. Yamada S, Oki K, Itoh Y, Kuroda S, Houkin K, Tominaga T, et al; Research Committee on Spontaneous Occlusion of Circle of Willis (Moyamoya Disease). Effects of surgery and antiplatelet therapy in ten-year follow-up from the registry study of research committee on moyamoya disease in Japan. *J Stroke Cerebrovasc Dis*. 2016;25:340–349. doi: 10.1016/j.jstrokecerebrovasdis.2015.10.003
25. Karzmark P, Zeifert PD, Bell-Stephens TE, Steinberg GK, Dorfman LJ. Neurocognitive impairment in adults with moyamoya disease without stroke. *Neurosurgery*. 2012;70:634–638. doi: 10.1227/NEU.0b013e3182320d1a
26. Miyamoto S, Kikuchi H, Karasawa J, Nagata I, Ikota T, Takeuchi S. Study of the posterior circulation in moyamoya disease. clinical and neuroradiological evaluation. *J Neurosurg*. 1984;61:1032–1037. doi: 10.3171/jns.1984.61.6.1032
27. Ahn JH, Wang KC, Phi JH, Lee JY, Cho BK, Kim IO, et al. Hemorrhagic moyamoya disease in children: clinical features and surgical outcome. *Childs Nerv Syst*. 2012;28:237–245. doi: 10.1007/s00381-011-1535-5
28. Ganesan V, Smith ER. Moyamoya: defining current knowledge gaps. *Dev Med Child Neurol*. 2015;57:786–787. doi: 10.1111/dmcn.12708
29. Kazumata K, Ito M, Uchino H, Nishihara H, Houkin K. Proposal for a prospective registry for moyamoya disease in Japan. *Neurol Med Chir (Tokyo)*. 2017;57:66–72. doi: 10.2176/nmc.st.2016-0153