Incidence, Prevalence, and Survival of Moyamoya Disease in Korea
A Nationwide, Population-Based Study

Il Min Ahn; Dong-Hyuk Park, MD, PhD; Hoo Jae Hann, MD, PhD; Kyoung Hoon Kim, MPH, PhD; Hyun Jung Kim, MPH, PhD; Hyeong Sik Ahn, MD, PhD

Background and Purpose—There is a scarcity of information on the epidemiology and natural course of moyamoya disease. The aim of this study was to investigate the nationwide epidemiological features of moyamoya disease in Korea, including incidence, prevalence, and survival.

Methods—We used the data from nationwide, population-based Health Insurance Review and Assessment Service claims database and Rare Intractable Disease registration program, which includes physician-certified diagnoses based on uniform criteria for moyamoya disease from 2007 to 2011. Age-specific incidence and prevalence were calculated, and survival was examined using Kaplan–Meier method.

Results—The total number of patients with moyamoya disease was 8154 in 2011, with a female-to-male ratio of 1.8. The incidence from 2007 to 2011 was 1.7 to 2.3/10^5, and the prevalence in 2011 was 16.1/10^5. In total, 66.3% of patients aged 0 to 14 years underwent surgery, whereas only 21.5% in the older than 15 years age group underwent surgery. The 1- and 5-year survival rates of adult patients were 96.9% and 92.9%, respectively, and of child patients were 99.6% and 99.3%, respectively.

Conclusions—The prevalence and incidence presented in this study are higher than those in previous studies. This study demonstrates that the burden of moyamoya disease in Korea is substantial. (Stroke. 2014;45:1090-1095.)

Key Words: epidemiology ■ incidence ■ Korea ■ moyamoya disease ■ prevalence ■ survival

Moyamoya disease is characterized by the bilateral stenosis or occlusion of the distal internal carotid artery bifurcation and compensatory arterial collateral networks at the base of the brain.1,2 Whereas the main clinical manifestation of moyamoya disease is cerebral hemorrhage in adults, repetitive transient ischemic attacks are more common in children. Moyamoya disease is the most common cause of strokes in children, accounting for ≈62% of cerebrovascular diseases in children requiring surgery.3–5

Moyamoya disease is known to be relatively common in Far Eastern countries, including Korea and Japan, but is rarely observed in Europe and the Americas, showing wide regional variation.6,7 Although the cause of moyamoya disease is largely unknown, the involvement of both genetic and environmental factors in its pathogenesis is clear.8 Recently, there has been much progress in understanding the genetic background of moyamoya disease. In 2011, a susceptible gene named RNF213 and the founder mutation p.R4859K were identified, and their strong association with moyamoya disease has been noted in Japan and Korea.9,10

There exist few epidemiological studies on moyamoya disease worldwide. There are reports on its nationwide epidemiology in Japan, but these reports only estimate prevalence rates based on cross-sectional surveys targeting health institutions with <60% response rate. Additionally, these studies were conducted in 1995 and 2003; so updates on the epidemiology of moyamoya disease are needed.11,12

The National Health Insurance (NHI) run by the Korean government is a nationwide universal insurance system, wherein all inpatient and outpatient healthcare utilization data are recorded in a comprehensive database. Within this system, the NHI has established a registration program for rare intractable diseases (RIDs), such as moyamoya disease, for copayment reduction. To be registered in this RID program, specific diagnostic criteria need to be met and the physician certified. Thus, the RID database allowed the current study to analyze reliable epidemiological features of moyamoya disease.
used this database to investigate its national incidence, prevalence, and survival in Korea. To our knowledge, the incidence, prevalence, and survival of moyamoya disease have not been described in a nationwide, population-based study.6

Methods

Data Source
This study used the nationwide and comprehensive Health Insurance Review and Assessment Service (HIRA) claims database, which is based on data from a universal health insurance system run by the Korean government. This system covers >49 million people.

Healthcare institutions send claims data in electronic form to HIRA, and HIRA integrates these data into the claims database. The claims database holds healthcare utilization information on inpatients and outpatients, including patient demographics, date of admission and discharge, date of visit, principal diagnosis, and comorbidities based on the International Classification of Diseases, 10th Revision, and RID registration information. The database also contains information on prescription history, type of surgical procedures, diagnostic procedures including laboratory tests and imaging studies, and healthcare expenditure.

Beginning in 2006, the NIH initiated a registration program for 138 RIDs, including moyamoya disease. Patients registered in this program become eligible for a copayment reduction after their diagnosis is approved by a physician. The diagnosis must be based on the RID diagnostic criteria provided by the NIH and reviewed by the corresponding healthcare institution before being submitted to the NIH. Thus, the data regarding RIDs are verified and reliable.

Our study only included moyamoya cases certified as RIDs in the HIRA claims database. We encrypted all personal identities and analyzed all data anonymously. The study protocol was approved by the Research Ethics Committee of Korea University Medical School.

Patient Selection

Patients who have been claimed for moyamoya disease from January 2007 to December 2011 to HIRA were included in the study. The diagnostic criteria for moyamoya disease used by the RID program are the following: findings obtained from cerebral angiography or MRI and magnetic resonance angiography must show: (1) stenosis or occlusion at the terminal portion of the internal carotid artery or the proximal portion of the anterior or the middle cerebral arteries, and (2) abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase. Patients with bilateral involvement were classified as definite cases, and patients with unilateral involvement were classified as probable cases.13 Both definite and probable cases are included in our data analysis.

Cerebrovascular diseases with the following disease conditions were excluded: arteriosclerosis, autoimmune disease, meningitis, brain neoplasm, Down syndrome, von Recklinghausen disease, head trauma, and irradiation to the head, among others.

For patients with moyamoya included in this study group, records of medical visits, hospitalizations, and surgeries from the HIRA database were used. Death status data were also obtained from the same database.

Statistical Analysis

This study evaluated the incidence of moyamoya disease in Korea between 2007 and 2011. A 2-year washout period (2005–2006) was used to prevent prevalent cases from interfering with the data. An incident case was defined as a person who was newly diagnosed and registered as a moyamoya patient by the RID program in the corresponding year. We calculated the incidence by dividing the number of new cases in the corresponding year by the population. A prevalent case was defined as a person registered in the HIRA–RID database as a moyamoya patient, including all patients treated for moyamoya disease in the corresponding year and patients registered as incident cases in previous years. We calculated the prevalence by dividing the number of prevalent cases in the corresponding year by the population. We calculated average age- and sex-specific prevalence and incidence by dividing the number of cases in each age and sex group by the age- and sex-specific population and averaging these data from 2007 to 2011. A surgical case was defined as an incident case that had a moyamoya disease–related operation (direct or indirect revascularization) during the study period after diagnosis. We used the population of Korea in June of each fiscal year in calculating incidence and prevalence.

Survival information obtained from the HIRA database was used in survival analysis. Survival was examined using the Kaplan–Meier method, with comparisons made using the log-rank test. The date of registration in the RID program was considered the date of diagnosis. The cumulative survival of moyamoya patients was compared with the survival of the age-/sex-matched Korean population using a log-rank test. Subgroup analysis of survival by age and surgical groups was performed.

Results

From 2007 to 2011, the total number of patients with moyamoya disease in Korea was 8154, of which 2928 were men and 5226 were women, rendering the female-to-male ratio at 1.8. The average patient age was 36.8 years, and the average patient age for men and women was 34.4 and 38.1 years, respectively (Table 1).

Incidence

From 2007 to 2011, the number of incident cases was 848 to 1192, and the annual incidence was 1.7 to 2.3 per 100000. The average patient age in these cases was 38.9 years, and the average patient age for men and women was 37.9 and 39.5 years, respectively.

The incidence by sex was 1.3 to 1.7 per 100000 for men and 2.1 to 3.0 per 100000 for women, with a female-to-male ratio of 1.9 (Table 1).

Table 1. Incidence and Prevalence of Moyamoya Disease in Korea, 2007 to 2011

<table>
<thead>
<tr>
<th>Year</th>
<th>Incident Cases</th>
<th>Prevalent Cases</th>
<th>Incidence* per 105/y</th>
<th>Prevalence† per 105/y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T</td>
<td>M</td>
<td>F</td>
<td>T</td>
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<tr>
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<td>848</td>
<td>321</td>
<td>527</td>
<td>4047</td>
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<tr>
<td>2008</td>
<td>950</td>
<td>347</td>
<td>603</td>
<td>4975</td>
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<tr>
<td>2009</td>
<td>1105</td>
<td>401</td>
<td>704</td>
<td>6038</td>
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<tr>
<td>2010</td>
<td>1048</td>
<td>399</td>
<td>649</td>
<td>7031</td>
</tr>
<tr>
<td>2011</td>
<td>1192</td>
<td>428</td>
<td>764</td>
<td>8154</td>
</tr>
</tbody>
</table>

F indicates female; M, male; and T, total.

*Incidence=(Incident cases/Total Korean population)×105.

†Prevalence=(Prevalent cases/Total Korean population)×105.
Age-specific incidence is presented in Figure 1. The age-specific incidence showed 2 peaks, which we identified as a peak in child group (<15) and a peak in the adult group (≥15). The peak in the child group occurred at age 5 to 14 years, accounting for 16.2% of all incident cases, and the peak in the adult group occurred at age 45 to 54 years, accounting for 22.8%. When the age groups were studied in increments of 5 years, incidence was highest for age 5 to 9 years in the child group, with 3.8 per 100,000, and age 45 to 49 years in the adult group, with 2.9 per 100,000. The age-specific incidence analyzed by sex also showed similar patterns in both sexes (Table I in the online-only Data Supplement).

Prevalence
When calculated with the 2011 population as the denominator, the crude prevalence was found to be 16.1 per 100,000. The prevalence for men and women was 11.5 and 20.6, respectively, with a female-to-male ratio of 1.8. The prevalence in 2007 was 8.2 per 100,000, with an average annual increase of 19.1%. Prevalence by sex showed a near 2-fold increase for both men and women during the study period, showing a similar pattern in both sexes (Table 1).

The age-specific prevalence in 2011 is presented in Figure 2. Similar to incidence, the age-specific prevalence showed 2 peaks, with 1 in the child group and the other in the adult group. The first peak occurred at age 10 to 19 years and accounted for 19.0% of all prevalent cases, and the second peak occurred at age 50 to 59 years and accounted for 19.7%. In contrast to the adult group peak for incidence, which spanned the age range of 45 to 54 years, the adult group peak for prevalence spanned the age range of 50 to 59 years, which can be attributed to the aging of surviving moyamoya patients. When prevalence was studied in 5-year increments, the age group of 10 to 14 years exhibited the highest prevalence in the child group, with 26.1 per 100,000, and the age group of 55 to 59 years exhibited the highest prevalence in the adult group, with 22.1 per 100,000. Age-specific prevalence analyzed by sex also showed similar patterns (Table II in the online-only Data Supplement).

Surgery
Among 5143 incident cases of moyamoya disease, 1551 cases (30.2%) had surgery within the study period. When analyzed by age, 66.3% of children aged 0 to 14 years, 32.4% of adolescents aged 15 to 29 years, 24.1% of adults aged 30 to 44 years, 18.3% of middle-aged adults aged 45 to 59 years, and only 7.7% of adults aged >60 years underwent surgery.

Of the surgical patients, 388 (25.0%) underwent direct revascularization, and 1135 (73.2%) underwent indirect revascularization. Surgical method preference also differed by age. Here, 97.7% of surgical children aged 0 to 14 years and 61.3% of surgical adolescents aged 15 to 29 years underwent indirect revascularization, whereas only 52.7% of surgical adults >30 years underwent indirect revascularization (Table 2).

Survival
In this study, 5143 incident moyamoya cases were followed for a total of 15,590 person-years from diagnosis. In total, 210 patients died during the median follow-up of 2.8 years.

The survival of moyamoya patients after diagnosis is illustrated in Figures 3 and 4. The overall survival of moyamoya patients was 97.2%. The 1- and 5-year survival rates were 98.4% and 96.1%, respectively. One- and 5-year survival among children aged 0 to 14 years were 99.6% and 99.3%, respectively, and among adults aged >15 years were 96.9% and 92.9%, respectively. The survival of the adult group was significantly lower than that of the general population (92.9% versus 97.8%). However, the difference in survival between moyamoya patients and the general population in the child group was smaller (99.3% versus 99.7%).

Survival was statistically not significant between the surgical and nonsurgical groups. Differences in survival were not observed between sexes.

Discussion
In this population-based study, the incidence of moyamoya disease was 1.7 to 2.3 per 100,000 from 2007 to 2011, and the prevalence was 16.1 per 100,000 in 2011. The incidence for men and women was 1.3 to 1.7 and 2.1 to 3.0 per 100,000, respectively, and the prevalence for men and women was 5.8 to 11.5 and 10.7 to 20.6 per 100,000, respectively. In both incidence and prevalence, women were reported to have higher rates.

Previous Japanese studies reported incidence and prevalence of 0.54 and 6.03 per 100,000 in 2003, respectively,
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which were lower than the rates found in our study.\textsuperscript{12} Although Korea may indeed have higher incidence and prevalence of moyamoya disease compared with Japan, it should be noted that a direct comparison with our study may be difficult because of differences in data collection methods and population characteristics; the Japanese study used data from a survey conducted in hospitals, with a response rate of 56.8%.\textsuperscript{11} Additionally, the Japanese study analyzed data in 1995 and 2003, whereas the current study analyzed data from 2007 to 2011. Thus, a progression of time may have rendered the rates in our study higher.

Our results confirm that the incidence of moyamoya disease in Korea is as high as in Japan, which is among the highest in the world. This can be partly explained by the genetic background of Korean and Japanese populations. Recent studies have demonstrated a strong association between the p.R4810K mutation in RNF213 and moyamoya disease and reported a relatively high prevalence of p.R4810K among East Asians.\textsuperscript{9,10,14,15}

The present study showed that prevalence increased annually. The prevalence increases from 8.2 per 100 000 in 2007 to 16.1 per 100 000 in 2011. This increase may partly be because of the increasing availability of MRI or magnetic resonance angiography diagnostic tests, which allowed the diagnosis of cases that would not have been possible in preceding years. Another potential explanation for this increase is the establishment of the registration program for RIDs. Because RID patients became eligible for copayment reduction in 2006, patients who previously avoided costly tests for moyamoya disease may have become more inclined to get tested and be diagnosed. The steeper rise in prevalence compared with the increase in incidence may be attributed to the fact that patients with moyamoya disease are demonstrating prolonged survival.

This study confirmed that moyamoya disease has a bimodal age distribution: the first peak occurs in early childhood, and the second peak occurs in the fourth decade of life. This pattern is similar to that reported in a previous study.\textsuperscript{12} As for sex, this study showed a female-to-male ratio of 1.8, also similar to rates reported in previous studies.\textsuperscript{11,12}

Surgical rates differed significantly based on age group. The higher surgical rate in children can be explained by the fact that physicians advise early surgical treatment for children, because moyamoya disease is usually expressed as cerebral ischemic symptoms in children, and revascularization is the treatment of choice to prevent ischemic symptoms. The low surgical rate in adults implies that ischemic symptoms are less common than hemorrhagic symptoms in adults, and it is still unclear whether revascularization is effective in preventing the recurrence of hemorrhage.\textsuperscript{16,17}

Surgical methods also differed by age group. Among surgical patients, 97.7% of children aged 0 to 14 years underwent indirect surgery, whereas 52.7% of adults aged >30 years underwent indirect surgery. The rate of indirect surgery may be high in children because indirect revascularization surgery is less invasive than direct surgery and involves an easier surgical technique.\textsuperscript{18} For adults, a higher rate of direct

\begin{table}
\centering
\caption{Age-Specific Surgical Rate of Moyamoya Patients in Korea, 2007 to 2011}
\label{tab:2}
\begin{tabular}{llllll}
\hline
Age Group & Total Incident Patients & Total Direct Revascularization & Indirect Revascularization & Both Revascularization & Surgical Rate*, %
\hline
0–14 & 992 & 658 & 12 & 643 & 3 & 66.3
15–29 & 725 & 235 & 81 & 144 & 10 & 32.4
30–44 & 1392 & 336 & 151 & 175 & 10 & 24.1
45–59 & 1565 & 286 & 128 & 152 & 6 & 18.3
≥60 & 469 & 36 & 16 & 20 & 0 & 7.7
Total & 5143 & 1551 & 388 & 1134 & 29 & 30.2
\hline
\multicolumn{6}{l}{*Surgical rate=(Surgical cases/Total incident patients)×100.}
\end{tabular}
\end{table}

Figure 3. Survival of child (<15;\textbf{A}) and adult patients (≥15;\textbf{B}) with moyamoya disease compared with corresponding general population. Vertical axis represents survival by percentage; horizontal axis represents months after diagnosis. GP indicates general population.
Revascularization surgery may be observed because this method is more effective than indirect surgery.\(^5\)

Five-year survival for child and adult groups was 99.3% and 92.9%, respectively. Previous studies reported that the mortality rate of moyamoya patients who had brain hemorrhages was as low as 6.8% and as high as 20%.\(^7\)\(^20\) The higher survival in the current study may be explained by the fact that the previous studies were based on hospitalized patients, whereas the present study was based on the entire population, including even mildly affected patients. Additionally, improvement in patient care capability has led to increased survival.

The survival was not significantly different between nonsurgical and surgical patients. However, this result should be cautiously interpreted because, first, selection bias exists as patient characteristics and severity are inherently different between surgical and nonsurgical groups, and, second, our study did not adjust for severity because we lacked detailed clinical information for patients. Thus, our results comparing survival features of surgical and nonsurgical groups are descriptive and should not be used to draw conclusions on the effectiveness of surgery in changing mortality or morbidity in moyamoya patients.\(^21\)\(^-\)\(^25\)

This study has certain limitations. First, because our data are based on insurance claims, detailed clinical information, such as symptoms, laboratory test results, or genetic information on patients, is lacking. Therefore, we are limited in our ability to describe clinical and genetic features or perform severity adjustments. Second, our study relied on administrative data, which may have questionable diagnostic reliability. However, the NHI has sent specific diagnostic criteria for RIDs to physicians for copayment reduction, and health institutions are required to review physician’s diagnosis before submitting this information to the NHI. Thus, the probability of misclassification is low, and the diagnosis can be considered reliable. Third, we do not know the exact registration rate of patients with moyamoya disease in the RID program and cannot completely exclude the possibility of some patients not registering in the program. However, because every Korean healthcare institution is aware of the RID program and registering in the program offers patients copayment reduction, we assume that the rate of registry for patients with moyamoya disease is very high.

A strength of this study lies in the fact that we examined the nationwide, population-based epidemiological features of moyamoya disease. To our knowledge, no other study has examined incidence, prevalence, and subsequent survival using a recent and nationwide data source. The large sample size and unbiased measures (ie, surgery and survival) in this study provide assurance that the data are not spurious and accurately represent information on moyamoya patients.

This is the first nationwide study on the incidence, prevalence, and survival of moyamoya disease in Korea. This study has important implications, because the incidence and prevalence of moyamoya disease are higher than previously reported. The prevalence has doubled from 2007 to 2011, perhaps because of improved prognosis or early diagnosis in recent years. This study indicates that more attention needs to be paid to moyamoya disease in Far Eastern nations.

Acknowledgments
We thank Ji Yang Song, Ji Won Baek, and Sang Hyuk Lee (Department of Preventive Medicine, College of Medicine, Korea University) for their assistance in preparing this article.

Disclosures
None.

References

Figure 4. Survival of child (<15; A) and adult patients (≥15; B) with moyamoya disease by surgical and nonsurgical groups. Vertical axis represents survival by percentage; horizontal axis represents months after diagnosis.


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*Stroke*. 2014;45:1090-1095; originally published online March 4, 2014; doi: 10.1161/STROKEAHA.113.004273

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/4/1090

Data Supplement (unedited) at:
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### Table I. Age-specific Annual Incidence of Moyamoya Disease in Korea, 2007-2011

<table>
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<tr>
<th>Age group (year)</th>
<th>Age-specific population*</th>
<th>Number of incident cases</th>
<th>Incidence† per 10⁵/year</th>
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<td></td>
<td>T</td>
<td>M</td>
<td>F</td>
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<tr>
<td>0-4</td>
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<td>5,933,984</td>
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<td>≥80</td>
<td>4,451,079</td>
<td>1,288,731</td>
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<td>Total</td>
<td>248,655,024</td>
<td>123,984,038</td>
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*Age-specific population = sum of population in corresponding age group (2007-2011)

†Incidence = incident cases/age-specific population *10⁵
Table II. Age-specific Prevalence of Moyamoya Disease in Korea, 2011

<table>
<thead>
<tr>
<th>Age group (year)</th>
<th>Age-specific Population*</th>
<th>Number of prevalent cases</th>
<th>Prevalence† per 10^5/year</th>
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<td>0-4</td>
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<td>80+</td>
<td>1,032,231</td>
<td>299,398</td>
<td>732,833</td>
</tr>
<tr>
<td>Total</td>
<td>50,734,284</td>
<td>25,406,934</td>
<td>25,327,350</td>
</tr>
</tbody>
</table>

*Age-specific population = sum of population in corresponding age group
†Prevalence = prevalent cases/age-specific population *10^5