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Pediatric Issue

Epidemiology of Moyamoya Disease in Korea: Based on National Health Insurance Service Data

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There have been a few studies reporting the epidemiology of moyamoya disease in Korea. Previous studies revealed relatively high prevalence and incidence of moyamoya disease in Korea and Japan. This study was designed to provide the latest epidemiologic information of moyamoya disease in Korea. We analyzed a database comprising of 50 million people covered in Korea by the National Health Insurance Service to calculate the prevalence. The incidence was estimated by eliminating the duplicated records of previous 3 years. We summarized the prevalence and incidence according to age, sex, and local distribution. In addition, the chronological changes were demonstrated with direct standardization using the 2010 population structure information. The standardized prevalence was 6.5 per 100000 persons in 2005, which was increased to 18.1 in 2013. In the same period, standardized incidence was increased from 2.7 to 4.3 per 100000 persons. The prevalence for men was 4.9 and 8.3 for women in 2005. In 2013, the prevalence had increased for men and women to 13.8 and 25.3, respectively. The incidence for men and women was 2.2 and 3.2, respectively, in 2005. It had increased to 3.5 and 5.7, respectively. The mean age of patients was 33.5 in 2005 and increased to 42.5 in 2013. The peak prevalent age group had shifted slightly to the older age groups, with chronologically consistent female predominance. The prevalence was highest in Jeollabuk province and lowest in Ulsan city.

Key Words : Epidemiology · Korea · Moyamoya disease.

INTRODUCTION

Moyamoya disease (MMD) is a rare disease characterized by spontaneous stenosis or occlusion of the distal internal carotid artery[18]. Abnormal development of the arterial collateral network is also accompanied with progressive stenosis[16]. Moyamoya, meaning "puff of smoke" in Japanese, was coined by Suzuki and depended on the shape of collaterals[19]. Several reports have revealed epidemiologic characteristic of MMD. First of all, the most prominent finding was the international difference in incidence and prevalence[8,10]. High incidence and prevalence were shown in Asian countries, especially Korea, Japan, Taiwan, and China[1,3,9,13]. The bimodal age distribution and gender difference were consistently reported by several previous studies[3,7,9,21].

On the other hand, there have been a few studies concerning the epidemiology of MMD in Korea[1,4,6,7]. Among them, two studies used institutional data that may not be considered as nationwide statistics. Other two studies utilized data from the National Health Insurance Service (NHIS), which has been run by the Korean government and covers almost the entire Korean population[1,7]. To provide up-to-date epidemiologic information of MMD in Korea, we reviewed NHIS data between 2005 and 2013.

MATERIALS AND METHODS

Data source

NHIS data used in this study included approximately 50 million people covered in Korea. These data were based on claims that were sent from healthcare institutions. All patients' data were given unique identification codes that masked their resident registration number. The claims database contained information about the utilization of healthcare system, including the total number of patients, expenditures, and date of visit, admission and discharge. These data could be divided by age, sex, and administrative district. And information regarding medical resources were obtained from the annual report by NHIS, which included the number of health care institutes and human resources.

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Patient selection

Using the International Classification of Diseases, 10th Revision (ICD-10) diagnostic code, we collected data from patients with MMD visiting healthcare institutions between 2005 and 2013. This diagnostic code was used in both the main diagnosis and sub-diagnosis for querying. It may be important to identify MMD patients with maximal estimation because the database from NHIS did not contain detailed information regarding symptoms and diagnostic methods.

Data analysis

Prevalent cases were defined as any patients that visited a healthcare institution with MMD, regardless of their symptoms and treatment history. Incident cases were extracted from prevalent cases by subtracting the patients who had any claim record in the previous 3-years. The population size of each group was obtained from the annual reports by Statistics Korea (www.kostat.go.kr), which could be searched in Korean Open Data Portal (www.data.go.kr). Prevalence and incidence were calculated as below.

$$\text{Prevalence}=\frac{\text{Number of prevalent cases in each group}}{\text{Population size in each group}}\times 100000$$

$$\text{Incidence}=\frac{\text{Number of incident cases in each group}}{\text{Population size in each group}}\times 100000$$

The annual prevalence and incidence were standardized using the population structure data in 2010, which was produced by a population census. The proportions of each age groups and sex were calculated in accordance to the result of census. The standardized prevalence and incidence were calculated by a weighted summation of crude prevalence and incidence for each group using the aforementioned proportional indices.

RESULTS

Prevalence and incidence

From 2005 to 2013, the number of MMD patients using healthcare services increased by <about> threefold from 3220 to 9997. The crude prevalence was 6.6 in 2005 and gradually increased to 19.5 in 2013. After standardization of sex and age, the prevalence was adjusted to 6.5 and 18.1 in 2005 and 2013, respectively (Table 1). An average annual increase of standardized prevalence was 22.3% (Fig. 1). In the same period, an average annual increase of the general population in Korea was estimated to be 0.6%.

There had been a total of 1324 incidences in 2005. Because the population size had been about 49 million, crude incidence had been 2.7 per 100000 person/year, which was same after standardization. In accordance to the increases of patients, crude incidence of MMD in Korea was calculated as 4.6 in 2013. The standardized incidence in 2013 was 4.3 (Table 1). The average annual increase of standardized incidence was 7.4% (Fig. 1).

Gender and age

The prevalence for men was 4.9 and 8.3 for women in 2005. In 2013, the prevalence had increased for men and women to 13.8 and 25.3, respectively. The female to male ratio of 1.8 was

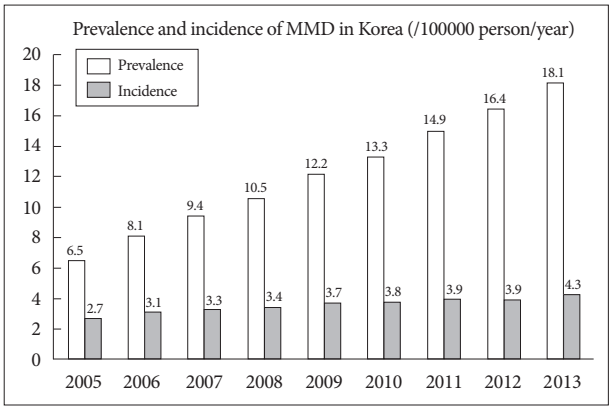

Fig. 1. The prevalence and incidence of moyamoya disease in Korea from 2005 to 2013.

Table 1. Prevalence and incidence of moyamoya disease in Korea from 2005 to 2013

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013
Population size (×1000)	48782	48992	49269	49540	49773	50516	50734	50948	51141
Prevalent cases	3220	4007	4736	5357	6256	7084	8055	8913	9997
Prevalence	6.5	8.1	9.4	10.5	12.2	13.3	14.9	16.4	18.1
Male	1196	1428	1667	1881	2208	2534	2833	3153	3527
Female	2024	2579	3069	3476	4048	4550	5222	5760	6470
Female to male ratio	1.7	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Incident cases	1324	1545	1657	1724	1906	2013	2123	2124	2340
Incidence	2.7	3.1	3.3	3.4	3.7	3.8	3.9	3.9	4.3
Male	538	562	636	663	762	826	801	839	884
Female	786	983	1021	1061	1144	1187	1322	1285	1456
Female to male ratio	1.5	1.7	1.6	1.6	1.5	1.4	1.7	1.5	1.6

The incidence and prevalence are presented as per 100000 annual (direct standardization with population structure in 2010). NHIS : National Health Insurance Service

Table 2. Age distribution of moyamoya disease in 2005 and 2013

	2005					2013				
	Male	Female	Total	Population size (×1000)	Prevalence (/100000)	Male	Female	Total	Population size (×1000)	Prevalence (/100000)
<10	178	256	434	5692	7.6	187	254	441	4624	9.5
10–19	280*	336	616*	6697	9.2	633	712	1345	6230	21.6
20–29	113	223	336	7627	4.4	298	527	825	6590	12.5
30–39	173	308	481	8822*	5.5	430	805	1235	8015	15.4
40–49	194	393*	587	8373	7.0	731*	1372	2103	8920*	23.6
50–59	177	344	521	5262	9.9*	711	1693*	2404*	8025	30.0*
60–69	67	142	209	3680	5.7	374	797	1171	4473	26.2
>70	14	22	36	2630	1.4	163	310	473	4265	11.1
Sum	1196	2024	3220	48782	6.6	3527	6470	9997	51141	19.5

*Highest value among groups. NHIS : National Health Insurance Service

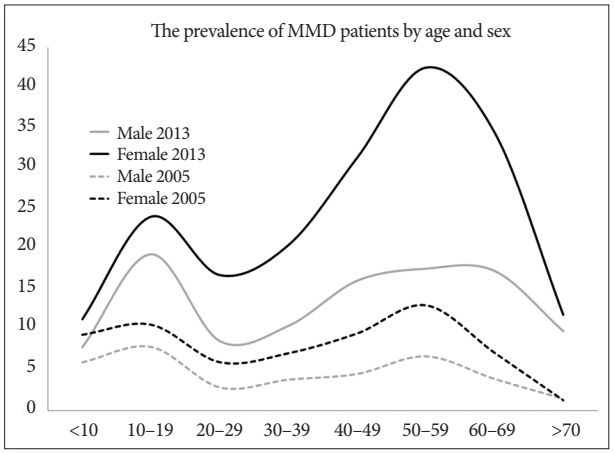

Fig. 2. The prevalence of moyamoya disease by age and sex in 2005 and 2013. The prevalence of moyamoya disease increased during this period. The largest increment of patients was seen in middle aged women.

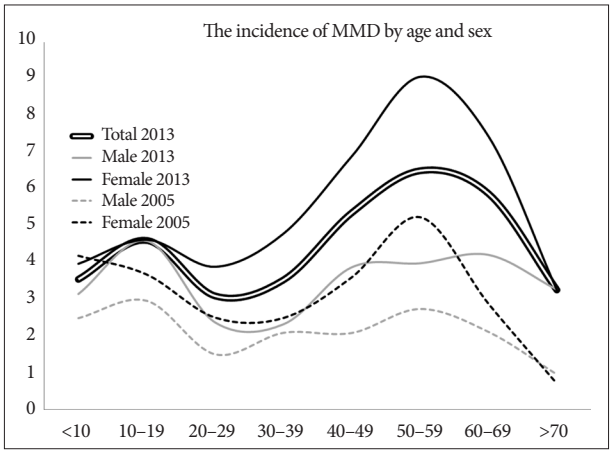

Fig. 3. The incidence of moyamoya disease by age and sex. In populations over 40 years old, the incidence change was prominent in women than in men. In 2013, the peak incidence was shown in ages 10–19 and 50–59.

maintained relatively constant. The age distribution showed a bimodal pattern. Most patients belonged to the age group of 10–19, followed by 40–49 in 2005. In the aspect of prevalence, highest group was age 50–59 and 10–19. However in 2013, the peak prevalent group was more prominent in age group of 50–59 (30.0 per 100000) (Table 2). As a result, the mean age of patients was 33.5 in 2005 and increased to 42.5 in 2013. In a data comparison between 2005 and 2013, the prevalence of middle-aged patients had increased more than the pediatric group in female (Fig. 2).

The incidence for men and women was 2.2 and 3.2, respectively, in 2005. From 2005 to 2013, male incidence of MMD had increased by 59.1%, from 2.2 to 3.5. On the other hand, female incidence had increased from 3.2 to 5.7 (76.3%) in the same period. The female to male ratio of incidence was observed variously in the range from 1.4 to 1.7 over 9 years. Bimodal age distribution of incidence was confirmed, and it was more prominent in women than in men (Fig. 3).

Regional distributions

With respect to local distribution of MMD in Korea, the crude prevalence had been highest in Jeollabuk province and lowest in Ulsan city as of 2013 (Table 3). The prevalence of MMD in Jeollabuk province was about 50% higher than in Ulsan city. From 2005 to 2013, all provinces experienced similar trends of increment in MMD prevalence. On the other hand, among the 16 provinces, 15 experienced an increase in incidence. The highest incidence was observed in Jeollabuk province (Fig. 4).

The regional distribution of medical resources was inspected and analyzed. In provinces with lesser general hospital per 100000 population (<0.5), both the crude prevalence (18.5±1.7 vs. 21.5±2.0, p=0.013) and crude incidence (4.1±0.6 vs. 5.2±0.9, p=0.027) were lower. However human resources, including the number of general practitioners and board certificated doctors (specialists), were not correlated.

DISCUSSION

In this study, we calculated the prevalence and incidence of MMD using a nationwide database. In 2013, the standardized prevalence and incidence of MMD was 18.1 and 4.3 per 100000,

Table 3. Regional distribution of moyamoya disease and medical resources in 2013

	Prevalence	Incidence	Population	General hospitals		Doctors		Specialists (all)	
				Number	Per 100000	Number	Per 100000	Number	Per 100000
Seoul	19.1	4.3	10191527	40	0.39	87244	116.8	19423	190.6
Busan	19.2	4.5	3525064	23	0.65	26481	133.1	5631	159.7
Daegu	19.1	3.9	2898125	7	0.24	18942	153.0	3941	136.0
Incheon	18.1	4.9	2504954	15	0.60	14387	174.1	3142	125.4
Gwangju	21.2	4.5	1477085	20	1.35	12184	121.2	2451	165.9
Daejeon	23.9	5.4	1534901	8	0.52	11517	133.3	2477	161.4
Ulsan	15.5	3.1	1165884	4	0.34	6428	181.4	1252	107.4
Gyeonggi	19.8	4.5	12364069	50	0.40	60975	202.8	14057	113.7
Gangwon	21.7	5.5	1539661	14	0.91	9301	165.5	1838	119.4
Chungcheongbuk	24.0	6.6	1586301	10	0.63	8269	191.8	1752	110.4
Chungcheongnam	19.1	4.7	2072201	10	0.48	10274	201.7	2174	104.9
Jeollabuk	24.3	6.8	1878881	11	0.59	12724	147.7	2541	135.2
Jeollanam	21.5	4.9	1911985	21	1.10	12821	149.1	2353	123.1
Gyeongsangbuk	21.1	5.3	2714604	18	0.66	14692	184.8	2919	107.5
Gyeongsangnam	19.5	4.3	3364561	23	0.68	19019	176.9	3791	112.7
Jeju	22.5	4.0	595639	7	1.18	4121	144.5	785	131.8

respectively. In Japan, the nationwide incidence of MMD was estimated to be 0.54 in 2003[9]. However, they used questionnaires, and the response rate was only 57%. Baba et al.[2] reported the incidence of MMD as 0.94 in the Hokkaido province of Japan. Although it was not a nationwide study, the investigators performed an all-inclusive survey.

Recently, Chen et al.[3] reported a nationwide epidemiology of Taiwan. They used the national database covering most of the population in Taiwan. The prevalence and incidence of MMD was 1.61 and 0.20, respectively, in 2011. Although these results were relatively low compared to ours, they revealed that the incidence had increased since 2000 in Taiwan. Moreover, the increment of incidence was largely due to an increase in the number of adult patients. Such phenomenon resembles our results. Recently, RNF213 was found to be a susceptible gene with MMD[12]. Liu et at.[11] presented a difference of genetic background between China and Korea/Japan. They found that p.R4810K was detected 0.43% in China, whereas 1.36% in Korea/Japan. Although it has not been fully elucidated, the difference of genetic background may play an important role in these regional differences of MMD in East Asia.

Female predominance has been a consistent trend reported by many articles[2,3,5,9,13,15,20-23]. Among these, relatively weak female predominance (<1.5) was reported in China and Taiwan[3,5,13]. Conversely, investigators from Korea and Japan, including this study, reported relatively strong female predominance (≥1.8)[2,7,9,21].

As it had been well known, bimodal age distribution of MMD was confirmed in Korea. The important change from 2005 was that the prevalence and incidence of MMD has increased much more for middle-aged patients than pediatric populations. Furthermore, this increment was more pronounced in women (Fig. 2, 3). This change should be interpreted carefully. Because patients who were diagnosed with MMD are entitled to economic benefit from NHIS in Korea, the diagnostic code for MMD could be over-issued for other atherosclerotic intracranial stenosis, which affect the older population. Nevertheless, similar trends of change were reported by foreign investigation, already. Baba et al.[2] reported that the highest peak of incidence shifted from children to adults, especially in women. Chen et al.[3] announced similar results, and they explained that increased prevalence of comorbid ischemic stroke was associated with this trend.

Although there had been a few reports regarding the epidemiology of MMD in Korea using national database, the knowledge of regional distribution had been minimal[1,7]. In this study, the prevalence and incidence of MMD were measured variously by region. And they were associated with the supply rate of general hospitals. This relationship could not be investigated with an international comparison due to different genetic background[11]. Further studies using data about distribution of diagnostic tools, including magnetic resonance image and digital subtraction angiography, would be helpful for understanding the relationship between the epidemiology of MMD and medical resources.

Although this study confirmed high prevalence and incidence of MMD in Korea based on a nationwide database, there were some limitations. First limitation of this study was its diagnostic accuracy. The database we used was comprised solely on the claims of healthcare institutes. Therefore, a validation of diagnostic criteria was impossible. Moreover, the data from NHIS were subject to change according to the diagnostic tool and pattern of patient follow-up. Because there was no clinical guideline for the follow-up of MMD patients, some doctors recommended frequent visits, while others did not. Secondly, because we applied the diagnostic code to both the main diagnosis and

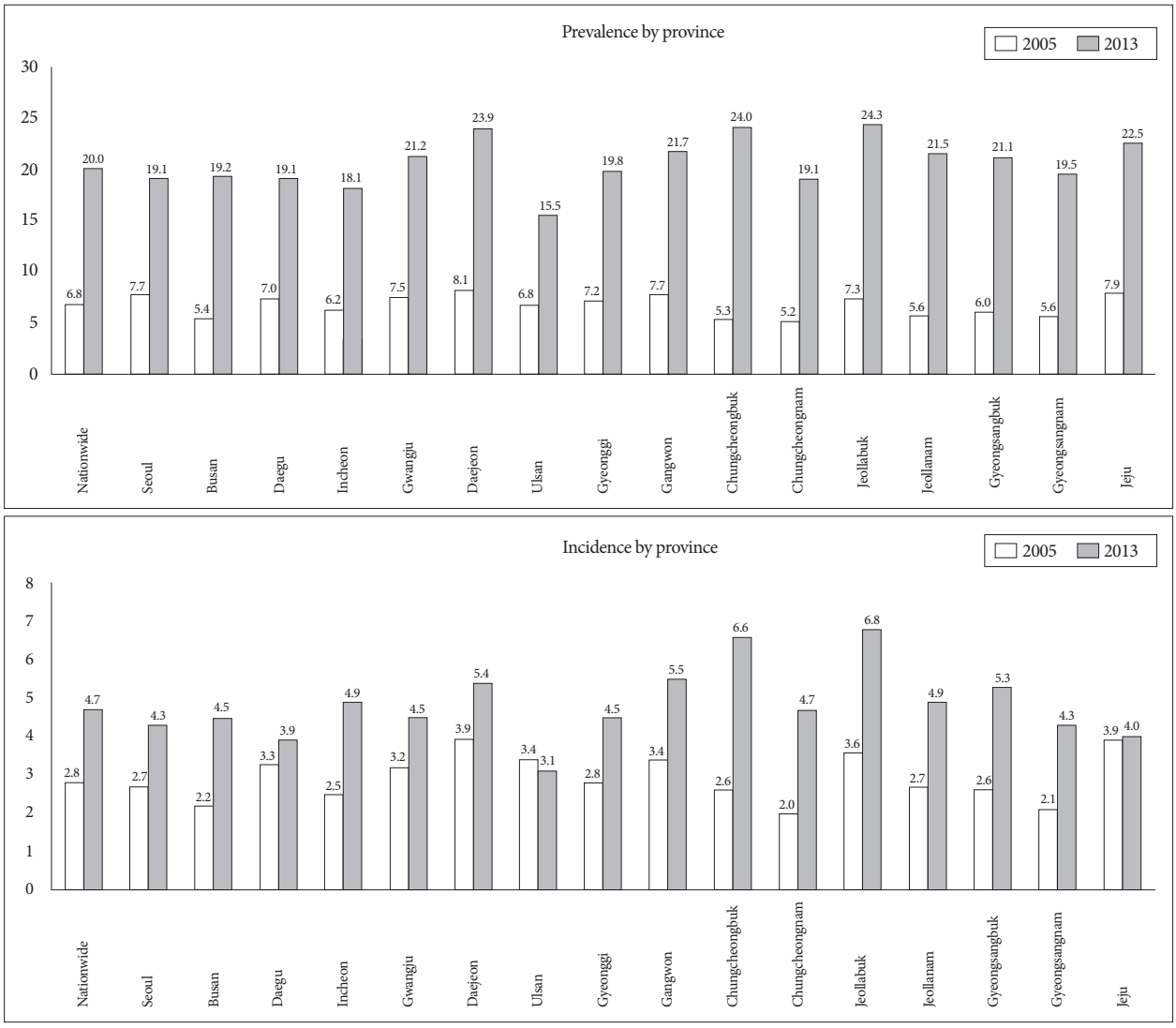

Fig. 4. The local distribution of prevalence and incidence of moyamoya disease. Jeollabuk was the province with highest prevalence and incidence in 2013.

sub-diagnosis, the calculated prevalence and incidence of MMD seemed to be the maximal estimation. The proportion of MMD as sub-diagnosis had been about 7% thoroughout the investigation period. The prevalence and incidence of MMD were reported in two previous studies using national database[1,7]. According to Ahn et al.[1], estimated prevalence and incidence were 10.0 and 1.9, respectively in 2008; Im et al.[7] reported that they were 9.1 and 1.0, respectively. The prevalence of previous studies was similar with our result, which was 10.5 in 2008. However, the incidence of MMD was relatively higher in this study (3.4 in 2008). Because Ahn et al.[1] used rare intractable disease (RID) registry, which was considered to have more tight inclusion criteria for identifying incident case, the estimated incidence could be lower.

Also, we could not distinguish between MMD presented with hemorrhage and MMD presented with ischemia. These two types of presentation were well-known as they differ in age distribution and prognosis[10,14,17]. Furthermore, it was difficult to differentiate symptomatic from asymptomatic or stable from progressive states of the disease in this study. For improving the accuracy of estimation, a comparative and analytic study with a database of RID from the national registration system for intractable diseases, including MMD, could provide more delicate epidemiologic information.

CONCLUSION

The prevalence and incidence of MMD in Korea had gradually increased, and they were 18.1 and 4.3 per 100000 annually with age and sex standardization, respectively, in 2013. The peak prevalent age group had slightly shifted to the older age groups, with higher female predominance. The local difference of prevalence and incidence was also found.

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