

## 研究成果の刊行に関する一覧表

	著者名	題名	書名	巻：頁 (西暦年号)
1	Mineharu Y, Inoue K, Inoue S, Kikuchi K, Ohishi H, Nozaki K, Hashimoto N, Koizumi A	Association analyses confirming a susceptibility locus for intracranial aneurysm at chromosome 14q23	J Hum Genet	2008 Feb 8; [Epub ahead of print]
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## Title

### **Novel epidemiological features of moyamoya disease**

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## **Abstract**

### **[Background]**

Many clinical features specific to moyamoya disease have been reported and cited in textbooks based on previous data. The purpose of this study is to investigate the present epidemiological features of moyamoya disease based on recently obtained regional all-inclusive data.

### **[Methods]**

The authors have performed an all-inclusive survey of moyamoya disease in Hokkaido, one of the major islands in Japan with a population of 5.63 million. The epidemiological features were analyzed based on the data from 267 newly registered patients with moyamoya disease in Hokkaido from 2002 to 2006. These analyzed data were adjusted to whole Japanese population at 2005.

### **[Results]**

The detection rate of the disease per year was 0.94 patients per 100,000 people, and prevalence was 10.5 patients per 100,000 people. The incidence of ischemia concerned with the disease was 0.53 patients per 100,000 people-years and hemorrhage was 0.2 patients per 100,000 people-years. The ratio of female to male patients was 2.18. The ratio of patients 10 and above to under 10 years of age at onset was 6.18. Two peaks for age of onset were seen; the highest observed between 45 and 49 years, and the second between 5 and 9 years. Asymptomatic patients comprised 17.8% of the total number of patients.

### **[Conclusion]**

The epidemiological features of moyamoya disease determined by this survey varied considerably from previous data. The detection rate and prevalence of the disease were higher than those reported previously. The highest peak of onset age was older than those reported previously. In addition, it was revealed that asymptomatic moyamoya patients are not always rare in Japan.

It is not always easy to determine the true epidemiological features of a specific disease with low incidence. Most published studies depend on patient data obtained from selected large hospitals or compiled from numerous previously reported literature. Consequently, these studies have many inherent selection biases. A nationwide all-inclusive study, which appears to be an ideal approach to exclude bias, is not always feasible since the registration of patients suffering from diseases with a low incidence takes several years; further, many omissions in registration can take place because of the weak incentives provided to doctors and patients. Indeed, the epidemiological data of many neurological diseases that appear even in textbooks may suffer from serious selection biases. Moyamoya disease is one such typical neurological disease that has a low incidence. The present epidemiological data for this disease has been mainly obtained from select community and university hospitals and may suffer from a serious selection bias.[1-4]

In addition, the development of a brain check-up system in Japan revealed many asymptomatic cerebrovascular diseases[5, 6] including cases of familial occurrence of moyamoya disease. This means that the previous epidemiological data may have been undercounting.

However, moyamoya disease has been designated as an intractable disease by the Japanese Ministry of Health, Labour and Welfare, which is fortunate from the point of view of disease tracking. Patients officially registered with moyamoya disease are qualified to receive a medical allowance from the government.[7] Therefore, nearly all patients are considered to have a strong incentive to seek registration. Hokkaido is the second largest island in Japan, and the data of patients with moyamoya disease have been well documented for the past several years, including demographic and radiological data. Therefore, the analysis of patient registry data in Hokkaido may help reveal the true features of the moyamoya disease. In this study, all-inclusive continuous data from a well-limited area in Japan are analyzed to reveal the contemporary epidemiological features of moyamoya disease.



## **PATIENTS AND METHODS**

### **Geographical facts**

Hokkaido is the second largest island in Japan with an area of 78 thousand square kilometers; it accounts for 22% of the area of Japan. This prefecture has a population of 5.63 million, which is 4.4% of the Japanese population. In addition, although Hokkaido is such a large island, it has one prefectural government of the 47 prefectures in Japan (fig.1). The other major islands are divided into many prefectures. Thus, Hokkaido presents us with an ideal opportunity to obtain sufficient data from a relatively isolated area that represents a single prefecture.

### **Patient registration**

This survey was based on the certification system of registered intractable diseases of the Ministry of Health, Labour and Welfare in Japan from 1979. Each prefectural government is required to certify, register, and provide financial support to the patients with moyamoya disease since it has been officially designated as an intractable disease by the Japanese government.[7] The patients who were suspected as moyamoya disease in hospital could apply an application to prefectural government with radiological information, including magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and/or conventional cerebral angiography data, in order to confirm the particular vascular changes associated with moyamoya disease including basal moyamoya vessels. These applications with radiological data were evaluated by the commission of certification with specialists in each prefecture. The applications were sorted to definite moyamoya disease, probable moyamoya disease (unilateral moyamoya disease) or improbable cases (e.g. atherosclerosis without moyamoya vessels or quasi-moyamoya disease related with other diseases) based on the criteria prepared by the Research Committee on Spontaneous Occlusion of the Circle of Willis (moyamoya Disease) in Japan. [8]

The subjects surveyed in this study were patients with definite and probable moyamoya disease as certified by the Japanese Ministry of Health, Labor and Welfare in Hokkaido from 2002 to 2006. We analyzed newly certificated data that was onset age with symptomatic

cases and detected age with asymptomatic cases, gender, clinical presentation at onset, familial disease from 2002 to 2006 and the number of already registered patients in 2005.

### **Analysis**

In this study, the types of clinical findings were divided into 4 subgroups: (a) ischemia, including infarction and transient ischemic attacks; (b) hemorrhage; (c) no symptoms. Asymptomatic patients were identified by the brain check-up system or by administration of screening examinations to individuals with familial history and; (d) other symptoms, including headaches, seizures, and involuntary movements. Furthermore, (1) detection rate, prevalence and incidence of ischemia and hemorrhage (2) gender differences, (3) age distribution at onset or detection, (4) type of clinical findings at onset and (5) proportion of family history were investigated. As far as the age and gender is concerned, the data in this study obtained in Hokkaido area was standardized based on data of the whole Japanese population at 2005. This figure of population was most accurate data based on nation census in the last years. The prevalence was calculated using all of registered patients at the point of 2005. The method of statistical analysis used was Chi-square test.

### **Protection of privacy act**

In this study, all data were obtained from data of the Department of Health and Welfare of Hokkaido Prefecture Government under the agreement. All data used in this study was irretrievably unlinked to personal information.

## RESULTS

### Detection rate, incidence and prevalence (table 1)

A total of 283 new applications for disease certification were submitted during the 5 years from 2002 to 2006. The applications for individuals who had already been diagnosed with the disease were filed for 592 cases in 2005. The new applications comprised 233 definite cases, 34 probable cases, and 16 improbable cases that did not meet the criteria for valid diagnosis. Therefore, a total of 267 newly enrolled cases were investigated in this study. The 60 definite cases (22.5%) were applied with only MR examination without cerebral angiography. The prevalence of risk factor mentioned within these applications, hypertension 0.3%, diabetes 0.3%, hyperlipidemia 0% and systemic atherosclerotic disease 0.7%. The detection rate of the disease per year was 0.94 patients per 100,000 people (95% confidence interval, CI: 0.71 to 1.24), and prevalence was 10.5 patients per 100,000 people (95% CI: 9.44 to 11.7). These figures are higher than those previously reported (table 1). The incidence of ischemia concerned with the disease was 0.53 patients per 100,000 people-years, and the incidence of hemorrhage was 0.2 patients per 100,000 people-years.

### Gender differences (table 1)

The ratio of female to male patients was 2.18. However, no significant gender differences were observed, although this figure appears to be slightly higher than that of 1.8 reported previously.[2]

### Age distribution (table 1, fig 2)

The percentage of patients under 10 years of age at onset was 15.1% (table 1). This percentage was significantly lower than that of 47.8% reported previously (table 1).[2] Fig. 2 shows the age distribution of the new patients. The highest peak of detection rate was observed from 45 to 49 years and a smaller peak was observed from 5 to 9 years. In female patients, two definite peaks in age distribution were observed—a higher peak from 45 to 49 years and a smaller peak from 5 to 9 years; this was similar to the pattern of total age distribution. In male patients, this two-peak pattern of age distribution was not clear. It appears that the age distribution pattern was mainly influenced by the female patients. This two-peak pattern

was also observed in the previous report.[2] However, the main peak was shifted toward the adult age group.

**Types of clinical findings** (fig 3, 4)

The percentage of hemorrhage cases was 21.3% and these cases showed only 1 peak at 35 to 59 years. The percentage of cases with ischemia was 56.9%; these cases showed 2 peaks—one at 5 to 9 years and the other at 45 to 49 years. The percentage of asymptomatic cases was 17.8% and had 2 small peaks at 5 to 9 years and adult age.

In the disease pattern by gender, the ratio of ischemia, 53.0% in female was significantly smaller than 65.9% in male ( $p<0.05$ ). Female patients showed a higher incidence of hemorrhage (22.2%) and asymptomatic patterns (20.5%) than male patients (19.5%, 12.2%). These data were not significantly ( $p=0.62$  and  $p=0.10$ ). In the disease pattern by age, 78.4% of the patients below 10 years of age showed ischemia pattern that was significantly larger than 53.5% of the patients of 10 years and upward ( $p<0.01$ ). In hemorrhage pattern, 2.7% of younger group were significantly smaller than 24.3% of older group ( $p<0.01$ ).

**Familial occurrence** (table 1)

Familial history was observed in 15.4% of patients. This figure was higher than that of 10.0% reported previously (table 1). [2] In the younger age group 37.8% patients were with familial moyamoya disease significantly higher than older age group 12.2% ( $p<0.01$ ).