MULTIPLE SCLEROSIS IN ASIA

Edited by
YOSHIGORO KUROIWA

MULTIPLE SCLEROSIS IN ASIA

Proceedings of the Asian Multiple Sclerosis Workshop held
March 13–14, 1975, Tokyo
Sponsored by the Japan Medical Research Foundation

Edited by
YOSHIGORO KUROIWA

UNIVERSITY OF TOKYO PRESS

JAPAN MEDICAL RESEARCH FOUNDATION
PUBLICATION NO. 1

UTP 3047–68418–5149
Printed in Japan.

Published by
UNIVERSITY OF TOKYO PRESS

MULTIPLE SCLEROSIS IN ASIA

Foreword

The development of modern medicine contributed to clarifying etiologies and treatment of various diseases as well as to elevating public health and welfare. However, there are many other diseases of unknown etiologies without effective treatment that leave patients in a chronic uncurable state. The number of such patients is estimated to be tremendously large. In order to promote research on the etiologies and treatment of such mysterious diseases, not only governmental projects but also non-governmental funds are considered to be very important. The Japan Medical Research Foundation has been in existence since October 1973 in order to meet such needs with aid from non-governmental financial sources. The purpose of the Foundation is to cover the areas or plans which governmental projects cannot cover because of certain regulations.

Multiple sclerosis is one such important disease affecting the central nervous system and one that affects many patients in the world. It is very worthwhile to have an Asian Multiple Sclerosis Workshop in order to exchange ideas or knowledge to stimulate research in this area and to clarify etiologies and treatments. The Japan Medical Research Foundation is very happy to support this Workshop, and I am happy the Proceedings of this Workshop is being published.

March 30, 1976

Masayoshi Yamamoto
President
Japan Medical Research Foundation

Preface

While multiple sclerosis (MS) is one of the most important diseases in the world, affecting young adults and producing various disabilities, the etiology and treatment of this illness are still unknown. In Asian countries, the morbidity rate from multiple sclerosis is still unveiled. In Japan multiple sclerosis has been increasingly recognized over the last 20 years. In 1971, the Japanese Government designated this disease as one of the "Specific Diseases," which need help for welfare and research, and with the support of the Ministry of Health and Welfare, the Japan Multiple Sclerosis Research Committee (chairman: Kuroiwa) was organized in 1972 and researches in multidisciplinary fields on multiple sclerosis have been proceeding since. There have been several studies on multiple sclerosis in Asia: Prof. Hung on Taiwan, Prof. Park on Korea, Prof. Vejjajiva on Thailand, and from India Drs. Bharucha, Dastur and Singhal.

Multiple sclerosis shows characteristic geographical distribution, which has been well documented by various neuroepidemiologists (Drs. Kurland, Kurtzke, Alter, etc.). Therefore it was considered worthwhile to have this Workshop attended by distinguished, leading neurologists from Asian countries and the U.S.A. to discuss the problems of this illness and other neurological problems in the Asian countries in hopes of contributing to solving the etiology and pathogenesis of these diseases.

As the chairman of the Workshop, I would like to express my cordial appreciation to those attending this meeting. I would also like to express my gratitude to the staff of the Japan Medical Research Foundation for sponsoring the meeting as well as to the staff of the Ministry of Health and Welfare for its kind cooperation and support.

I hope that this meeting will become an important milestone in the neurological collaborative effort for our mutual benefit and welfare.

Yoshigoro Kuroiwa
Chairman of the
Asian Multiple Sclerosis Workshop

Contents

II PATHOLOGY AND PATHOGENESIS OF MULTIPLE SCLEROSIS

III SYNTHESIS

I REGIONAL EPIDEMIOLOGY AND CLINICAL STUDIES

History of Multiple Sclerosis Studies in Japan

*Yoshigoro Kuroiwa**

At the beginning of this Workshop, I would like to briefly review the study of multiple sclerosis in our country.

The evolution of MS recognition in Japan proceeded thus:

1. Period of neglect (1910–1950)
2. Period of recognition (1950–1970)
3. Period of development (1972–present)

The period of neglect: As early as 1911[1] Prof. Miura, pupil of Charcot, stated that MS was almost nonexistent in Japan. After that it was generally believed that MS was not present here. In 1929 Woods[2] reported that MS was rare among the Chinese in Peking (1.5 per mill among neurologic cases). At this period there were reports of cases labeled Devic's disease, however typical MS was strongly neglected.

The period of recognition: By this time modern neurology in Japan had developed apart from the neuropsychiatric tradition, and some cases were clinically diagnosed as MS. The existence of MS-like disease in Japan was discussed in neurological circles. In 1955 Imamura,[3] a pupil of Prof. Okinaka, reviewed cases with demyelinating diseases reported in the literature of Japan, and he concluded that MS existed in Japan. Okinaka and his colleagues,[4] including myself, reported clinical and pathological cases with MS around this period. In 1955 Okinaka, Tsubaki, Kuroiwa reviewed 270 cases of MS and allied diseases collected throughout Japan (Symposium on the Annual Congress of the Japanese Society for Neurology and Psychiatry, 1955). Through this report the existence of MS in Japan became evident. However problems on the clinical features of MS in Japan remained, as the collected cases consisted of 66 of MS and 175 of neuromyelitis optica variety.

Around the same time (1957)[5] Profs. Uchimura and Shiraki reported

* Neurological Institute, Faculty of Medicine, Kyushu University, Fukuoka, Japan

on post-rabies vaccination encephalomyelitis, which strikingly resembles human MS pathologically in spite of its monophasic course.

At this time, I met with Dr. Kurland in the U.S.A. and a large scale international epidemiological study group was organized under Prof. Okinaka composed of the following:

ORGANIZATION OF EPIDEMIOLOGICAL SURVEYS IN JAPAN (1958–62)

Chairman: Prof. Okinaka
Coordinators: Drs. Kurland (NIH) and Kuroiwa (Fukuoka)
Regional directors: Profs. Miyagawa, Katsuki, Suwa, and Ueki
Neurologists: Drs. McAlpine, Reese and Araki
Neuropathologist: Prof. Shiraki
Surveyed cities: Kumamoto, Fukuoka, Niigata, and Sapporo

The procedures were similar to those which were used in the United States or elsewhere in MS studies. The prevalence rate was 2–4 per 100,000 population,[6,7] lower than those of Western countries of the same latitude. There was no northsouth gradient seen, and optic spinal form was seen in 1/3 of the cases collected.

In 1969 the first MS symposium in Asia[8] was held in conjunction with the 10th Congress of the Japanese Society of Neurology (Fukuoka) with Drs. Kuroiwa and Kurland as chairmen. The prevalence rates in Asian countries were similar to those of Japan, although the rates were very preliminary.

In 1972, the Japanese Ministry of Health and Welfare started the Specific Disease Contract as the first step of public health policy, and MS was selected as one of nine Specific Diseases which need research support and welfare policy. The National Committee of Multiple Sclerosis was organized (Chairman: Kuroiwa) and funded with a generous grant and 25 members joined the studies on the epidemiology, etiology and pathogenesis of the diseases. Nationwide surveys on MS were done, and new diagnostic criteria were established for general practitioners. Since then, knowledge and concern about this disease have greatly increased in Japan. Since 1973 all MS patients in Japan have become eligible for exemption from medical charge which is covered by governmental financial support.

I find that since the age of neglect of MS in Japan, there has been considerable change in academic knowledge as well as public welfare policy with respect to MS. Although MS is a classical disease, described by Charcot more than 100 years ago, remarkable changes in the

concepts of morbidity and diagnostic ciriteria have been seen only in the last 3 decades.

I hope studies in Japan will be helpful in clarifying the etiology and treatment of this disease.

REFERENCES

1. Miura, K.: Serologisches zur multiplen Sklerose (Nonne, M. u. Holzmann, W.) Discussion. *Deutsche Ztschr. Nervenh.* **41**, 146 (1911).
2. Woods, A. H.: The nervous diseases of the Chinese. *Arch. Neurol. & Psychiat.* **21**, 542–570 (1929).
3. Imanura, Y.: Clinical consideration on multiple sclerosis. Review of reported cases in Japan and doubt on the non-existent theory of multiple sclerosis. *Saishin Igaku* (Jap.) **10**, 1256–1268 (1955).
4. Okinaka, S., Tsubaki, T., Kuroiwa, Y., Toyokura, Y., Imamura, Y. and Yoshikawa, M.: Multiple sclerosis and allied diseases in Japan. *Neurology* **8**, 756–763 (1958).
5. Uchimura, Y. and Shiraki, H.: A contribution to the classification and the pathogenesis of demyelinating encephalomyelitis with special reference to the central nerovous system lesions caused by preventive inoculation against rabies. *J. Neuropathol. & Exp. Neurol.* **16**, 139–203 (1957).
6. Okinaka, S. et al.: Multiple sclerosis in northern and southern Japan. *World Neurol.* **1**, 22–42 (1960).
7. Okinaka, S. et al.: The prevalence of multiple sclerosis and other neurological diseases in Japan. *Acta Neurol. Scand.* (suppl. 19) **42**, 68–76 (1966).
8. Kuroiwa, Y. et al.: Multiple sclerosis in Asia. *Clin. Neurol.* (Jap.) **10**, 18–46 (1970).

DISCUSSION 1

*Tadao Tsubaki**

I will discuss briefly Dr. Kuroiwa's presentation on "History of Multiple Sclerosis Studies in Japan."

In 1955, Okinaka, Tsubaki and Kuroiwa[1] collected 270 reported cases of demyelinating diseases in the Japanese, of which 66 cases were MS and

* Department of Neurology, Brain Research Institute, Niigata University, Niigata, Japan

175 cases were Devic's disease or the optic-spinal form of MS (Table 1). In 1966, Tsubaki[2] reviewed cases reported from 1956 to 1965, of which 148 were MS and 93 were Devic's disease. Recently the National MS Study Team of Japan collected 866 cases of MS and 82 of Devic's disease.

TABLE 1. Number of reported cases of demyelinating diseases in Japan

Types	Years		
	1890–1955*	1956–1965**	1967–1973***
Multiple sclerosis	66	148	866 (79.8%)
Devic's disease	175	93	82 (7.6%)
ADEM	16	40	136 (12.6%)
Diffuse sclerosis	4	33	
Unclassified	9	14	
Total	270	328	1084

* Okinaka, Tsubaki, Kuroiwa[1]
** Tsubaki[2]
*** National MS Study Team of Japan

In the early report, Devic's disease was more common than MS. I guess this is due to two reasons. 1. Devic's disease or the optic-spinal form of MS is more easy to diagnose. 2. In early reports in Japan, the optic-spinal form of MS was diagnosed as Devic's disease.

Clinical characteristics of MS in the Japanese proposed before 1971 included the following three points. 1. MS is less prevalent in Japan than in European countries and the United States of America, a finding which was also confirmed by several population surveys. 2. Optic-spinal form and/or Devic's disease are relatively common. (Many recent studies do not support this and this hypothesis is not confirmed.) 3. Acute form is relatively

TABLE 2. Frequency of suspected lesions in MS patients in Japan

Author	Cerebrum	Optic nerves	Spinal cord	Brain stem	Cerebellum	No. of MS cases
National MS Study Team*	35%	72.7%	67.9%	55.3%	34.4%	1084
Goto	44	84	80	68	28	25
Tsubaki	53	83	70	62	49	47
Satoyoshi	28.1	77.1	92.1	78.1	52.1	96
Araki (Autopsy cases)	80	80	88	76	44	25

* Including Devic's disease and possible MS cases

common. (This is reported by some neuropathologists but clinical studies do not support it.)

Table 2 shows frequency of suspected lesions in Japanese MS patients. This shows that not only optic nerves and spinal cord but also cerebrum, brain stem and cerebellum are commonly affected.

It is clear that demyelinating diseases are less prevalent in the Japanese, but other clinical characteristics have to be confirmed by further investigation.

REFERENCES

1. Okinaka, S., Tsubaki, T. and Kuroiwa, Y.: Demyelinating diseases (Clinical aspect). *Saishin Igaku* (Jap.) **10**, 1256–1269 (1955).
2. Tsubaki, T.: Clinic and diagnosis of multiple sclerosis. *Clinical Neurology* (Jap.) **6**, 675–680 (1966).

DISCUSSION 2

*Shukuro Araki**

Until about 20 years ago, multiple sclerosis was believed to be very rare or nonexistent among the population of Japan. Knowledge of MS was insufficiently understood, and almost all clinicians were negative disposed to making a diagnosis. Autopsy-proved cases of MS were also lacking at that time.

I would like to mention three important factors which contributed to progress in MS studies in Japanese history.

First was an epidemiological survey of MS carried out in Japan between 1958 and 1959. This population study in four Japanese cities was the first authorized one and stimulated Japanese medical science. I want to acknowledge the efforts and contributions of Prof. Okinaka, Prof. Kuroiwa, Dr. Kurland of NIH, and other members who participated in the survey. This survey was in fact the initiation of MS study in Japan.

The second important factor was the development of neurology in

* Department of Internal Medicine, Kawasaki Medical College, Kurashiki, Japan

Japan. The Japanese Society of Neurology was founded in 1960 with about 400 members. Over the past 15 years, membership has increased from 400 to 2500, and as knowledge about the disease has progressed, clinically diagnosed MS cases have also gradually increased. The increase in the number of patients with MS seems probably due to improved recognition of clinical symptoms and signs by neurologists.

The third important factor was the reports of autopsy-proved cases of classical MS after 1966. In early September, 1973, at the International Symposium of MS in Kyoto, I contributed a paper on clinical features of autopsy-proved MS among Japanese. We had obtained 25 autopsy-proved cases collected over a 7-year period from the Japanese literature. We found that there was no significant difference in age at onset, symptoms and signs, and clinical course between Japanese patients and patients from Western countries. The most predominant sites of lesion in patients with MS were optic nerves and spinal cord, next were cerebral and brain stem. Cerebellum was least frequently involved.

In 1958 and 1959, previous population studies in 4 Japanese cities disclosed that Japan has a lower prevalence of MS than Western countries. Recent studies will be reported by Prof. Kuroiwa this afternoon, they show a similar prevalence rate in Japan (Fig. 1). Inspite of increase of neurologists and knowledge about the disease, Japan has a low prevalence rate of the disease. To disclose the secret of this low prevalence among the population of Japan would be a worthwhile challenge to pursue next.

Lastly, I would like to mention two distinguished neurologists who participated in the first epidemiological survey in the late 1950s.

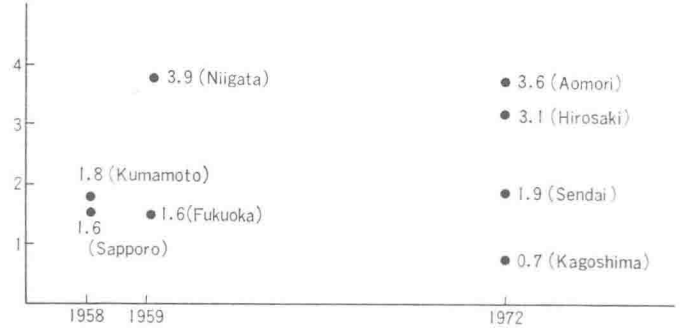

FIG. 1. Prevalence rate of MS in Japanese cities (per 100,000 population).

Dr. Douglas McAlpine (England), emeritus consultant to the Middlesex Hospital, and also honorary consultant physician to Maida Vale Hospital.

Dr. Hans H. Reese (U.S.A.), an emeritus professor of Neurology, Wisconsin University, who passed away in July, 1973. They made a great contribution and stimulated the development of Japanese Neurology, through his study of MS.

We would like to thank them and also emeritus Prof. Okinaka, Prof. Kuroiwa and Dr. Kurland of Mayo Clinic for their most outstanding contributions.