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AN EPIDEMIOLOGICAL STUDY OF SUBACUTE SCLEROSING PANENCEPHALITIS IN JAPAN, 1976

YOSHIOMI OKUNO

Department of Virology, Research Institute for Microbial Diseases, Osaka University, Yamada-kami, Suita, Osaka 565

TOORU NAKAO

Department of Pediatrics, Sapporo Medical College, Chuo-ku, Sapporo, Hokkaido 060

NAKAO ISHIDA and TASUKE KONNO

Department of Bacteriology and Department of Pediatrics, Tohoku University School of Medicine, Seiryo-cho, Sendai, Miyagi 980

HIROMICHI MIZUTANI

Virus Laboratory and Pediatric Clinic, The Kanto Teishin Hospital, Gotanda, Shinagawa-ku, Tokyo 141

TAKESHI SATO

Department of Neuropathology, Brain Research Institute, Niigata University, Asahimachi-dori, Niigata, Niigata 951

SHIN ISOMURA

Department of Pediatrics, Nagoya University School of Medicine, Showa-ku, Nagoya, Aichi 466

SHIGEHARU UEDA

Department of Bacteriology, Hyogo College of Medicine, Mukogawa-cho, Nishinomiya, Hyogo 663

ISAMU KITAMURA

Department of Pediatrics, Okayama University School of Medicine, Shikata-cho, Okayama, 700

MASARO KAJI

The First Department of Internal Medicine, Kurume University, School of Medicine, Asahi-cho, Kurume, Fukuoka 830

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SUMMARY The National Registry for subacute sclerosing panencephalitis (SSPE) of Japan was established in 1976 at the Research Institute for Microbial Diseases, Osaka University, under the auspices of the Ministry of Health and Welfare. By

March 1977, forty five clinically confirmed cases of SSPE were reported to the Registry, with onset of symptoms occurring between 1966 and 1976. Histories of measles were available in 42 of these cases. Thirty nine patients with known histories had measles prior to onset of SSPE and 3 had no history of measles illness. Twenty eight (71.8%) of the 39 patients had measles before the age of 2 years. All cases were 1 to 14 years old at the time of onset of SSPE and the mean interval between measles and SSPE was 6.1 years. One of the 3 cases with no history of measles was a recipient of measles killed vaccine, but no case of SSPE was reported among recipients of measles live, attenuated vaccine.

INTRODUCTION

Subacute sclerosing panencephalitis (SSPE) is a rare but fatal, degenerative disease of the central nervous system of children and adolescents (Sever and Zeman, 1968). Although measles virus has been isolated from the brain and lymphnodes of cases of SSPE (Baublis and Payne, 1968; Chen et al., 1969; Horta-Barbosa, Fuccillo and Sever, 1969; Horta-Barbosa et al., 1969; Katz, Oyanagi and Koprowski, 1969; Payne, Baublis and Itabashi, 1969; Kettyls et al., 1970; Horta-Barbosa et al., 1971; Degré, Vandvik and Hoving, 1972; Sato et al., 1972; Greenham et al., 1974; Ueda et al., 1975; Makino et al., 1977), the pathogenesis of SSPE is poorly understood. No effective therapy for SSPE is known.

In the United States, the National Registry for SSPE has been maintained since 1969 and its reports provide the most reliable data on the epidemiology of SSPE (Jabbour et al., 1972; Modlin et al., 1977). In Japan, Iizuka and Nishibori (1959) first reported a case of

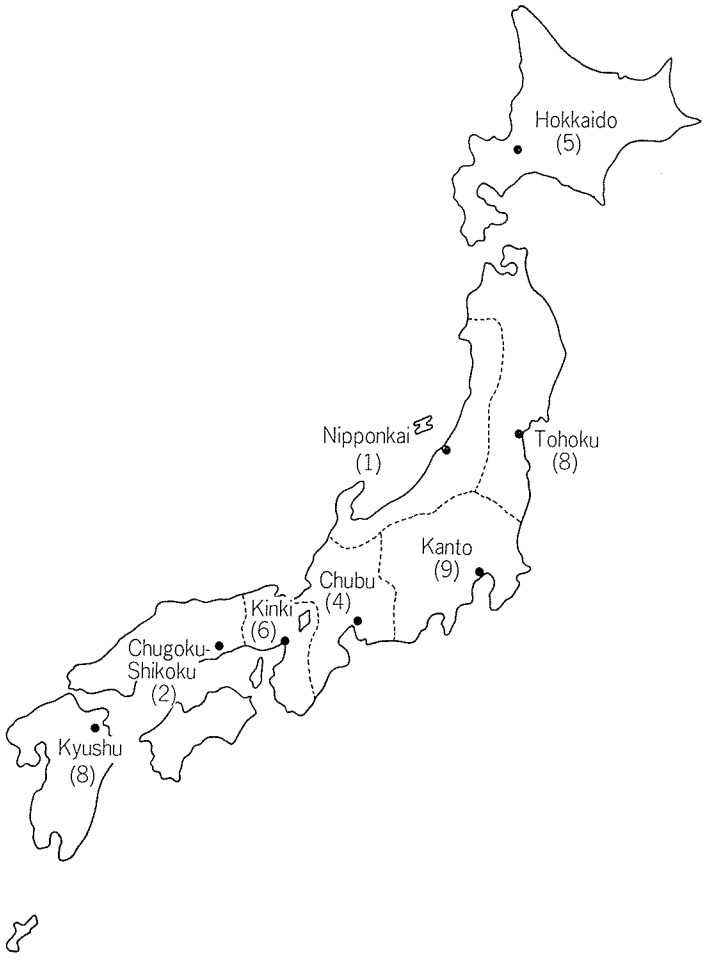

FIGURE 1. Distribution of cases of SSPE. Numbers in parentheses indicate numbers of cases.

inclusion body encephalitis of Dawson type in 1959. Several cases of SSPE have been reported since then, and about 20 cases of SSPE were collected by Mizutani and Nihei by 1975 (Mizutani and Nihei, 1975). However, there was no national registry for SSPE and the establishment of a surveillance system for SSPE was needed in connection with measles vaccination. Moreover, in 1975, Dr. G. M. Baer (CDC, Lawrenceville, Georgia, USA) suggested to one of the authors (Y. O.) that Japan and the USA should collaborate in a survey of SSPE. Therefore, we established the National Registry for SSPE in 1976 at the Research Institute for Microbial Diseases, Osaka University, under the auspices of the Ministry of Health and Welfare.

This report presents results of an epidemiological study on SSPE conducted from April, 1976 to March, 1977.

METHODS

The criteria for the diagnosis of SSPE reported by Jabbour et al. (1972) were followed.

For the survey Japan was divided into 8 regions: Hokkaido, Tohoku, Kanto, Nipponkai, Chubu, Kinki, Chugoku-Shikoku and Kyushu districts (Fig. 1); R. N., N. I. and T. K., H. M., T. S., S. I., S. U., I. K. and M. K., respectively, were made responsible for survey in these regions, while Y. O. took general control of the survey.

A questionnaire of a similar form to that of Schacher (1968) was sent to all pediatric department in hospitals of medium to large size throughout Japan. Patients with four or more of the criteria were registered.

RESULTS

In the 1976 survey for SSPE, 45 clinically confirmed cases of SSPE were recorded from 23 of the 48 prefectures in Japan (Table 1); there were more cases of SSPE in Hokkaido, Aichi and Osaka than in other regions.

The 45 cases of SSPE occurred during 1966 through 1976 (Table 2); 3 to 5 cases have been reported annually since 1969, except in 1971 and 1975 when 10 and 9 cases, respectively, were reported.

Measles histories were available in 42 (93.3%) of the 45 cases of SSPE. Among these 42 patients, 39 (92.9%) had histories of measles before the onset of SSPE, and among the latter, 28 (71.8%) had had measles before

TABLE 1. *Prefectural distribution of cases of SSPE*

Prefecture	No. of cases	Prefecture	No. of cases
Hokkaido	5	Aichi	4
Aomori	2	Osaka	4
Miyagi	2	Hyogo	2
Yamagata	2	Hiroshima	1
Fukushima	2	Kagawa	1
Niigata	1	Oita	1
Tochigi	1	Kumamoto	1
Gunma	1	Nagasaki	1
Chiba	1	Miyazaki	1
Saitama	3	Kagoshima	3
Tokyo	1	Okinawa	1
Kanagawa	2	Unknown	2
		Total	45

TABLE 2. *Year of onset of SSPE*

Year	No. of cases
1966	1
1967	0
1968	0
1969	3
1970	3
1971	10
1972	3
1973	4
1974	4
1975	9
1976	5
Unknown	3
Total	45

TABLE 3. *Age at onset of measles*

Age (year)	No. of cases
0	16
1	8
2	4
3	6
4	5
No history	3
Unknown	3
Total	45

TABLE 4. *Measles vaccine and SSPE*

Vaccine	No. of cases
Killed	1
Live	0
Not received	38
Unknown	6
Total	45

TABLE 5. *Age at onset of SSPE*

Age (year)	No. of cases
1	2
2	0
3	2
4	3
5	4
6	10
7	6
8	3
9	4
10	3
11	1
12	1
13	1
14	2
Unknown	3
Total	45

they were 2 years old (Table 3). One of the 3 patients without a history of measles illness had received a shot of killed vaccine at the age of 2 years. There were no cases of SSPE who had received measles live, attenuated vaccine (Table 4).

TABLE 6. *Time between measles and SSPE*

Time (years)	No. of cases
0	1
1	2
2	0
3	2
4	3
5	4
6	9
7	6
8	0
9	3
10	4
11	1
12	0
13	0
Unknown	10
Total	45

TABLE 7. *Sex of cases of SSPE*

Sex	No. of cases
Male	19
Female	23
Unknown	3
Total	45

All cases were between 1 and 14 years at the time of onset of SSPE and their mean age was 7.1 years (Table 5). The mean time between the onsets of measles and SSPE was 6.1 years (range, 1 to 11 years) (Table 6).

The male to female ratio of the cases was 1 to 1.2 (Table 7).

DISCUSSION

The first systematic survey for SSPE in Japan was carried out in 1976, and 45 clinically confirmed cases of SSPE were reported to the SSPE Registry from all over Japan. There

have been 3 to 5 cases reported annually since 1969, except in 1971 and 1975 when two to three times as many cases were reported in one year, for some unknown reason.

Of the 39 cases with histories of measles illness, 72% had had measles before the age of 2 years old. A similar trend was found in the United States (Jabbour et al., 1972; Modlin et al., 1977). One patient without a history of measles who contracted SSPE at the age of 5 years had received a shot of measles killed vaccine at the age of 2 years. As it can be denied that killed vaccine induced SSPE, this child may have had inapparent infection with measles virus at some time. No cases of SSPE were reported among recipients of measles live, attenuated vaccine in this 1976 survey.

In Japan, measles vaccination was begun in 1966, mostly by the combined use of killed (K) and live, attenuated (L) vaccines. Since 1971, only live, further attenuated (FAL) vaccine has been used, and during the past decade about half a million injects of KL or FAL vaccine have been given annually to children of over one year old. Modlin et al. (1977) reported that the mean interval between measles vaccination and the onset of SSPE was 3.3 years and that the incidence of SSPE following measles vaccination was 0.5 to 1.1 cases per million recipients. Five years have passed since the vaccination of at least half the 5.5 million children vaccinated in Japan, and fortunately no cases of SSPE among them have been reported.

Less than 50 cases of SSPE were found in this survey. Modlin et al. (1977) reported very few cases of SSPE among blacks, and Kuroiwa et al. (1977) reported that there were fewer cases of multiple sclerosis (MS) in Japan and Asian countries than in countries of white races. Therefore, it is conceivable that, as with MS, race or the HLA may contribute to the pathogenesis of SSPE in addition to measles virus.

Further continuous international surveillance will be necessary to understand and control SSPE.

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REFERENCES

Baublis, J. V. and F. E. Payne. 1968. Measles antigen and syncytium formation in brain cell cultures from subacute sclerosing panencephalitis (SSPE). Proc. Soc. Exp. Biol. Med. 129: 593–597.

Chen, T. T., I. Watanabe, W. Zeman and J. Meaky, Jr. 1969. Subacute sclerosing panencephalitis: Propagation of measles virus from brain biopsy in tissue culture. Science 163: 1193–1194.

Degré, M., B. Vandvik and T. Hovig. 1972. Subacute sclerosing panencephalitis: Isolation and ultrastructural characterization of a measles-like virus from brain obtained at autopsy. Acta Pathol. Microbiol. Scand. [B] 80: 713–723.

Greenham, L. W., D. B. Peacock, T. J. Hill, B. Brownnell and W. H. Schutt. 1974. The isolation of S.S.P.E. measles virus in newborn mice. Arch. Gesamte Virusforsch. 44: 109–120.

Horta-Barbosa, L., D. A. Fuccillo, W. J. London, J. T. Jabbour, W. Zeman and J. L. Server. 1969. Isolation of measles virus from brain cell cultures of two patients with subacute sclerosing panencephalitis. Proc. Soc. Exp. Biol. Med. 132: 272–277.

Horta-Barbosa, L., D. A. Fuccillo and J. L. Sever. 1969. Subacute sclerosing panencephalitis: Isolation of measles virus from a brain biopsy. Nature 221: 974.

Horta-Barbosa, L., R. Hamiltone, B. W. Witting, D. A. Fuccillo, J. L. Sever and M. L. Vernon. 1971. Subacute sclerosing panencephalitis: Isolation of suppressed measles virus from lymph-node biopsies. Science 173: 840–841.

Iizuka, R. and K. Nishibori. 1959. A case report of inclusion body encephalitis (Dawson). Seishin-Shinkei-gaku Zasshi 61: 1043–1052. [In Japanese]

Jabbour, J. T., D. A. Duenas, J. L. Sever, H. M. Krebs and L. Horta-Barbosa. 1972. Epidemiology of subacute sclerosing panencephalitis (SSPE). A report of the SSPE registry. JAMA 220: 959–962.

Katz, M., S. Oyanagi and H. Koprowski. 1969. Subacute sclerosing panencephalitis: Structures resembling myxovirus nucleocapsids in cells cultured from brain. Nature 222: 888–890.

Kettyls, G. D., H. G. Dunn, N. Dombsky and I. M. Turnbull. 1970. Subacute sclerosing panencephalitis: Isolation of a measles-like virus in tissue culture of brain biopsy. Can. Med. Assoc. J. 103: 1183–1184.

Kuroiwa, Y., T.-P. Hung, D. Landsborough, C. S. Park, B. S. Singhal, S. Soemargo, A. Vejjajiva and H. Shibasaki. 1977. Multiple sclerosis in Asia. Neurology 27: 188–192.

Makino, S., K. Sasaki, M. Nakagawa, M. Saito, Y. Shinohara, F. Goto and T. Okabe. 1977. Isolation and biological characterization of a measles virus-like agent from the brain of an autopsied case of subacute sclerosing panencephalitis (SSPE). Microbiol. Immunol. 21: 193–205.

Mizutani, H. and K. Nihei. 1975. SSPE in Japan. Presented at the 1975 symposium on slow virus infections, March 11–12, Tokyo.

Modlin, J. F., J. T. Jabbour, J. L. Witte and N. A. Halsey. 1977. Epidemiologic studies of measles, measles vaccine, and subacute sclerosing panencephalitis. Pediatrics 59: 505–512.

Payne, F. E., J. V. Baublis and H. H. Itabashi. 1969. Isolation of measles virus from cell cultures of brain from a patient with subacute sclerosing panencephalitis. N. Engl. J. Med. 281: 585–589.

Sato, T., K. Oguchi, T. Tsubaki, T. Kumanishi. Y. Doi, T. Sampe and H. Ito. 1972. Isolation of measles agent from a patient with subacute sclerosing panencephalitis and inoculation in animals. Shinkei-gaku Topics 2: 71–77. [In Japanese]

Schacher, S. A. 1968. An epidemiological approach to subacute sclerosing panencephalitis. Neurology 18 (part 2): 76–77.

Sever, J. L. and W. Zeman [ed.]. 1968. Proceedings of the conference on measles virus and subacute sclerosing panencephalitis. Neurology 18 (part 2): 1–192.

Ueda, S., Y. Okuno, Y. Okuno, Y. Hamamoto and H. Ohya. 1975. Subacute sclerosing panencephalitis (SSPE): Isolation of a defective variant of measles virus from brain obtained at autopsy. Biken J. 18: 113–122.