行政院國家科學委員會專題研究計畫　成果報告

台灣多發性硬化症患者之臨床分析及生活品質

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Introduction

Multiple sclerosis (MS) has a lower prevalence rate in Orientals than in Caucasians. The Japanese are by far the best studied of the non-Caucasoid populations. In Chinese, there have been reports from Hong Kong, mainland China, and Taiwan. From Taiwan, Hung et al.(1976) described 25 patients, including two autopsied patients. Tsai et al. reported 43 cases from Veterans General Hospital, Taipei in 2002. In this report, clinical findings of 100 patients in Taiwan with definite MS according to Poser's criteria and positive findings on magnetic resonance imaging have been reviewed. The aim of this report is to highlight the clinical course and pattern of presentation in the largest sample of cases managed so far in Taiwan.

During the past 10 years there have been unprecedented advances in the development of new disease-modifying therapies for multiple sclerosis (MS). The emergence of interferon-ß and glatiramer acetate that appear to alter the natural history of MS is encouraging. These agents were introduced to Taiwan in recent years.

We also present our preliminary results of interferon –ß treatment in patients with relapsing-remitting MS.

Material and methods

The study took place at National Taiwan University Hospital, Taipei, Taiwan. From January 1990 to April 2003, patients with clinically definite MS according to Poser et al.'s criteria and positive findings on MRI were selected. For the primary progressive (PP) form, the criteria recently proposed by Thompson et al. were adopted. All patients with other clinical conditions and/or other laboratory findings were excluded[e.g., lupus erythromatosus, Behcet's disease, Sjogren disease, vasculitis, leukodystrophy, lymphoma]. Demographic data, presenting symptoms, clinical course and pattern of progression were recorded. The clinical course was classified as relapsing-remitting (RR), PP and secondary progressive (SP). Disability was measured using the Expanded Disability Status Scale (EDSS), as described by Kurtzke.

At the end of December, 2002, 29 patients had used interferon –ß for different periods of times. Patients had been regularly treated for more than 12 months were included. All were diagnosed to have clinically definite RR MS and an expanded disability status scale(EDSS) scores of 0- 5. They had at least two relapses during the two years before treatment. All patients were treated with interferon –ß Ia (Rebif), 3×22 mcg /week. One patient received interferon –ß Ib (Betaferon) 3×8.0 MIU/week for two years and followed by Rebif. We compare the number of relapses and EDSS before and after treatment.

Results

There were 102 patients fulfilled the criteria. Among them, two were Caucasians and their data were not included. Women represented 83% of cases giving a gender ratio of 4.9:1 female:male. For the surviving patients, the mean age was 40.9 years(range 20-82). The mean age of onset for the entire group of 100 patients was 32.6 years (range 12-65). The RR form was the most common clinical presentation, with 83cases(83%) followed by SP with 14 cases(14%) and PP with 3 cases(3%). No patient had positive family history of the disease.

The most common presenting symptom was weakness in one or more limbs(48%). Table 1 shows the frequency of presenting symptoms for the whole group.

Table 1. Presenting symptoms

Symptoms	**Number**	**%**
Weakness	48	48
Sensory impairment	25	25
Sphincter disturbance	18	18
Visual impairment/optic neuritis	25	25
Vertigo/ataxia	13	13
Diplopia/ophthalmoplegia	8	8
Drowsiness, cognitive impairment	5	5
Seizure	1	1
Foix-Chavany-Marie syndrome	1	1

Two patients presented with a picture similar to acute disseminated encephalitis. The neurologic symptoms during the course of illness (including the presenting symptoms) are summarized in Table 2.

Table 2. Neurologic symptoms during the course of illness

Symptoms	**Number**	**%**
Weakness	84	84
Sensory impairment	54	54
Sphincter disturbance	25	25
Visual impairment/optic neuritis	45	45
Vertigo/ataxia	22	22
Diplopia/ophthalmoplegia	15	15
Drowsiness, cognitive impairment	7	7
Seizure	1	1
Foix-Chavany-Marie syndrome	1	1
Involuntary movements(tremor)	1	1
Parkinonism	2	2

The opticospinal form comprises 23%. The optic-spinal-brainstem type comprises 5%. 12% presented with recurrent myelopathy. Involvement of the optic nerve and spinal cord, with or without the brainstem, comprises 28% of our MS cases. Together, about 40% of patients showed predominant involvement of spinal cord.

Three patients expired, one due to gastric cancer and two due to conditions related to MS disabilities. For the surviving patients, The EDSS score can be determined in 84 patients. Table 3 shows the distribution.

Table 3 EDSS scores

EDSS	0	1	1.5	2.0	2.5	3.0	3.5	4	4.5	5.0	5.5	6	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0
No.	3	8	0	20	7	5	7	3	1	7	1	2	7	5	2	3	2	1	0	2

Most patient were ambulatory, 15.5% were wheelchair bound or bed ridden.

The treatment group included 12 female patients (80%) and 3 male patients (20%). The mean age was 32.1 y ± 2.5 (mean±SEM). The mean ages of female (33.5±2.8) and male (26.7±5.6) patients were not significantly different (P=0.298, t test). The median baseline annual relapses of female (1.75±1.4, median± IQR) and male patients (2±1.3) were not significantly different (P=0.825, Mann-Whitney U test). However the median baseline EDSS of female (3.5±1.0) was significantly higher than that of male patients (2.5±0.0, P=0.046, Mann-Whitney U test).

Table 4. Demographic data, relapse rate, and EDSS scores.

Case	Age	Sex	Relapses/24monthes	Relapses/follow-up period(months)	EDSS before	EDSS after
1	31	F	4	3/29	4.0	2.0
2	53	F	2	0/24	3.5	3.5
3	25	M	7	4/28	2.5	2.0
4	20	F	9	5/26	3.0	2.0
5	37	M	2	0/24	2.5	1.0
6	27	F	5	0/22	2.5	2.0
7	18	M	4	0/22	2.5	0
8	25	F	2	1/21	4.0	4.0
9	29	F	4	0/20	3.0	1.0
10	31	F	5	2/20	4.0	4.0
11	42	F	3	1/19	3.5	3.5

12	25	F	2	3/14	2.0	2.0
13	34	F	3	0/12	4.0	4.0
14	47	F	3	0/19	3.5	3.5
15	38	F	5	4/40	4.5	4.5

All of the 15 cases showed decreased annual relapses after treatment. There were 7 of 15 (47%) cases showed decreased EDSS score after treatment, the other 8 cases showed no change. The median annual relapses (0.6±1.2) was significantly lower than baseline annual relapses (2.0±1.3, P=0.004, Wilcoxon Signed-Rank Test). Of note, 7 of 15 cases remained relapse free in the treatment period. The median follow-up EDSS (2.0±2.0) was also significantly lower than baseline EDSS (3.5± 1.5, P=0.018, Wilcoxon Signed-Rank Test). By the comparison of median annual relapses and EDSS between baseline and follow-up results, the efficacy of treatment was quite significant in this study. Side effects were evaluated in 25 patients. Three patients had no side effects. Others complained of headache(7), fatigue(5), myalgia(3), nausea(2), poor appetite(2), and depression(1). These symptoms were generally mild and did not lead to cessation of usage.

Table 5. Descriptive Statistics for variables analyzed

Variables	N	Mean	Std. Dev.	Min	Max	Percentiles		
						25th	50th	75th
Baseline Annual Relapses	15	2.0	1.0	1.0	4.5	1.2	2.0	2.5
Follow-up Annual Relapses	15	0.8	0.9	0.0	2.6	0.0	0.6	1.2
Baseline EDSS	15	3.3	0.8	2.0	4.5	2.5	3.5	4.0
Follow-up EDSS	15	2.6	1.4	0.0	4.5	2.0	2.0	3.8
Follow-up Period (Months)	15	22.7	6.6	12	40	19.0	22.0	26.0
Age, y	15	32.1	9.8	18	53	25	31	38

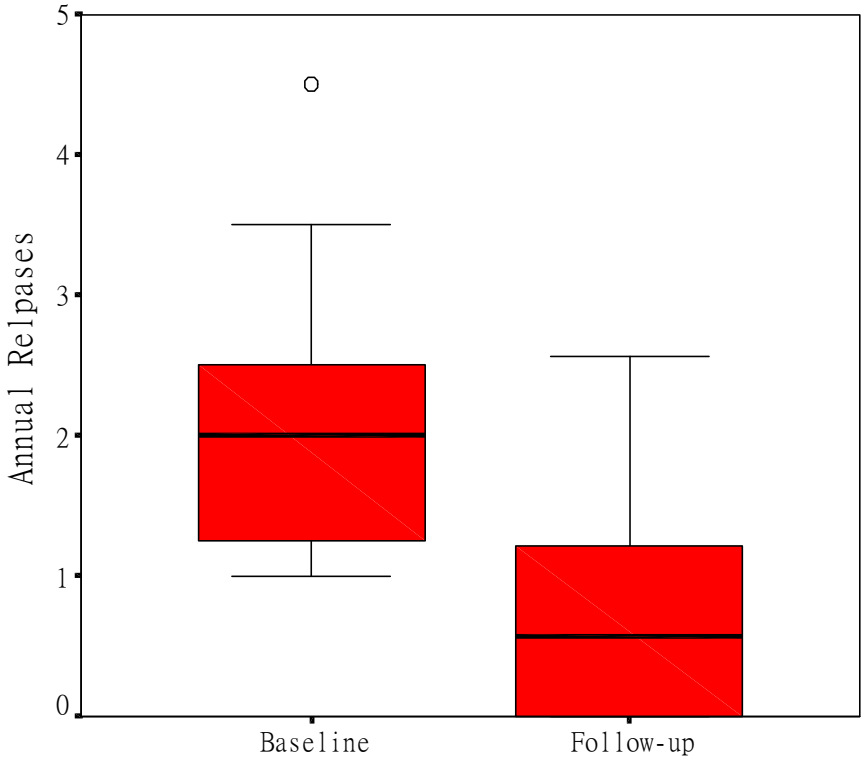

Figure 1. Boxplot of annual relapses for all 15 cases. (Cases with values between 1.5 and 3 box lengths from the upper or lower edge of the box will be considered as outlier.)

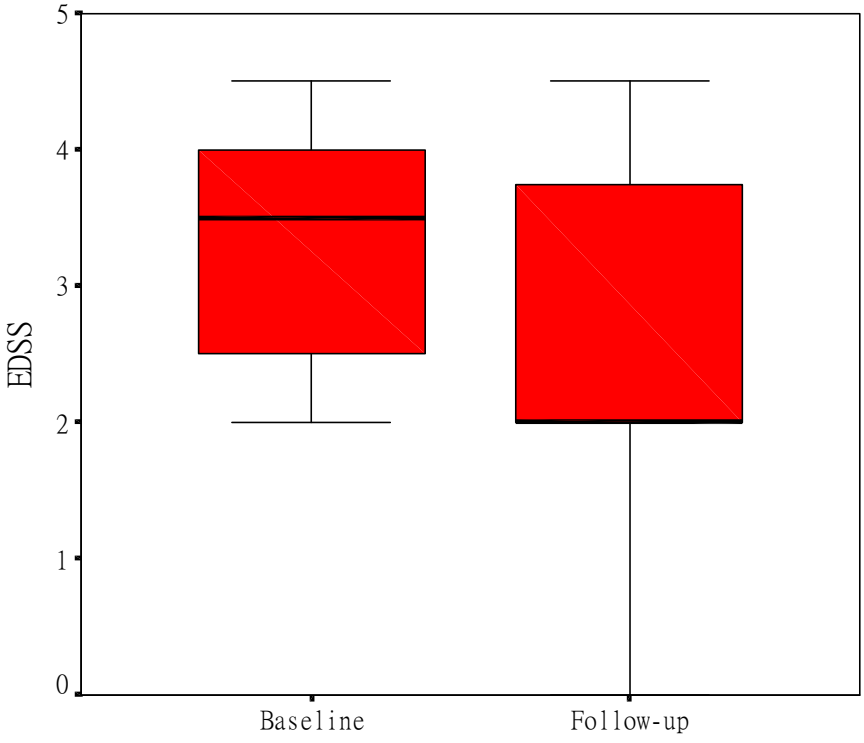

Figure 2. Boxplot of EDSS for all 15 cases.

Discussion

The clinical findings of 100 definite MS cases in Taiwan were reviewed. It is the largest sample of case managed so far in Taiwan. Taiwan is traditionally thought to be situated in a low risk zone for MS. There had been no national survey data on MS in Taiwan. However, MS is one of the "Serious Diseases" listed by the Bureau of National Health Insurance and patients can have medical expense reduction if they register. At the end of April, 2003, totally 450 patients were registered in this category. The population was 22,520,776 at the end of 2002. The prevalence rate is around 2.0 per 100,000 by using the registered data. It can be under-estimated because of under-registration. The figure is much lower than in western countries at similar latitudes. Yu et al (1989) studied multiple sclerosis amongst Chinese in Hong Kong and report a prevalence of 0.9/100000-with a similar clinical phenotype to other affected orientals. Hung (1982) reported the prevalence rates of the disease in Taipei, northern Taiwan for 1975 and 1980 were 0.8 and 0.9/100000 in a population of 1.9-2.2 million. At present, the current impression in Taiwan is that more cases are being diagnosed. This may be explained by increased survival, improved case ascertainment, increased disease awareness or improved laboratory and radiological diagnosis. The sex ratio(F/M) in our study is 4.9, which is higher than most published data.

RRMS is the most frequent type of presentation. In this study we found only 3% of patients with PPMS. SPMS comprises 14% of patients. The time from first attack to the progressive course ranged from 3-16years(average 9.64).

Involvement of the pyramidal system was the most common mode of presentation. By location, spinal cord was 35%, optic nerve 25%, brainstem 24%, cerebellum 1 %, and brain 18%. Three patients had optic nerve involvement plus other locations. The opticospinal form(23%), spinal form(12%), optic-spinal-brainstem (5%) comprises 40% of patients. The higher frequency of opticospinal form than in Western MS is confirmed in this series.

For patients receiving interferon beta, annual relapse rates were significantly reduced. The EDSS score was significantly lower. The side effect profiles were acceptable. The rationale for treatment with interferon beta is essentially the same in Chinese and Caucasians alike.

For the health related quality of life in MS patients, we are dealing with copyright issues and the data could not be revealed at present time.

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