DOES ASIAN MS FAVOR AN EXOGENOUS AGENT AS THE CAUSE?

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SUMMARY

Morbidity of MS in Japan was summarized as follows: 1) lower prevalence rates compared with those at similar latitude in the Western countries (about one tenth), 2) increase of the prevalence rates in the areas of higher latitude in Japan, except Okinawa Island, 3) higher rate (about 2 per 1oo,ooo) in Okinawa (latitude 26 N) compared with the adjacent part of Japan (about 1 per 1oo,ooo or below).

Evidently the geographical factor seen in Japan advocates the exogenous cause. The higher incidence in Okinawa also suggests a relation to exposure to the American population there since 1945 (exogenous cause).

The relative protection of the Japanese to MS, wherever their living places are, points to an endogenous protective factor(s) with regulatory function.

Clinical and pathological manifestations of the Japanese and other Asian MS often show hyperergic responses (acute or severe manifestations in visual impairment, spinal cord lesion, etc.). In CSF pictures increased pleocytosis or increase in total protein is observed. Considering the different relationship with HLA haplotypes from that of the western MS (in Japanese MS

no association with DW2), such hyperergic responses might be a modification of the same demyelinating disease as in the western MS.

I. INTRODUCTION

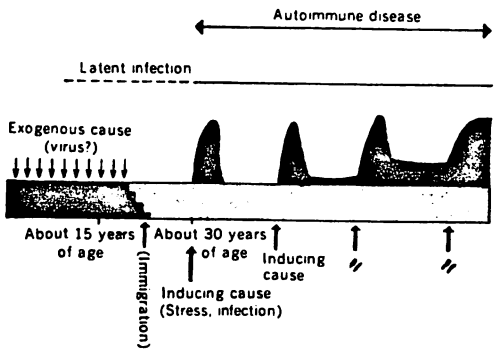
GENERAL MECHANISMS OF DEMYENATING PROCESSES IN MS

The etiopathogenesis of multiple sclerosis (MS) involves various factors and problems such as viral, immunological, metabolic, genetic, etc. It is quite difficult to amalgamate various salient facts into a single theory on pathogenesis of MS.

Fig. 1 shows the schematic illustration of the possible mechanisms of MS. In this figure, childhood exposure to the exogenous cause (based on the immigration studies), long latent period over 1o years, average age of onset at about 3o years, and multiphasic bouts are shown. Latent infection (broken horizontal line) changes to the solid line, which means clinical manifestation. During the process of clinical manifestation immunological processes (e.g. autoimmunization) might play a role.

Fig. 1

Mechanism of the Development of MS (Kuroiwa)

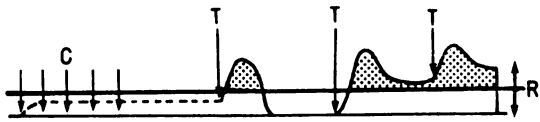


Acquisition of susceptibility to MS by living in the high risk areas seems to be established. However, most of the phenomena in the clinical phase are rather acute, with inflammatory processes in the CNS, which does not fit to the more general characteristics of slow virus infection. Rather, hypersensitization to the encephalitogenic factor(s) might be involved. Thus, Fig. 1 may satisfy various investigations, including epidemiological, clinical, virological, and immunological methods.

However, in order to analyze these complex circumstances, I would like to propose the schematic illustration in Fig. 2 in defining more precisely various factors.

Fig. 2

HYPOTHETICAL PATHOGENESIS OF MS



C : Causative factor (exogenous)
T : Trigger factors (exogenous)
Non-specific infection or stress
R : Regulatory factors (endogenous,
(slice level) exogenous)

In Fig. 2, basic causative factors (marked C), triggering factor(s) (T) and regulatory factor(s) (R) are separately shown. Triggering factor(s) (T) according to our clinical studies mostly seem to be exogenous, such as overwork (55%), psychic stress (38%), anorexia (46%), fever (26%), common cold (25%), surgery (5%), trauma (4%), etc. These stimuli may act on the immunological systems involved.

Regulatory factor(s) (R) may protect certain ethnic groups from MS, or they may modify the disease in terms of severity and acuteness.

The purpose of this paper is to analyse these factors utilizing the studies on Asian or Japanese MS which have been reported elsewhere (Kuroiwa et al.)[2-7].

II. EPIDEMIOLOGICAL STUDIES

1. Prevalence Rate Studies in Japan

Prevalence rate studies of MS in Japan were carried out by Okinaka, Kurland and Kuroiwa[8-9] revealing rates of 1.6 - 3.9 per 1oo,ooo population. Recent studies by the Multiple Sclerosis

Research Committee (Demyelinating Disease Research Committee) of Japan (chairman Y. Kuroiwa) in selected cities or areas of Japan show very similar results (Table 1). Prevalence rates for MS were lower by a factor of approx. 1o compared with those reported for Western areas of similar latitudes. In other degenerative diseases such as amyotrophic lateral sclerosis or myasthenia gravis, remarkable differences in the prevalence rates between the Japanese and the Caucasians have not been observed.

In other Asian countries, MS is also very rare[1o].

Table1 Prevalence rate of MS in Japan (/100.000)
(Japan Ministry of Health and Welfare
Demyelinating Disease Research Committee)

City	Latitude (N)	Investigator	Year	Population	Prevalence MS	ALS	MG
Asahikawa	44	Suwa	1975	323.000	2.5	1.2	
Aomori	41	Matsunaga	1978	250.000	3.6	2.0	3.7
Hirosaki	41	Matsunaga	1978	160.000	3.8	2.5	5.1
Gosegawara	41	Goto	1974	52.000	3.9		
Morioka	40	Mitsui	1977	225.000	4.0		
Sendai	38	Itahara	1972	575.000	1.9		
Kanazawa	37	Yamaguchi	1976	400.000	1.5	5.0	
Yonago	35	Takahashi	1979	124.000	2.4	3.3	7.5
Miyazaki	32	Araki	1979	251.000	0.8		
Kagoshima	32	Igata	1977	417.000	0.9	3.2	
Naha	26	Hika	1978	310.000	1.9	3.0	

2. Relationship with Latitude

In Fig. 3 prevalence rates are correlated to the latitude. There seems to be a clear relationship, rates being higher in the North and lower generally in the South. At 4o°N the prevalence rates were about 4 per 1oo,ooo and at 32°N the rates were about o.8. This North-South gradient may indicate the existence of exogenous grographical factor(s). Interestingly, in Okinawa the rate seems to be higher than expected from the latitude. Okinawa is a specific area in Japan. It was under the US regime from 1945 to 1972, and there is a large American base even today. Also there was a large

4. Comparison of MS and Behcet Disease (Neuro-Behcet Disease)[12]

It is interesting to compare the morbidity of MS and Behcet disease (neuro-Behcet) in the world. Both diseases are inflammatory ones affecting the CNS with remissions and exacerbations. In Japan the prevalence of MS is consistently lower compared to Western countries, as mentioned before. However, Behcet disease is more common in Japan than in Western countries, namely about 1o per 1oo,ooo population in the mainland of Japan (Shimuzu)[12]. Prevalence of neuro-Behcet (NB) can be estimated as 1-2 per 1oo,ooo (about half of MS) in Japan (Kuroiwa). On the other hand, in the Western countries NB is extremely rare, and there are no statistics on the frequencies.

Behcet disease is rare in Okinawa and in Hawaiian Japanese[14]. This may indicate some difference in the causative and regulatory factors in Behcet disease and in MS. Consistently lower prevalence of Asian MS without geographical difference may show strong endogenous suppression, while in Behcet (neuro-Behcet) disease exogenous factors are more effective. Further comparative studies might be important.

III. CLINICAL AND PATHOLOGICAL FEATURES OF ASIAN MS

Comparison of clinical features of MS among the various ethnic groups is very difficult due to various biases. There can be no doubt, however, that racial or ethnic factors do influence the development of MS[1,5,6,1o,15,17].

Common facts in these reports are 1) rarity of MS among Asian, and 2) if once affected, relatively severe visual impairment, 3) frequent acute transverse myelitis, 4) common painful tonic seizures, etc.

We have compared the clinical features of MS of various nationalities utilizing the same coding sheet used for the Japan National Survey (Kuroiwa, et al.)[4] and for Asian MS Survey[5,1o,15]. The results are shown in Table 2.

Some similarity of features such as age of onset, sex ratio, average duration, frequency of acute onset, ratio of remissions and exacerbations is obvious. However, there also are remarkable

Table 2

NATURAL HISTORY OF MS IN CAUCASIANS AND ORIENTALS

	Kyushu Univ. (83)*	Japan Nationwide (1084)	Hawaii (Oriental) (15)	Hawaii (Caucasian) (25)
Sex ratio (M / F)	1 : 1.1	1 : 1.3	1 : 2.8	1 : 3.2
Age at onset (mean)	32	33	31	30
Duration (mean, years)	5	6	12	12
Acute onset (%)	69	47	86	69
Remissions and exacerbations (%)	78	74	80	76
1. Optic				
Severe visual loss	?	30%	40%	4%
2. Spinal				
Acute transverse myelopathy	39	?	67	12
Spinal sensory level	48	?	67	24
Painful tonic seizure	16	12	13	4
3. Optic-(brainstem-) spinal form	51	?	80	16
"Devic syndrome"	6	8	13	0

differences, e.g. with respect to severe visual impairment and severe spinal cord lesion (transverse myelitis). Devic's syndrome is sometimes seen in the Oriental group, but not in the Caucasian. These data indicate that Asian MS tends to show more severe demyelinating responses than the Western type.

An increase of total protein beyond 1oo mg/dl was occasionally observed in Japanese MS, which is very rare in the Caucasian MS (less than 1%)[1].

In Asian MS, there are severe necrotic lesions besides the typical MS plaques[5,18]. Two autopsy cases in Taiwan Chinese exhibited severe demyelination[16].

Thus it can be concluded that hyperergic responses in the demyelinating processes are more common among the Asian MS.

IV. IMMUNOGENETIC COMPARISON

Western MS tends to be associated with HLA haplotypes, especially with DW2. In collaborative studies with Drs. Naito and Sasazuki, the Japanese MS did not show association with HLA A3, B7 nor DW2[1,7,8,19]. Such difference in the association with HLA between Japanese and Western MS might explain the modified features of demyelinating responses.

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