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ORIGINAL COMMUNICATION

Multiple sclerosis in Japan appears to be a milder disease compared to the UK

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Abstract Multiple sclerosis (MS) is relatively common in the West, but rare in Japan. In the literature, there are few comparative data regarding disease severity throughout the world. The objective of this study was to compare disability in patients from a UK and a Japanese MS cohort. We retrospectively analysed the clinical features of patients with MS from a UK and Japanese MS centre. The Multiple Sclerosis Severity Score (MSSS), which adjusts the Expanded Disability Status Scale score according to disease duration, was used as a marker of disease severity. One thousand one hundred forty-eight UK patients and 104 Japanese patient were identified representing the relative national prevalence. Demographics and disease duration did not differ between the groups. Median MSSS was significantly different between the two groups (Japan 3.34 vs. UK 5.87, $p < 0.001$). Primary progressive MS was more common in the UK (12.9 %) than in the Japanese cohort (3 %, $p = 0.044$). The majority of Japanese patients (83.7 % vs. UK 17 %) had been exposed to disease modifying treatments (DMTs). Exposure to DMTs did not show a significant effect on disability. In conclusion, this study suggests that MS in Japan may be associated with less disability than in UK. More Japanese patients were treated with DMTs. Differences in treatments do not seem to explain the disparity in disability severity. This suggests either genetic or environmental influences on disease severity.

Keywords Multiple sclerosis · Prognosis · Disability · Disease modifying treatments

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Introduction

Multiple sclerosis (MS) is a relatively common neurological condition, mainly affecting young adults and characterised by inflammatory plaques of demyelination within the central nervous system. Damage is thought to be primarily auto-immune T cell mediated [1, 2]. However, the trigger for damage is unknown, but many genetic and environmental factors have been hypothesised. Clustering of disease within families suggests a genetic component which is strengthened with multiple HLA loci being the focus of genes associated with increased susceptibility. Reduced levels of vitamin D have been implicated as a trigger [3] as well as infective factors such as previous exposure to Epstein–Barr virus (EBV) [1, 4].

Epidemiological studies have established the variation in prevalence throughout the world with higher rates seen

in the west [5] than the east, and in regions further away from the equator. However, this generalisation hides parts of the world, such as the New Zealand Maori population in whom the prevalence is very low. It is therefore likely an overriding genetic factor or local environmental trigger between different racial or ethnic groups exists to determine susceptibility. Furthermore, individuals who migrate generally take on the incidence risk of their new location provided they move before early adulthood.

The prevalence in England has been estimated to be approximately 120–180 per 100,000 population [6], and is significantly higher than in Japan (7.7 per 100,000, including neuromyelitis optica [NMO]) [7–9] where it is believed to be rising and a north–south gradient is also developing [7, 9]. As far back as 1977, lower susceptibility was demonstrated in Americans of Japanese descent compared to Caucasian, American born individuals [10]. Traditionally, a high frequency of optic nerve and bilateral visual defects has been suggested as characteristic of MS in Japan. However, most of these patients are now recognised to have NMO in Japan [7, 11–13].

Previous studies have characterised MS prevalence in different parts of Asia [14], but there are few comparative data regarding disease severity throughout the world. Anecdotal evidence from our clinical practice raises the question as to whether patients in Japan develop less disability over time. We aimed to quantify this and to compare levels of disability between individuals with MS in the UK and in Japan.

Methods

This retrospective study used data collected from two specialist centres in the UK (John Radcliffe Hospital, Oxford) and Japan (Tohoku University Medical School, Sendai). The Oxford Multiple Sclerosis Database holds anonymous data on MS patients of our region whilst similar data have been recorded from clinical notes in Sendai. Both databases contained patients with MS only and excluded those with NMO. We included patients who fulfilled the diagnosis of clinically definite MS, according to Poser criteria [15], seen up until June 2013. Data were collected for patients' date of birth, onset date of MS, exposure to disease modifying treatments (DMTs) and expanded disability status scale (EDSS) score. Where more than one EDSS score was available, the most recent was used. EDSS has been demonstrated as a validated measure of disability; however, it is only a snapshot of disease at a certain point in time [16]. The Multiple Sclerosis Severity Score (MSSS) is a number generated from the EDSS and number of disease years at that point and ranks the patient within a standardised MS population [17]. It is expected to remain stable over time for an individual patient and provides a reflection of disease severity with higher scores being given if patients have taken a shorter time to reach a particular level of disability. The score is automatically generated by inputting EDSS values into freely available software and allows comparison between two or more cohorts of patients [18–20]. EDSS and MSSS comparisons were made between both cohorts as whole groups as well as stratifying by age of onset.

Because there was a higher proportion of primary progressive patients in the UK cohort, we also analysed data for the relapsing remitting (RR)/secondary progressive (SP) cohort separately.

Statistical analysis was performed with IBM SPSS v20.0 and the MSSS software. Comparative analysis of median values was obtained and Mann–Whitney U test was used to compare groups. Two-way ANOVA was used to assess the effect of ethnicity and exposure to DMTs on disability. Significance was determined at the 95 % confidence interval with $p < 0.05$.

Results

Whole cohort

A total of 1,252 patients were identified between the two cohorts with at least one EDSS score recorded after the onset. One hundred and four of these were Japanese patients (all of Japanese ethnicity) and 1,148 UK patients were identified from the UK database. There were significantly more PP patients in the UK cohort (12.9 % in UK cohort vs. 3 % Japan cohort, $p = 0.044$) and more patients treated with DMTs in the Japanese cohort. Sex, age of onset and disease duration were comparable and none was significantly different (Fig. 1).

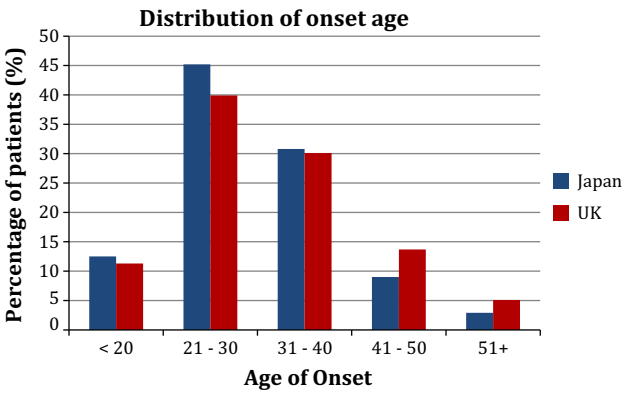

Fig. 1 Comparison of onset age between UK and Japanese groups. Age of onset was comparable in the UK and Japanese whole cohorts. Older age of onset (>41 years) was more common in the UK cohort although this was not significant ($p = 0.47$)

Table 1 Demographics and comparison of disability between the UK and Japanese whole cohorts

	UK	Japan
N	1,148	104
Female, %	73	75
Median age onset (IQR)	30.0 (24.0–38.0)	29.0 (24.0–36.0)
Treatment, %	17	83.7
Primary progressive patients, %	12.9	3
Median disease duration (IQR)	10.0 (4.0–17.0)	9.0 (4.0–15.0)
Median EDSS (IQR)*	5.0 (2.0–6.0)	2.0 (1.0–4.0)
Median MSSS (IQR)*	5.9 (2.6–7.9)	3.3 (1.8–5.7)

* Significant difference between UK and Japanese cohorts $p < 0.001$

Table 2 EDSS spread across the Japanese and UK cohorts

EDSS	Japan (%)	UK (%)
≤2	51	27.6
2.5–4	29.8	18.5
4.5–6	8.7	25.7
≥6.5	10.5	28.2

Older age of onset (>41 years) was more common in the UK cohort although this was not significant ($p = 0.47$), and this was related to more primary progressive patients in the UK cohort in this age of onset group.

Median EDSS for Japanese patients (2.0) was significantly lower than UK patients (5.0) ($p < 0.001$). Median MSSS was also lower in Japanese patients (3.34 vs. UK 5.87, $p < 0.001$) (Table 1).

Only 10.5 % of Japanese patients had reached EDSS 6, in comparison to 28.2 % of UK patients. In fact, the majority of Japanese patients (80.8 %) had EDSS scores of 4 or less (Table 2).

Relapsing cohort

Because there were more PP patients in the UK cohort (which is recognised to be associated with a poorer prognosis over time), we re-analysed the data for the RR/SP cohort alone.

Again the UK and Japanese cohorts were matched for proportion of female (Japan 76 % vs. UK 75 %), median age of onset (Japan 28 years vs. UK 29 years), distribution of age of onset and median disease duration (Japan 9 years vs. UK 10 years) (Table 3).

Median EDSS and MSSS were significantly higher in UK cohort (EDSS 4.0, MSSS 5.2) compared with the Japan cohort (EDSS 2.0, MSSS 3.3), even when grouped according to age of onset (Fig. 2).

DMTs

A much higher proportion of Japanese patients had been exposed to DMTs (83.7 % vs. UK 17 % in the whole cohort, 83.2 % vs. UK 22.6 % in the RR/SP cohort alone).

Table 3 Demographics and comparison of disability between the UK and Japanese RR/SP cohorts

	UK	Japan
Female, %	75	76
Median age onset (IQR)	29.0 (24.0–36.0)	28.0 (24–35.5)
Treatment, %	22.6	83.2
Median disease duration (IQR)	10.0 (4.0–17.0)	9.0 (3.5–15.0)
Median EDSS (IQR)*	4.0 (2.0–6.0)	2.0 (1.0–3.5)
Median MSSS (IQR)*	5.2 (2.4–7.6)	3.3 (1.7–5.4)

* Significant difference between UK and Japanese cohorts $p < 0.001$

A univariate analysis of variance (two-way ANOVA) was conducted on the whole cohort to examine the effect of ethnicity, exposure to DMTs and their interaction on disability, measured as MSSS. There was a statistically significant main effect for ethnicity [$F(1, 1{,}248) = 17.37$, $p < 0.005$]. The main effect for treatment [$F(1, 1{,}248) = 0.011$, $p = 0.915$] and the interaction effect [$F(1, 1{,}248) = 0.480$, $p = 0.489$] did not reach statistical significance.

We can conclude there was not a statistically significant interaction between the effects of ethnicity and exposure to DMTs on MSSS.

Discussion

Our results suggest that Japanese MS patients living in Japan may have milder disease than MS patients in the UK. This may be partly related to a lower proportion of PP patients in the Japanese cohort, as already reported [21]. However, even in the relapsing cohort, median EDSS and MSSS scores are consistently higher in the UK group within all age groups, and also when taking into consideration DMTs. This translated into a much smaller proportion of Japanese patients having ambulatory difficulties over a similar median duration of disease.

A recent study noted similar demographics in a Japanese cohort with similar average EDSS (2.6) and age of onset (28.3 years) [13]. In contrast to our findings, three previous

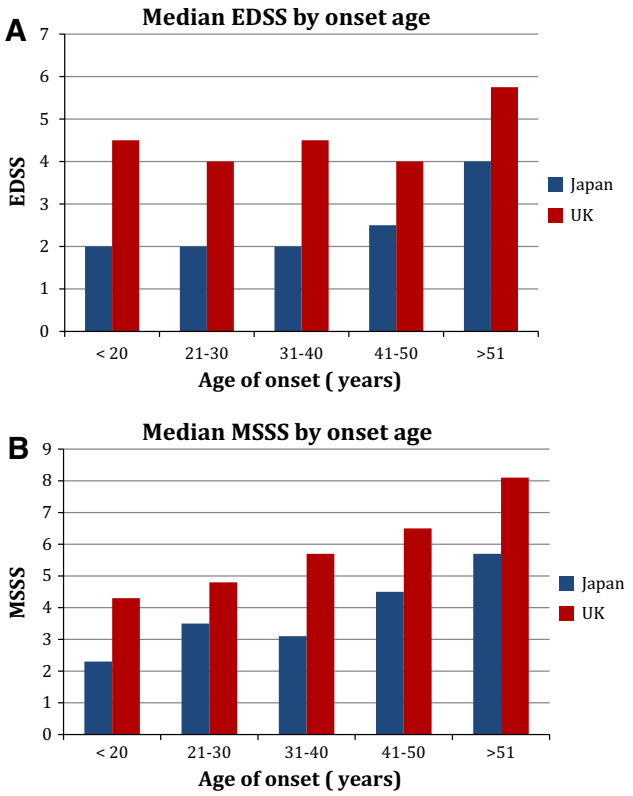

Fig. 2 Distribution of median EDSS and MSSS between UK and Japanese RR/SP cohorts stratified by age of onset. Median EDSS (**a**) and MSSS (**b**) were significantly higher in UK cohort (EDSS 4.0, MSSS 5.2) compared with the Japan cohort (EDSS 2.0, MSSS 3.3), even when grouped according to age of onset

Asian studies have suggested a worse MS outcome than reported in Caucasian population [22–24]. However, these studies did not include specific laboratory tests for NMO [23, 24], or only tested patients for NMO IgG and not for AQP4 Ab [22]. This could have lead to a misdiagnosis of MS instead of NMO, which is now recognised to have a poorer prognosis [25]. Studies that do not differentiate between MS and NMO are likely to include more NMO cases in Asian populations where MS is rare and NMO relatively more common and the opposite situation occurs in western populations. Our cohorts specifically excluded patients with NMO, ensuring we were comparing outcome in MS cohorts only and our study reports differences across ethnic groups living in two different countries. Thus, genetic and environmental factors are both possible influences of our observed outcome. Migration studies have previously demonstrated an independent environmental effect on the risk of developing MS [26].

The difference in the proportion of treated patients between the two cohorts is an interesting observation but difficult to draw conclusions from. Only limited availability of DMTs was present in the UK until 2002 when all three beta-interferon products and glatiramer acetate became available for all patients with two relapses in the prior 2 years. These national guidelines may explain why higher disability scores were noted in those UK patients who received DMTs compared to untreated patients, due to selection of patients with more active disease. In Japan, Iβ-1b was available from 2000, Iβ-1a from 2006 and similar eligibility criteria were used until around 2006 when a single relapse allowed their prescription and this may have led to milder patients being treated. Median disease duration at start of treatment was shorter in the Japanese patients than in the UK ones (2.4 vs. 5.9 years) and this supports the observation of milder patients earlier in the disease course receiving DMTs in the Japanese cohort compared to those not on DMTs, and the opposite observation in the UK cohort. However, the MSSS was still greater for the UK treated and untreated groups stratified by age of onset, when compared to the Japanese cohorts (Suppl. Table and Suppl. Figure 1).

There are limitations to our results, most notably the discrepancy in sample sizes. Although the sample sizes reflect to a large degree the difference in prevalence between the two countries, small samples increase the risk of both type 1 and 2 errors. Second, considering the retrospective nature of the study, we cannot rule out a referral/ascertainment difference between the two centres although we were unable to identify any obvious bias. Both centres take all MS patients within their immediate catchment area, and a selection within their wider catchment area (of 1.5–2 million population). The Japanese unit tends to follow-up patients until they are unable to attend hospital, whereas more disabled patients in Oxford might be seen in a separate Neurorehabilitation Unit. Thus, if anything one might expect more of the disabled patients would be seen in the Japanese centre. Other limitations are the use of the non-linear EDSS scale and the variability in its use across doctors. This is more of an issue at short follow-up times at lower EDSS levels but is less of a problem when patients are followed up over longer periods and at higher EDSS values. It is reassuring that our patients were fairly well matched for disease duration distributions, but we also used the MSSS as a tool which can adjust for the effects of disease duration on EDSS more accurately [20, 27]. This scale may be less reliable over shorter disease durations due to greater variability.

To conclude, we have identified significantly more PP patients in a UK cohort than in a Japanese one. Independently to this, we have observed a difference in disability severity which does not appear to be explained by treatment differences. Taken with similar results in NMO patients [28], this further supports the presence of genetic or environmental factors influencing disease phenotype. Further studies to confirm our findings in other cohorts are required

as well as studies of 'migrated' patients from or to Japan to distinguish the genetic from the environmental influences.

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Conflicts of interest Dr. Piccolo reports no disclosures. Dr. Kumar reports no disclosures. Dr. Ichiro Nakashima has served on the scientific advisory boards for Biogen Idec Japan and Novartis Pharma, has received funding for a trip and speaks from Biogen Idec Japan, Tanabe Mitsubishi, and Novartis Pharma, has received grant support from LSI Medience Corporation. Dr. Misu has received speaker honoraria from Bayer Schering Pharma, Biogen Idec Japan, Mitsubishi Tanabe Pharma Corporation, Asahi Kasei Medical Co., and Astellas Pharma Inc. and has received research support from Bayer Schering Pharma, Biogen Idec Japan, Asahi Kasei Kuraray Medical Co., The Chemo-Sero-Therapeutic Research Institute, Mitsubishi Tanabe Pharma Corporation, Teijin Pharma, and Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Technology, and the Ministry of Health, Labor and Welfare of Japan. Dr. Kong reports no disclosures. Dr. Wakerley has been sponsored by Novartis in the past. Dr. Ryan reports no disclosures. Ana Cavey is the Coloplast Neurogenic Nurse Advisory Board March 2014. Dr. Fujihara serves on scientific advisory boards for Bayer Schering Pharma, Biogen Idec, Mitsubishi Tanabe Pharma Corporation, Novartis Pharma, Chugai Pharmaceutical, Ono Pharmaceutical, Nihon Pharmaceutical, Merck Serono, Alexion Pharmaceuticals, Medimmune and Medical Review; has received funding for travel and speaker honoraria from Bayer Schering Pharma, Biogen Idec, Eisai Inc., Mitsubishi Tanabe Pharma Corporation, Novartis Pharma, Astellas Pharma Inc., Takeda Pharmaceutical Company Limited, Asahi Kasei Medical Co., Daiichi Sankyo, and Nihon Pharmaceutical; serves as an editorial board member of Clinical and Experimental Neuroimmunology (2009–present) and a advisory board member of Sri Lanka journal of Neurology; has received research support from Bayer Schering Pharma, Biogen Idec Japan, Asahi Kasei Medical, The Chemo-Sero-Therapeutic Research Institute, Teva Pharmaceutical, Mitsubishi Tanabe Pharma, Teijin Pharma, Chugai Pharmaceutical, Ono Pharmaceutical, Nihon Pharmaceutical, and Genzyme Japan; is funded as the primary investigator (#26293205, 2014–2016) and the secondary investigator (#22229008, 2010–2015) by the Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Technology of Japan and as the secondary investigator by the Grants-in-Aid for Scientific Research from the Ministry of Health, Welfare and Labor of Japan (2010–present). Dr. Palace is partly funded by highly specialised services to run a National congenital myasthenia service and a neuromyelitis service. She has received support for scientific meetings and honorariums for advisory work from Merck Serono, Biogen Idec, Novartis, Teva, Chugai Pharma and Bayer Schering, and unrestricted grants from Merck Serono, Novartis, Biogen Idec and Bayer Schering. Her hospital trust receives funds for her role as clinical lead for the RSS, and she has received grants from the MS society and Guthie Jackson Foundation for unrelated research studies. She is a board member for the charitable European MS foundation 'The Charcot Foundation' and on the steering committee for a European collaborative MS imaging group 'MAGNIMS'.

Ethical standard This study fulfilled the local ethical requirements.

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