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Progressive Onset Multiple Sclerosis: Demographic, Clinical and Laboratory Characteristics of Patients With and Without Relapses in the Course

Bahar KAYMAKAMZADE[1], Ahmet Kasım KILIÇ[2], Aslı TUNCER KURNE[3], Rana KARABUDAK[3]

[1]Department of Neurology, Near East University Faculty of Medicine, Nicosia, Cyprus
[2,3]Department of Neurology, Hacettepe University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Amaç: Primer progresif multipl skleroz (PPMS) ve progresif relapsing multipl skleroz (PRMS) başlangıçtan beri olan progresyon ile karakterize MS tipleridir. Nadir görülmelerinden dolayı, literatürde diğer MS formlarına göre daha az bilgi bulunmaktadır. Bu çalışmanın amacı progresif başlangıçlı MS (PBMS) hastalarında klinik ve laboratuvar özelliklerini ortaya koymaktır.

Yöntem: PBMS hastaları 2010–2014 yılları arasında değerlendirilip demografik, klinik özellikleri ve beyin omurilik sıvısı (BOS) bulguları belirlendi.

Bulgular: Otuz iki PBMS hastası ile ilgili veriler değerlendirildi. Hastalık seyri 24 hastada relaps olmadan (PPMS), sekiz hastada ise relapslı progresifti (PRMS). Kadın/erkek oranı tüm grupta 1'di. Ortalama başlangıç yaşı tüm grup için 40 (23–55) yaştı. Gruplar arasında hastalık başlangıç yaşı ortancası anlamlı farklı bulunmadı (p=0,053). En sık prezantasyon belirtisi motor bozukluklardı. Relapslar tüm hastalarda hastalığın ilk 10 yılında görüldü. BOS analizinde oligoklonal bant pozitifliği ve artmış IgG indeksi açısından gruplar arasında fark saptanmadı (p=0,938, p=0,058). Hastalık süresi her iki grupta da benzer olduğu halde, PPMS grubunda değerlendirme sırasında ortanca EDSS skoru daha yüksek bulundu (p=0,020).

Sonuç: Çalışmamız Türk PBMS hastalarının klinik seyir ve laboratuvar bulgularına odaklanmış ilk çalışmadır. İki grubun klinik ve laboratuvar bulgularının karşılaştırılması benzer sonuçlar göstermiştir. Gruplar arasında hastalık başlangıç yaşı ve artmış IgG indeksi açısından farklılık olup olmadığını netleştirmek için gelecekte daha geniş örneklemli çalışmalar yapılması gerekmektedir.

Anahtar Kelimeler: kronik progresif multiple skleroz, multipl skleroz, primer progresif multiple skleroz, beyin omurilik sıvısı

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INTRODUCTION

Multiple sclerosis (MS) is a common and chronic inflammatory disease of the central nervous system (1). It is the most disabling disease of young adults. The main clinical subtypes of MS are relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS). The RRMS is characterized by attacks of acute neurological deterioration (relapses), followed by partial or complete recovery (remission) and accounts for 85% of MS patients. 60–70% of patients with RRMS switch to SPMS which is characterized by progressive deterioration over months or years. In about 10–15% of MS patients, the disease starts with progressive neurological impairment, and has a constant progression from onset with or without relapses (2). Primary progressive MS (PPMS) and progressive relapsing MS (PRMS) are the subtypes of progressive onset MS. PPMS patients have progressive disease without relapses. PRMS is diagnosed when a patient with at least one year of progressive onset MS experiences one or more relapses. Approximately 15% of all MS patients show progressive disease course, and 28% of progressive onset MS patients was reported as having relapses as PRMS (3). Because of the rare prevalence of progressive onset forms of the disease, the knowledge is less than other forms in the literature. The influence of genetic factors and geographical localization are well known in the course of MS (4–6). Hence, the studies exhibiting the characteristics of the disease in a population are valuable. The aim of this study is to exhibit the demographic, clinical properties and characteristics of the cerebro-spinal fluid (CSF) analysis of progressive onset Turkish MS patients (PPMS and PRMS) followed up in our tertiary care neuroimmunology unit.

METHODS

Patients with progressive onset MS were evaluated between 2010 and 2014. Progression was defined as continual worsening of symptoms, progressive accumulation of disability for a period of at least one year. Patients who met revised McDonald's 2010 criteria for MS with progression from onset were included the study. The diagnosis required one year of disease progression (retrospective or prospective), and at least two of the following three criteria:

1. Evidence for dissemination in space (DIS) in the brain based on ≥1 T2 lesions at least one area characteristic for MS (periventricular, juxtacortical or infratentorial).

Correspondence Address: Bahar Kaymakamzade, Department of Neurology, Yakın Doğu University Faculty of Medicine, Nicosia, Cyprus • **E-mail:** bkaymakamzade@yahoo.com
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2. Evidence for DIS in the spinal cord based on ≥2 lesions in the cord.
3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index) (7).

Exclusion criteria included history of MS relapse in the first year of the disease, pure cerebellar progressive syndrome pure visual progressive syndrome or a pure cognitive progressive syndrome, history or evidence of vasculitis, any rheumatologic or autoimmune disorder, presence of cervical spinal cord compression on screening magnetic resonance imaging (MRI), relevant history of vitamin B12 deficiency. We assessed demographic and clinical characteristics, including neurological status evaluation with Kurtzke Expanded Disease Status Scale (EDSS), findings on evoked potentials (P100 latency used for evaluation of visual evoked potentials (VEP)) and CSF analyses (protein, glucose, IgG index, oligoclonal band (OCB)) were recorded. Brain and spinal MRI results were analysed by an experienced clinician in neuroimmunology unit confirming the final diagnosis. Patients were classified into two groups according to the existence of relapses as: PPMS and PRMS. Relapses were defined as a sudden onset of new neurological deficit of persisting minimum 24 hours without any precipitating infectious disease. The medical ethical committee of Hacettepe Üniversity approved the study and written informed consent was obtained from all participants.

Statistical Analysis

Descriptive statistics were performed and demonstrated in Table 1. The Mann-Whitney U test was used to compare continuous variables between groups. Pearson or Fisher's exact test was performed for categorical variables. Accepted as a level of significance was $\alpha<0.05$. All computations were performed using SPSS 18 software (SPSS Inc., Chicago, IL, USA).

Table 1. Demographic, clinical and laboratory characteristics of groups

	PPMS (no: 24)	PRMS (no: 8)
Age (median, year) (max-min)	52.5 (31–65)	44.5 (34–50)
Female/Male ratio	1.18	0.6
Age at the onset (median, year) (max-min)	41.5 (23–55)	37 (24–44)
Symptom of onset: no.		
Motor disturbances	13	5
Sensory disturbances	3	2
Cerebellar imbalance	5	0
Diplopia or other brain stem symptoms	2	1
Bladder dysfunction	1	0
Optic neuritis	0	0
Duration of Disease (median, year) (max-min)	7.5 (2–26)	9 (2–13)
Symptom onset to diagnosis time (median, year) (max-min)	5 (1–32)	2.5 (2–12)
EDSS (median, year) (max-min)	6 (1.5–9)	3.5 (2–7.5)
CSF data (available PPMS: 17 PRMS: 8)		
Oligoclonal band positivity: no. (%)	13 (76)	6 (75)
Elevated IgG index: no. (%)	4 (23)	5 (62)
Electrophysiological studies		
Prolonged P100 latencies in VEP: no. (%) (available PPMS: 13 PRMS: 5)	7 (53)	4 (80)
SEP: no. (%) (available PPMS: 8 PRMS: 2)	7 (87)	2 (100)

CSF, cerebrospinal fluid; EDSS, expanded disability status scale; IgG, immunoglobulin G; no., number; PPMS, primary progressive multiple sclerosis; PRMS, progressive relapsing multiple sclerosis; SEP, somatosensory evoked potentials; VEP, visual evoked potentials.

RESULTS

Demographics

The data of 32 patients with progressive onset MS was analysed. The disease course was progressive without any relapse (PPMS) in 24 patients, whereas 8 patients experienced relapses (PRMS). Our PRMS patients (8 patients) compose 25% of our study group of patients with progressive onset disease. The demographic and clinical characteristics of the PPMS and PRMS groups are summarized in Table 1. The female/male ratio was 1 in total POMS population. There was no difference in gender predominance between the subgroups of progressive onset patients (p=0.685). The median age of patients was 48.5 (31–65) years at the time of evaluation. PPMS patients were older than PRMS patients in our study (p=0.022). The median age of onset was 40 (23–55) years in the whole group. There was no significant difference in median onset age between two subgroups (p=0.053).

Clinical Features

The most common presentation symptom was motor disturbances (Table 1). Eleven patients were presented with weakness in the lower extremities and report progressive shortening of walking distance. Seven patients experienced weakness in one lower extremity. Eight cases described at least one exacerbation after one year of progressive onset disease and classified as PRMS. Relapses occurred in the first 10 years of the disease in all patients. Two patients reported two attacks while other patients reported one relapse. Four patients had motor deficits at the relapses. Five patients had brainstem symptoms (3 diplopia, 1 trigeminal neuralgia, 1 with peripheral facial palsy). One patient was polysymptomatic at the exacerbation. Three patients with PRMS (including the patient with multiple symptoms) were given five- or seven-day pulse steroid therapy (1 gr/day methylprednisolone) according to the healing of the symptoms. All 3 patients had almost total recovery of the relapse symptoms. The rest of the patients (were not admitted to any hospital or admitted to another clinic) did not receive pulse steroid treatment but they describe spontaneous regression of the symptoms caused by the relapse. There was no statistically significant difference in the duration of the symptoms between groups (p=0.694). No significant difference was detected for duration between the onset of symptoms and the diagnosis between groups (p=0.334).

CSF Findings

Cerebro-spinal fluid analysis results were obtained from 25 patients in all groups. CSF/blood glucose ratio was normal in all subjects. No difference was detected between groups according to OCB positivity and increased IgG index (p=0.938, p=0.058).

Radiological Findings

Brain and cervical spinal cord MRI findings were compatible with MS in all patients. Twenty patients (15 PPMS and 5 PRMS) had at least one contrast enhancing brain or spinal cord lesion in the evaluated MRI scans. Three patients had prominent spinal cord atrophy.

Electrophysiological Findings

No statistically significant difference was found for the frequency of increased P100 wave latency in the VEP between groups (p=0.59).

Disability

Fifteen patients (46%) needed at least intermittent or unilateral constant assistance (had EDSS 6 or more) at the time of evaluation. The median EDSS score was higher in PPMS patients (p=0.020).

Treatment

Five- or seven-day pulse steroid therapy was administered to 10 patients (1 gr/day methylprednisolone). Three out of 10 patients have PRMS, and pulse steroid therapy was given in relapse period. Other 7 patients with PPMS were treated because of progressively worsening neurological status. All the patients described somewhat improvement after pulse steroid therapy.

Immunosuppressants (IS) were used (azathioprine in 4, methotrexate in 23). Five patients were not under any treatment. In the majority of patients IS started soon after the diagnosis. The dosage was 100–150 mg/day for azathioprine (AZA), 7.5 mg/week for methotrexate (Mtx).

DISCUSSION

The demographic, clinical, and laboratory results of 24 PPMS and eight PRMS patients were evaluated and compared. The disease courses of progressive onset MS patients exhibit a different clinical pattern than other subtypes of MS. The dissimilar clinical course of progressive onset and relapsing onset patients are well known, whereas the data comparing the characteristics and the course of the disease between PPMS and PRMS groups are limited in literature (8). It is known that RRMS is more likely to be seen in 30's while PPMS begins in 40's (9, 10). Disease onset age of the progressive onset MS patients in our study was compatible with the literature (40 years). It was reported that PRMS patients are younger than PPMS patients at the onset of the disease (10). In our group, the difference approached but did not reach to significance. Presumably, if it had been possible to obtain a larger sample this disparity may have been significant. It is known that patients with RRMS show female dominance, while PPMS patients had nearly equal predominance in female/male ratio (10, 11). PPMS patients had a similar ratio, but PRMS patients had lower female/male ratio in our study (1.18 versus 0.6), but the difference was not statistically significant. Both groups exhibited statistically similar results for female/male ratio in previous studies (12–15). We did not detect any difference for the time interval between the first symptom of the disease to final diagnosis. The differential diagnosis in progressive onset MS varies extensively (e.g., cord compression, spastic paraplegia, leukodystrophies, motor neuron disease etc.), and it seems that in our county the patients with progressive onset were not diagnosed easily even in the patients with definite exacerbations. Patients with RRMS usually present with optic neuritis (ON), brainstem, and spinal cord symptoms whereas progressive onset MS patients show the spinal cord, brainstem, and cerebellar symptoms mostly (9, 10, 14, 16). Similar to the literature, in our study the most common side of localization for the initial symptoms was spinal cord. Most of the patients presented with bilateral or unilateral pyramidal findings (8, 15, 16). The following most common symptoms were cerebellar and brainstem symptoms respectively. It is well known that ON occurs very rarely in progressive onset patients (9, 10, 14). Similarly, none of our patients presented or experienced ON. Our patient number was not enough to compare PPMS and PRMS groups according to initial symptoms. Other studies did not show any difference according to the initial symptom (10, 12). Although the duration of disease was similar for two groups, PPMS patients were more disabled than PRMS patients at the time of evaluation in our study. Although there was no difference between two groups in the progression in previous studies, it was reported that older age of onset was an independent predictor for progression to EDSS 6.0 (12, 17). It was reported that although progression is more rapid in PPMS, age-related disability milestones are identical to relapsing-onset disease (18).

The majority of patients (approximately 80%) with PPMS tested positive for the presence of oligoclonal bands in cerebrospinal fluid, and/or increased IgG index, and/or increased IgG synthesis (19, 20). CSF oligoclonal band positivity was reported about 90% of RRMS patients and about 80% of PPMS patients (15). Despite being as a known form of MS, still there is no sufficient data about the CSF findings of PRMS form. 76% of PPMS and% 75 of PRMS group patients had positive OCB in our study. Elevated IgG index was detected in 23% and 62% of PPMS and PRMS patients respectively. This percentage difference did not reach to significance. We could not find any study concerning the comparison of the CSF analysis between PPMS and PRMS in the literature. None of the patients had a history of ON whereas 83% of all cases showed significant delay in one or both eyes on VEP. It was also noted that VEP abnormalities or retinal nerve fibre (RNFL) thinning detected by optical coherence tomography (OCT) could be seen without any clinical event (21, 22). Asymptomatic optic nerve involvement is a very supportive finding of axonal neurodegeneration and could be very helpful in the diagnosis. Disease pathology differs between relapsing-remitting and progressive courses but it's not well known if progressive relapsing course has a different immunopathology from remitting, primary progressive or secondary progressive diseases (23). OCT could also be helpful to understand the ongoing immunopathological process in progressive onset patients as a non-invasive screening tool. As the majority of PPMS cases present with progressive myelopathy somatosensory-evoked responses can demonstrate central conduction delays and add an additional information for the diagnosis. It was reported that multimodal evoked potentials correlate well with the disability in PPMS and allow some prediction of the disease course over three years (24). We aimed to focus on the clinical and laboratory findings of progressive onset MS and only review the compatibility of the MRI for the diagnosis and to rule out other possible causes such as spinal cord compression. MRI showed at least one contrast enhancing lesion even in brain or spinal cord in 20 patients. Also, three patients had spinal cord atrophy. Because the radiological circumstances were not similar for all the patients and we didn't make a radiological comparison between two groups. Grey matter and white matter of the brain are abnormal in both early RRMS and PPMS whereas cord atrophy is present in PPMS (25). Early spinal cord atrophy can be seen in PPMS patients and gadolinium enhancement is seen less frequent than RRMS patients (15, 25). These three patients had a long disease duration and higher EDSS, hence they were not in the early stage of the disease. In addition, new MRI techniques such as magnetisation transfer ratio or diffusion tension provides more accurate measurements for cord atrophy (26) than conventional MRI.

We were not able to evaluate the response to long term treatment with immunosuppressant as the study was cross-sectional. All the patients who received high dose methylprednisolone treatment in the past either for relapses or not described somewhat improvement. Some important clinical benefits have been observed with pulse steroid therapy alone or in conjunction with mitoxantrone or cyclophosphamide in cases with PPMS (27–30).

As a conclusion, our study is a retrospective, single centre study. The clinical and laboratory comparison of two groups showed mainly similar results which were compatible with the literature. It is important to clarify if any difference exists between groups for the onset age and frequency of raised IgG index in the future studies with larger sample size. The major limitations of this study include its retrospective design and the number of patients, particularly with PRMS was small. The study involved retrospective analysis of MRI; we would have got more information from the imaging if the imaging data could have been reinforced. To our knowledge, this is the first study focusing on the clinical course and laboratory findings of primary onset Turkish MS patients. Further studies with a larger group of patients are necessary to detect the national or geographical differences in the characteristics of the disease. In addition to clinical assessments, pathological studies investigating the two subgroups of progressive onset are valuable in order to determine the similarities and differences, and understand underneath pathophysiological process.

Ethics Committee Approval: The study was approved by the Ethics Committee Hacettepe University.

Informed Consent: Written informed consent was obtained from all participants.

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