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The initial symptoms in multiple sclerosis: clinical and demographic data of Çorum province

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ABSTRACT

Aims: Multiple sclerosis, which has individual and societal effects such as being observed in young and middle-aged people and its long and expensive treatment process, has become an important public health issue.

Methods: Between January 2022 and January 2023, 103 patients with MS were evaluated using anamnesis, neurological examinations, and neuroimaging results. The patients' initial findings upon their MS diagnosis, the duration of diagnosis, their neurological observations in the past month, and their clinical categorization were examined.

Results: Out of the 103 patients, 70 (67.96%) were female, and 33 (32.04%) were male, which was detected as a female-to-male ratio of 2.12/1. The average age of the patients was 34.41±8.4 years, and the average disease duration was 8±5.8 years. The initial findings in females were as follows; 25 patients (35.7%) had sensory, 13 patients (18.6%) had motor (pyramidal), 17 patients (24.3%) had brain stem-cerebellar, 10 patients (14.3%) had a visual impairment, and 5 patients (7.1%) had other findings. The distributions of the initial symptoms in males were as follows; 12 patients (36.4%) were motor (pyramidal), 10 patients (30.3%) were sensory, 5 patients (15.1%) were brain stem-cerebellar, 5 patients (15.1%) had visual impairment, and 1 patient (.3.1%) had other findings. The mean Expanded Disability Status Scale (EDSS) at the time of initial diagnosis was 2.5± 1.5. Among the 60 patients with RRMS who were first diagnosed, the duration elapsed between initial symptom onset and diagnosis was 12.8± 5.7 months.

Conclusion: Demographic information of the MS patients followed up in our clinic, their initial complaints, frequency of clinical subtypes, differences between clinical subtypes, their clinical status in the last month, and their EDDS at their initial diagnosis and last follow-up are presented. As this represents the first data on the epidemiology of MS in our city, we believe it will contribute to the national data of Turkey and help raise MS awareness among clinicians.

Keywords: Multiple sclerosis, symptom, disability

INTRODUCTION

Multiple sclerosis (MS) is a chronic progressive disease observed during early adulthood. Depending on the localization of the lesion, it can manifest with diverse symptomatology. The disability caused by the progression of the disease after the initial symptom gives rise to novel challenges and uncertainties in numerous aspects of the patient's personal and social life. The loss of an emerging workforce and the prolonged, costly treatment procedure also position MS as a significant public health issue. With the advancements in neuroimaging, since they are faster and more accessible, and due to the precision of diagnostic criteria, the diagnosis of MS can be achieved with greater certainty and speed.[1] Numerous disease-modifying treatments with significant effects in controlling disease activity and reducing long-term morbidity are currently employed.[2] In terms of the initial symptoms, exercising caution at primary care centers can help to shorten the diagnostic process.

METHODS

The study was carried out with the permission of Hitit University Medical Faculty Clinical Researches Ethics Committee (Date: 14.06.2023, Decision No: 20323-75). All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki.

Between January 2022 and January 2023,103 patients who were followed up with the MS diagnosis in the neurology clinic, diagnosed per the 2018 McDonald criteria, and had regular data in their patient follow-up files were examined. Patients were evaluated with anamnesis, neurological examinations, and neuroimaging results.

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The initial symptoms observed in patients diagnosed with MS were classified as sensory, pyramidal, cerebellar and brain stem, and visual pathway-related findings; additionally, cognitive or mental function-related symptoms under the category of other functions, bladder-bowel and sexual dysfunctions, and other neurological manifestations associated with MS. Based on the clinical course, the patients were categorized into primary progressive MS (PPMS), secondary progressive MS (SPMS), and relapsing-remitting MS (RRMS) and their neurological functioning was assessed using the Expanded Disability Status Scale (EDSS) scores during the initial and final outpatient clinic evaluations.

RESULTS

Out of the 103 patients, 70 (67.96%) were female, and 33 (32.04%) were male, which was detected as a female-to-male ratio of 2.12/1. The average age of onset for the patients was 34.41±8.4 years, the average age of onset for males was 29.84±6.9 years, and the average age of onset for females was 30.30±5.6 years. The average duration of the disease was 8±5.8 years. Regarding the clinical course, 62 (60.2%) patients were determined to be followed up with the diagnosis of RRMS, 31 (30.1%) of SPMS, and 10 (9.7%) of PPMS. Analyzing the clinical course specifically in female patients, 42 (60%) were identified as RRMS, 21 (30%) as SPMS, and 7 (10%) as PPMS. Regarding male patients, 20 (60.6%) were diagnosed with RRMS, 10 (30.3%) with SPMS, and 3 (9.1%) with PPMS. When the clinical classification of the patients was made according to their gender, it was observed that the incidence rates of RRMS in both sexes were high (**Table 1**). When we look at the initial symptoms; it was detected that 35 patients (34%) presented with sensory findings, 25 patients (24.3%) with motor (pyramidal) findings, 22 patients (21.3%) with brain stem - cerebellar findings, 15 patients (14.6%) with visual impairment and 6 patients (5.8%) with other findings (pain, mental changes, sphincter disorders). The initial findings in females were as follows; 25 patients (35.7%) had sensory, 13 patients (18.6%) had motor (pyramidal), 17 patients (24.3%) had brain stem-cerebellar, 10 patients (14.3%) had visual impairment, and 5 patients (7.1%) had other findings. The distributions of the initial symptoms in males were as follows; 12 patients (36.4%) were motor (pyramidal), 10 patients (30.3%) were sensory, 5 patients (15.1%) were brain stem-cerebellar, 5 patients (15.1%) had visual impairment, and 1 patient (.3.1%) had other findings (**Table 2**). While the most sensory findings in females were paresthesia and hypoesthesia in the extremities and body, mono paresis was frequently detected among the motor (pyramidal) symptoms. In males, hemiparesis and hemihypoesthesia as a sensory or motor (pyramidal) symptom were more prominent. A deterioration in visual acuity was more common as a visual impairment. Other results in the females included L-hermitte and trigeminal neuralgia in two patients, cognitive regression in two patients, inability to control due to urinary incontinence in one patient, and in males, neuropathic pain in the left upper and lower extremities was detected as the initial symptom in one patient (**Table 3**). When comparing the symptoms of onset based on gender, it was observed that motor (pyramidal) symptoms and onset rates were more prevalent in male patients, while other systemic manifestations were predominant in the female gender ($p<0.001$). The mean EDSS at the time of initial diagnosis was 2.5±1.5. Among the 60 patients with RRMS who were first diagnosed, the duration elapsed between initial symptom onset and diagnosis was 12.8±5.7 months. Our SPMS and PPMS patients had previously been diagnosed at external facilities and were now under our clinic's follow-up. The average time to diagnosis for these patients was 26.1±9.7 months. During the outpatient examinations conducted in the last month, the mean EDSS score 0-3 was 60 (58.25%), with 33 (32.05%) patients scoring between 3.5-6 on the EDSS, and 10 (59.70) patients scoring between 6.5-8 (**Table 4**). When SPMS and RRMS were compared; the mean disease duration was longer in SPMS than in RRMS. The mean initial EDSS score and the mean EDSS score in the final outpatient clinical control were higher in SPMS than in RRMS. Onset with motor (pyramidal) symptoms was detected more in SPMS compared to RRMS, while PPMS had a significant superiority in favor of PPMS over SPMS ($p<0.001$). When RRMS and PPMS were compared; in terms of motor (pyramidal) symptom and onset, PPMS was again significantly superior to RRMS in favor of PPMS ($p<0.001$). Positive family histories were detected in seven patients (6.79%). Of these, one of the siblings of 3 patients, one of the cousins of 3 patients, and the mother of one patient were detected to have MS.

Table 1. MS clinical classification based on sex

SEX	RRMS	PPMS	SPMS
Female	42 (60%)	7 (10%)	21 (30%)
Male	20 (60.6%)	3 (9.1%)	10 (30.3%)
	62 (60.2%)	10 (9.7%)	31 (30.1%)

RRMS: relapsing-remitting multiple sclerosis, PPMS: primary progressive multiple sclerosis, SPMS: secondary progressive multiple sclerosis, MS: multiple sclerosis

Table 2. Initial symptom distribution based on sex

SEX	Motor symptoms	Sensory symptoms	Brain stem-cerebellar symptoms	Symptoms related to vision	Other symptoms
Female	13 (18.6%)	25 (35.7%)	17 (24.3%)	10 (14.3%)	5 (7.1%)
Male	12 (36.4%)	10 (30.3)	5 (15.1%)	5 (15.1%)	1 (3.1%)

Table 3. Other symptoms

Sex	Symptom
Female (n=70)	L-hermitte 1
	Trigeminal neuralgia 1
	Cognitive regression 2
	Urinary incontinence 1
Male (n=33)	Neuropathic pain 1

Table 4. EDSS values of the patients at the last outpatient clinic controls

EDSS	0-3	3,5-6	6,5-8
Patient (n=103)	60 (58.25%)	33 (32.05%)	10 (59.70)

EDSS expanded disability status scale

DISCUSSION

The clinical onset of MS typically occurs between the ages of 20 and 50, although the prodromal phase may begin years earlier, and its clinical manifestations are likely to differ among individuals.[3-5] In industrialized societies, the female-to-male ratio becomes more pronounced, increasing up to 3/1, which was approximately twice as high in our study. The exact etiology remains unknown, but genetics, environmental factors, nutrition, smoking, viral infections, and vitamin deficiencies impact the development and prognosis of the disease. The global prevalence of MS ranges from 5-300/100,000 individuals.[6,7]

The rise in the prevalence of MS further supports the contribution of genetic factors in its etiology. Extensive mapping studies have identified numerous distinct genetic variations associated with an elevated risk of MS, with the HLA-DR1 1501 allele being the most prevalent risk factor linked to MS. MS is an autoimmune disorder caused by self-reactive cells that trespass the blood-brain barrier and attack the central nervous system (CNS). Principal subsets of T cells implicated in MS comprise CD8+ T cells, CD4+ Th1 cells, and Th17 cells. Interferon-gamma, IL-17, and granulocyte-macrophage colony-stimulating factors are cytokines produced by self-reactive T cells that potentially contribute to the pathophysiology of MS. Elevated levels of immunoglobulin in the cerebrospinal fluid (CSF) indicate the involvement of B cells in MS. A majority of B cells in the CSF and brain parenchyma are CD27+ memory B cells.[8-11]

The diagnosis of MS relies on the revised McDonald criteria, which encompass a combination of clinical findings, neuroimaging, and laboratory data.[12] MS is a disease in which demyelination and inflammation can affect gray matter and cortical region or medulla spinalis, although mostly white matter in the brain, and symptoms may vary according to localization of the lesion. After the acute phase, MS lesions turn into a chronic phase in which a combination of remyelination, inflammation, and myelin degeneration can be observed. With this transformation, new symptoms or changes in the severity of symptoms are seen in the clinic. MS can be observed as a clinically isolated condition in patients and may present with single or multiple symptoms depending on the localization of the lesion. Brain stem, spinal cord syndrome, and optic neuritis are among the common clinical presentations; however, a variety of clinical symptoms may be observed, including cortical manifestations such as dominant parietal lobe syndromes. Numerous clinical manifestations are indicative of MS, yet only a few are pathognomonic. MS episodes typically emerge over hours or days, with gradual improvement observed over weeks. Following this healing process, residual effects may remain. The clinical symptoms, results, and progression of MS are assessed across a broad spectrum. MS is characterized by intermittent periods of neurological abnormalities, referred to as "attacks," that may exhibit remission and initially occur more frequently. In the subsequent periods, a process called SPMS may develop in which permanent neurological deficits develop and clinical disability occurs. And PPMS is characterized by a progressive course from the onset. The most prevalent form, as we detected also in our study, is RRMS. It is recognized that this clinical course entails periods of remission periods between the periods of attacks. Due to CNS damage in MS patients; visual symptoms such as weakness in the extremities, sensory symptoms, ataxia, bladder problems, fatigue, diplopia, blurred vision, dysarthria, memory-concentration-attention disorder can be seen, while movement disorders, epileptic seizures, headaches, cognitive impairment, cortical symptoms, hearing loss, amyotrophy are among the rare symptoms and findings.[13-16] Acute demyelinating optic neuritis is the symptom of application in 20% of MS patients and affects approximately half of MS patients at some point in the course of the disease.[17] Some eye movement abnormalities can be observed in MS patients. These eye movement abnormalities may present with diplopia or oscillopsia.[18] Vertigo is seen in 30-50% of MS patients. In a retrospective study, the most prevalent cause of vertigo in MS patients has been identified as benign positional paroxysmal vertigo.[19] Motor signs and symptoms typically manifest as paraparesis, quadriparesis, hemiparesis, or monoparesis. They are often accompanied by other symptoms. Spasticity is frequently present, with a more pronounced manifestation observed in the lower extremities compared to the upper extremities.[20] Sensory symptoms are frequent initial manifestations and occur in nearly all patients during the disease. The disease causes both positive and negative sensory symptoms. Sensory loss, paresthesias, dysesthesias, and hyperesthesias are commonly reported. Impairment in vibration and proprioception may result from demyelination in the posterior cord. Rarely, a condition resembling Brown-

sequard syndrome, characterized by a spinal cord half-incision-like presentation, may occur. The most common finding is L-hermitte, which is observed with a rate of 3% as the initial symptom and 30-40% in the whole period.[21] Bowel dysfunction is reported in approximately 50 percent of patients with MS, and bladder dysfunction is reported up to 75 percent.[22] Sexual dysfunction is observed frequently in MS patients.[23] However, due to societal and social reasons, there is not much application as it being the first symptom. Rare cases of MS have been reported in the literature.[24] Among the cases we followed, neuropathic pain occurred as the first symptom in a total of 3 cases. In female patients, L-hermitte and neuralgia in the trigeminal region were described, while in male patients, neuropathic pain in the left hemibody was reported. In the literature, publications on pain associated with MS under the title of neuropathic pain syndrome show that we should forget that the first symptom in these patients may be pain.[25,26] MS patients presenting with uncommon yet significant symptoms such as incontinence and cognitive impairment also underscore the importance of considering MS in the distinctive diagnosis for patients referred from different clinics.[27-28] EDSS is utilized to assess and monitor clinical manifestations in MS. In addition to the disease's clinical course, numerous factors influence the EDSS score. Disease activity and progression are typically assessed through relapses, MRI activity, and disability progression. However, it is employed to track increased disease activity and newly formed lesions on MRI scans.[29] While various studies in the literature discuss the duration from initial symptoms to the conclusive diagnosis of MS in MS patients, this duration diminishes with advancements in accessibility and technology of neuroimaging, yet disregarding sensory symptoms frequently leads to an extended period between the onset of the initial symptom and the actual diagnosis.[30] We think that this process takes long in patients with an old diagnosis in the patient group we follow, because of the referral of patients to external facilities for MS and due to social reasons. The most important limitations of our study are that we could not perform genetic analysis and it is a single-centered study. However, we have observed that our results are directly proportional to the literature data.

CONCLUSION

Demographic information of the MS patients followed up in our clinic, their initial complaints, frequency of clinical subtypes, differences between clinical subtypes, and their EDDS are presented. As this represents the first data on the epidemiology of MS in our city, we believe it will contribute to the national data of Turkey and help raise MS awareness among clinicians.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Medical Faculty Clinical Researches Ethics Committee (Date:14.06.2023 Decision No:20323-75).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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