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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Evaluation of the Factors Affecting the Clinical Course and Prognosis in a Group of Patients with Transverse Myelitis

Transvers Miyeliti Olan Bir Grup Hastada Klinik Seyir ve Prognozu Etkileyen Faktörlerin Değerlendirilmesi

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ABSTRACT

Aim: Acute transverse myelitis is a spinal cord inflammatory disease that can occur at various spinal levels. It is extremely rare but can cause severe disability and even death. In this study, we aimed to evaluate the clinical findings, etiologic factors, and their effects on prognosis in a group of patients with acute transverse myelitis.

Material and Method: The study included 30 patients with acute transverse myelitis who were hospitalized at our clinic between January 2012 and December 2018. Hospitalization and discharge modified Rankin Scales, basic demographic data, treatments, lesion level, imaging, and CSF findings were recorded.

Results: Sixteen (53%) of the patients were male and 14 (47%) were female. The mean age was 54 years (16-84 years). While 13.3% of the cases developed into multiple sclerosis during follow-up, the etiology was malignancy in 16.6%, neuromyelitis optica in 6.6%, and infectious pathologies in 6.6%. Gender, age, parity of sphincter involvement, CSF protein, high hospitalization MRS score, and number of hospitalization days were identified as prognostic factors (p values were p=0.017, p=0.002, p=0.0013, p=0.019, p=0.001, p=0.002, respectively). High hospitalization rankin score and increased number of hospitalization days were correlated with poor prognosis at discharge (Pearson correlation coefficient r=0.886, p<0.001; r=0.675, p<0.001, respectively).

Conclusion: Acute transverse myelitis may have many different etiologies. Even in patients who meet the diagnostic criteria, multiple sclerosis can develop during follow-up. Long-term monitoring and paraneoplastic processes should be considered in myelitis. Furthermore, determining the factors affecting prognosis is useful in predicting the long-term clinical course of patients and guiding treatment.

Keywords: Clinical findings, etiology, prognosis, transverse myelitis

ÖZ

Amaç: Akut transvers miyelit omuriliğin çeşitli spinal seviyelerinde görülebilen enflamatuvar bir hastalığıdır. Oldukça nadir rastlanmakla beraber ağır engellilik ve hatta ölüme neden olabilir. Bu çalışmada akut transvers miyelit ile takip edilen bir grup hastanın klinik bulguları, etiyolojide yer alan faktörlerin değerlendirilmesi ve prognoza etkilerinin araştırılması planlandı.

Gereç ve Yöntem: Kliniğimizde Ocak 2012-Aralık 2018 tarihleri arasında yatırılarak incelenen 30 akut transvers miyelit hastası çalışmaya dahil edildi. Hastaların yatış ve taburculuk modifiye rankin skalaları, temel demografik verileri, uygulanan tedaviler, lezyon seviyesi, görüntüleme ve BOS bulguları kayıt edildi.

Bulgular: Hastaların 16'sı erkek (%53), 14'ü (%47) kadındı. Yaş ortalaması 54 (16-84 yıl) bulundu. Vakaların %13.3'ü takipte multiple skleroza dönüşürken, %16.6'sında etiyolojide malignite, % 6.6'sında nöromyelitis optika, % 6.6'sında ise enfeksiyöz patolojiler tespit edildi. Prognoza etkili faktörler cinsiyet, yaş, sfinkter tutulumu eşlikçiliği, BOS proteini, yatış MRS skorunun yüksek olması ve yatış gün sayısı olarak belirlendi (p değerleri sırasıyla p=0.017, p=0.002, p=0.013, p=0.019, p=0.001, p=0.002). Yüksek yatış Rankin skoru ve yatış gün sayısının artışı taburculukta kötü prognozla korele bulundu (r=0.886, p<0.001; r=0.675, p<0.001).

Sonuç: Akut transvers miyelitin etiyolojisinde birçok farklı neden bulunabilmektedir. Tanı kriterlerini tam olarak karşılayan hastalarda dahi takipte multiple skleroza dönüşüm olabilmektedir. Miyelitte uzun süreli takip ve paraneoplastik süreçlerin yer alabileceği akılda tutulmalıdır. Ayrıca prognoz üzerine etkili faktörlerin belirlenmesi uzun vadede hastaların klinik seyrini öngörmede ve tedaviyi yönlendirmede değer taşımaktadır.

Anahtar Kelimeler: Etiyoloji, klinik bulgular, prognoz, transvers miyelit

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INTRODUCTION

Acute Transverse Myelitis is a spinal cord inflammatory disease that can develop from a variety of causes and manifests as a wide range of clinical findings ranging from non-specific mild sensory symptoms to severe paralysis (1). This extremely rare disease has an annual incidence of 1-8/1.000.000. (2). The thoracic spinal cord is the most commonly affected spinal cord region (3).

A variety of factors could be involved in the etiology of acute transverse myelitis. These generally include parainfectious, paraneoplastic, drug/toxin-induced, systemic autoimmune diseases, and acquired demyelinating diseases of the central nervous system (2). When an underlying cause is discovered, it is referred to as secondary transverse myelitis; otherwise, it is referred to as idiopathic transverse myelitis. In 15-30% of the cases, no etiologic cause can be found. Today, the idiopathic group is gradually decreasing as a result of advanced diagnostic tests and increased recognition of NMO (4).

The clinical presentation of acute transverse myelitis syndromes may occasionally cause diagnostic difficulties (1). Back pain, paraparesis, paresthesia, level sensory deficit, and bladder-bowel symptoms are the most common symptoms (3). A thorough history, neurological examination, cerebrospinal fluid (CSF) examination, and neuroimaging are all important in making a diagnosis. CSF examinations play an important role in understanding demyelinating disorders and inflammatory processes (5). Since the condition can cause severe disability, both early diagnosis and effective treatment are important.

The purpose of this study was to retrospectively evaluate the demographic, etiologic, and clinical characteristics of patients with acute transverse myelitis in the light of imaging and laboratory findings, to investigate the underlying pathologies, to examine them in terms of follow-up and treatment, and to determine the associated factors that may affect the prognosis in the short term.

MATERIAL AND METHOD

In this study, 45 medical epicrisis documents of patients between the ages of 16 and 85 years who were hospitalized at Erciyes University, Faculty of Medicine, Department of Neurology between January 2012 and December 2018 and whose neurologic system examination findings were suggestive of inflammatory processes with spinal cord involvement were retrospectively reviewed. Ten patients were excluded from the study because they had previously been diagnosed with MS. Three patients were excluded due to a spinal cord infarction, and two patients were excluded due to existing spinal cord involvement caused by a tumoral lesion. Thirty patients with no prior neurologic symptoms or history and who met the diagnostic criteria for acute transverse myelitis according to the transverse myelitis consortium working group (TMCWG) criteria were included in our study. These diagnostic criteria were as follows: (1)- sensory, motor, or autonomic dysfunction attributable to the spinal cord; (2)- symptoms must be bilateral (not necessarily symmetrical); (3)- clearly defined level of sensory deficit; (4)- progression to the worst level in less than 21 days after onset of symptoms; (5)- T2 hyperintense signal change on neuroimaging (MRI or myelography), brain abnormalities suggestive of MS, and exclusion of extra-axial compressive etiology (6)- pleocytosis or increased Immunoglobulin G (IgG) index in CSF (4).

Patients with MS diagnosed at follow-up were diagnosed according to the 2018 McDonald criteria. MS patients with a first episode of myelitis were included in our study.

Gender, age, presenting complaints, medical history, season of presentation, blood tests, presence of autonomic symptoms, treatments and clinical improvement were all studied retrospectively. The time to diagnosis was defined as the interval between the onset of the first symptom after hospitalization and the clinical diagnosis of ATM. Sphincter involvement was questioned. Lumbar puncture (LP) was performed on all patients. The value of CSF protein, viral serology, oligoclonal band positivity, immune globulin G index, and CSF cytology were all evaluated. Blood tests included serologic tests, vasculitis, celiac disease, and cancer markers in addition to routine complete blood and biochemistry examinations. All patients underwent Aquaporin-4 Antibody IgG test for NMO diagnosis. Viral serology was performed in CSF, and the Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV), Herpes Simplex Virus (HSV Types 1–2), and Varicella Zoster (VZV) were tested. In addition, VDRL and TPHA for Neurosyphilis, Borrelia Burgdorferi IgM for Lyme disease, Neurobrucellosis examinations, as well as CSF PCR, and CSF culture for tuberculosis were performed.

All patients underwent 1.5 T brain and spinal MRI. The location and distribution of lesions, the extent of lesions, the number of involved segments, and the presence of gadolinium contrast enhancement were recorded. A sagittal spinal examination defined long segment spinal involvement as involvement of three or more vertebral segments and short segment spinal involvement as involvement of one or two vertebral segments.

Based on hospitalization and discharge examination findings, the clinical prognosis of the patients was evaluated using the Modified Rankin Scale (MRS). As a result, those with an MRS score of less than 2 were considered to have a good prognosis, while those with an MRS score of 2 or higher were considered to have a poor prognosis.

Approval for the study was obtained from Erciyes University Ethics Committee. (2018/40)

Statistical Analysis

Statistical analyses were performed using the SPSS (Statistical Package for The Social Sciences) program version 26 (Armonk, NY, IBM Corp.,released 2019). Categorical measurements were summarized as numbers and percentages, and numerical measurements as mean and standard deviation (median, minimum, and maximum as needed). A chi-square test was used to compare categorical data. In the comparison of two independent groups, Student's t-test was used for the data fitting the normal distribution, and the Mann-Whitney U test was used for the data not fitting the normal distribution. In correlation analysis, the Pearson correlation coefficient was applied to normally distributed data. The statistical significance value was accepted as $p < 0.05$.

RESULTS

The study included 30 patients, ranging in age from 16 to 84 years old. Sixteen (53%) of the patients were male and 14 (47%) were female. The mean age was 54 years (16-84 years). The average length of hospitalization was 19.73 (7-42) days. **Table 1** displays the basic demographic data for the entire patient group.

Table 1: Basic demographic data of the patients

Variables	N(%)
Age, mean±Std (min-max)	53.3±16.0(16-84)
Days of hospitalization, mean±Std (min-max)	19.7±11.9(7-62)
Season of hospitalization	
Spring	9(30.0)
Summer	11(36.7)
Autumn	4(13.3)
Winter	6(20.0)
Symptom at hospitalization	
Sensory deficit	4(13.3)
Motor deficit	3(10.0)
Both motor and sensory deficits	23(76.7)
CSF protein (mg/dL), mean±Std (min-max)	52.0±32.7(25-170)
CSF glucose, mean±Std (min-max)	76.4±24.4(28-139)
Blood WBC at hospitalization, mean±Std (min-max)	9426±3706(4140-18400)
Blood Hgb at hospitalization, mean±Std (min-max)	12.9±1.7(9,3-16,4)
Blood PLT at hospitalization, mean±Std (min-max)	259.000±92.648(117.000-471.000)
Number of segments retained, mean±Std (min-max)	3.8±2.2(2-10)
MRS score at hospitalization, mean±Std (min-max)	3.5±1.3(1-5)
MRS score at discharge, mean±Std (min-max)	2.6±1.5(0-5)

The average length of stay in the intensive care unit for one patient hospitalized there was 16 days. In terms of hospitalization season, 11(36.7%) patients were admitted during the summer, 9(30%) in the spring, 6(20%) in the winter, and 4(13.3%) in the autumn. The symptoms at hospitalization were motor loss and numbness in 23 patients (76.7%), numbness in 4 patients (13.3%), and motor loss in 3 patients (10%). Loss of strength was symmetrical in 22(73.3%) patients and asymmetrical in 8(26.7%) patients. The average time between symptom onset and admission was 3 months in two patients and 8 (1-15 days) days in the other patients.

Respiratory distress was observed in 1 patient who was hospitalized in the intensive care unit. The patient was in respiratory distress, and the lesion began at the C3 level, was contrast-enhancing, expansile, and extended up to the T8 level. In the following period, the patient's CSF examinations revealed that the condition was associated with TB. The patient had pulmonary involvement. He was extubated and discharged without respiratory distress after receiving appropriate treatment. None of our patients had excitus. Before the disease, four (13.3%) patients had a history of upper respiratory tract infection. Three (10%) patients had autonomic dysfunction. Two of these patients had ileus, and one had orthostatic hypotension. During the subsequent period, one patient who was diagnosed with ileus was later diagnosed with rectal cancer. The other orthostatic hypotensive patient had diffuse medulla spinalis involvement, and the etiology was TB. Sphincter involvement was found in 10 (33.3%) of the patients.

All patients underwent LP. The mean CSF protein value was 52.0 (25-170) mg/dL. The normal CSF protein values in our laboratory were 15–45 mg/dL. Values above 45% were considered high. 10 (33.3%) patients had high protein values. CSF OCD was analyzed in all patients. CSF OCD Type 1 was found in 5 patients, Type 2 in 3 patients, and Type 4 in 1 patient. Anti-aquaporin-4 antibodies were analyzed for NMO and found positive in one patient.

While 4 (13.3%) patients were diagnosed with Multiple Sclerosis, 5 (16.6%) patients were diagnosed with malignancy (1 with laryngeal cancer, 1 with ovarian cancer, 1 with renal cell carcinoma, 1 with metastasis of an undetermined primary, and 1 with lymphoma). Antigliadin antibodies were found to be positive in 1 patient, and celiac disease was diagnosed as a result of further investigations, while Behcet's (beh-CHETS) disease was detected in 1 patient and NMO was detected in 2 patients. In 1 patient, TB infection was identified as the etiologic cause, and in 1 patient, HSC-2 type 2 was. In 15 out of 30 patients, an etiologic cause could be identified (50%).

When screenings were analyzed, it was observed that all patients underwent cranial and spinal magnetic resonance imaging (MRI). Cervical involvement was observed in 4 (13.3%) patients, cervicothoracic in 6 (20%) patients, thoracic in 9 (29.7%) patients, thoracolumbar in 1 (3.3%) patient, lumbar in 8 (26.7%) patients, sacral in 1 (3%) patient and conus medullaris in 1 (3%) patient. Contrast enhancement was observed in 19 (53.3%) patients. An MRI of 2 patients with NMO revealed long segment spinal involvement beginning at C2 and extending to the T3 level. Contrast uptake was present in 1 patient and absent in the other. All 4 patients with MS had short-segment cervical spinal involvement. Contrast uptake was observed in 2 patients. Long segment spinal involvement was detected at various spinal levels in 14 of the remaining 26 patients. Three of these patients were diagnosed with malignancy, one with celiac disease, one with TB, and one with HSV-2. Contrast enhancement was observed in all patients with malignancy.

It was determined that 4 patients received pulse steroid alone, 10 patients continued oral steroid for one month after pulse steroid, 9 patients underwent plasmapheresis due to lack of clinical improvement after pulse steroid, one patient received pulse steroid, then PF, then IVIG, 4 patients underwent plasmapheresis alone, one patient received pulse steroid after IVIG, and one patient continued with oral steroid after IVIG.

Patients were also evaluated with MRS for short-term hospitalization and discharge prognosis. As a result, MRS less than 2 was considered good prognosis, while MRS 2 and above was considered poor prognosis. The parameters that made a significant difference in prognosis were gender, age, parity of sphincter involvement, CSF protein, high hospitalization MRS score, and the number of hospitalization days (p values were p=0.017, p=0.002, p=0.0013, p=0.019, p=0.001, p=0.002, respectively) (**Table 2**).

Table 2: Comparison of variables that may be effective in myelitis prognosis according to the results of the Modified Rankin Scale

Variables	Modified Rankin below 2	Modified Rankin above 2	p
Gender F/M, n (%)	8/1(50/7.1)	8/13(50/92.9)	0.017
Age, mean (SD)	38.7 (4.2)	59.7 (12.4)	0.002
Autonomic Finding Exist, n%)	0(0)	3(14.3)	0.534
Sphincter Involvement Exist, n(%)	0 (0)	10 (47.6)	0.013
History of previous infection exist, n(%)	0 (0)	4 (19)	0.287
Etiology idiopathic, n(%)	3(33.3)	12(57.1)	0.427
CSF protein, mean (SD)	40.7 (11.0)	56.9 (37.6)	0.019
MRS score at hospitalization, mean (SD)	2.0 (0.7)	4.2 (0.8)	0.001
Days of hospitalization, mean (SD)	12.2 (4.7)	22.9 (12.6)	0.002
Number of involved segments, mean (SD)	3.7 (2.2)	4.0 (2.5)	0.814
Contrast-enhanced, n(%)	5(55.6)	12(57.1)	0.936

High hospitalization rankin score and increased number of hospitalization days were correlated with poor prognosis at discharge (Pearson correlation coefficient r=0.886, p<0.001; r=0.675, p<0.001, respectively).

DISCUSSION

The adult age group has a much higher incidence of ATM than the pediatric age group. Approximately 20% of cases are seen in the pediatric age group, while 80% are in adults (6). The mean age of transverse myelitis in our study, which included adults, was 53.3±16.0 years. The mean age in the Chaves et al. study was found to be 45.8 years, 43 years in another study including a large series, and 39.4 years in a study conducted in our country (7,8). The disease shows a bimodal distribution. It tends to peak in the 2nd and 4th decades of life (3).

The study included 30 patients, 16 of whom were male (53%) and 14 of whom were female (47%). In terms of gender, there are comparable rates in the literature. Despite a slight female predominance, the frequency of men and women being affected is close to each other (3). Our patients were mostly hospitalized in the spring and summer seasons. Although no significant seasonal increase in myelitis has been reported, it is known that it may occur more frequently, particularly during the summer and fall (9). While numbness alone (13.3%) and motor deficit alone (10%) were uncommon presenting symptoms, the onset of both motor and sensory deficits was the most common complaint. Only about 15% of cases are expected to have sensory deficits. Both motor and sensory involvement is the most common presentation (10).

Four of our patients had a history of infection in the two weeks preceding the disease, and they all presented with various upper respiratory tract symptoms. Bacterial and viral serologic tests, as well as CSF cultures, were performed on all patients, and TB was detected in 1 patient and HSV-2 was detected in 1 patient. A positive CSF PCR reaction is used in the diagnosis of transverse myelitis due to HSV-2. HSV-2 can cause radiculomyelitis and necrotizing myelitis. It is a very rare etiology of myelitis (11). It is most commonly seen in immunocompromised patients. Our patient was not immunocompromised, so antiviral treatment with acyclovir was continued. Significant clinical improvement was observed. Tuberculosis was discovered, but brain imaging revealed no pathology. However, he had pulmonary involvement and respiratory distress. In addition, CSF glucose was very low and CSF protein was high. CSF was dominated by polymorphonuclear cells. The diagnosis was confirmed by CSF culture. This patient's lesion showed a long spinal involvement in the cervicothoracic region and was edematous and contrast-enhanced. Spinal neurologic manifestations due to

tuberculosis are mostly intramedullary tuberculoma, leptomeningitis, and extradural involvement. Although transverse myelitis is a rare complication of tuberculosis-related neurologic involvement, it should be considered in the differential diagnosis.

Gastrointestinal dysfunction may be observed in myelitis due to the involvement of autonomic pathways. During the acute phase of spinal shock, gastroparesis, paralytic ileus, and acute gastric dilatation may be observed (3). In our series, two patients developed ileus, and one was later diagnosed with colon cancer. Autonomic involvement may also be seen as orthostatic hypotension. If the lesion is large and edematous, the possibility of occurrence increases, particularly in cervical spinal segments above T6. In these patients, a combination of orthostatic hypotension in the acute phase, also known as autonomic dysreflexia, and sudden hypertensive episodes in the later phase may be seen. Meanwhile, a sudden change in heart rate and accompanying piloerection, sweating, and facial flushing may be observed (13). Our patient with orthostatic hypotension had extensive spinal involvement, with an expansile lesion above the T6 level. No cause of myelitis was found in the etiology of this patient.

Urethral and/or anal sphincter involvement was detected in 10 (33.3%) patients. Sphincter involvement is a common complication of transverse myelitis and may persist even after motor recovery (3). According to the report of Cobo Calvo et al., 68% of 85 patients had anal and/or urethral sphincter involvement (14). Sphincter involvement did not occur in any of the MS patients in our study. Of the 10 patients with sphincter problems, 8 had long segment spinal involvement, 3 had cervicothoracic lesions, 4 had thoracic lesions, 1 had conus medullaris, 1 had sacral lesions, and 1 had lumbar lesions.

Three of the three patients with oligoclonal band type 2 positivity were diagnosed with MS. One of our MS patients had an oligoclonal band type 1 detected. Type 2 oligoclonal band positivity in CSF examination was thought to be an important marker in the investigation of MS. NMO was detected in 2 patients and was negative in the other patients. While lesions involving 8 and 9 cervical spinal segments were detected in our patients with NMO, one had contrast enhancement and the other did not. Aside from the NMO patients, 14 others had longer segmental spinal involvement, 6 of whom had no etiologic cause and the others did. Long spinal involvement was thus discovered in a total of 16 patients, with an etiology identified in 8 of them. Long segment spinal involvement is particularly associated with NMO, and NMO is detected in 60% of these cases, according to the literature, and it is emphasized that it is associated with non-idiopathic transverse myelitis in cases where NMO is not found (7). However, only 50% of the long segment spinal involvement in our patient series had an etiology.

Although the TMCWG criteria allow for a more objective diagnosis of myelitis, conversion to MS is expected in around 10% of patients, even in those who fully meet the criteria. The number of cases included in our study was limited, and the follow-up period was brief. Nevertheless, 4 patients were diagnosed with MS during follow-up. Patients who are followed up according to the diagnostic criteria in the studies are expected to show an average of 3–14% MS transformation in a 5-year follow-up, although different rates have been reported in different publications (15).

The rankin scale was noted for short-term prognosis at both hospitalization and discharge. Accordingly, male gender, advanced age, sphincter involvement, high Bos protein level, high MRS scale at admission, and long hospitalization were found to be higher in the poor prognosis group.Many factors have been identified as contributing to a poor prognosis in myelitis. These include motor involvement, rapid progression, relapse, severe functional deficit, sphincter involvement, and involvement of a long spinal segment (15,16,17). The bad prognostic markers discovered in our study back up the literature. When we evaluated the prognosis in terms of long spinal segment involvement, we found a higher MRS score even though there was no statistically significant difference. We discovered no link between the presence of contrast enhancement and progosis. We think that evaluation in large series with a large number of cases will be useful in this regard. In addition, although we could not detect statistical significance in some data, such as the presence of autonomic symptoms, respiratory distress, and a history of previous infection due to the limited number of patients in our study, we found that the discharge MRS score was higher in the presence of these findings.

One of the limitations of our study is that, despite being one of the most important centers where patients with the diagnosis of radiculomyelitis are referred from many cities in the Central Anatolia Region, our hospital is a single center with a limited number of patients. As a result, it can be considered limited in terms of generalizing the data. Nonetheless, it is significant in terms of describing the clinical course and disease characteristics of a group of patients who were hospitalized, followed, and investigated over a long period of time in a single center. Another limitation is that the study was retrospective and evaluated short-term treatment responses, with no long-term regular follow-up examination results.

In conclusion, our study demonstrated that there may be many different causes in the etiology of myelitis, and some markers may guide the prognosis. The number of spinal segments and the location of the lesion, as well as CSF findings, were among the markers in our case series that shed light on the transformation to MS and

NMO during the follow-up period. Another important point has been paraneoplastic processes in the etiology of myelitis. Our case series demonstrated that different types of underlying malignancies may cause similar myelitis symptoms, and that long-term follow-up and detailed examinations are critical for early diagnosis and treatment in this patient group. In this regard, large-scale multicenter epidemiologic studies are required.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was obtained from Erciyes University Ethics Committee (2018/40).

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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