Original Article

Etiological profile of noncompressive myelopathies in a tertiary care hospital of Northeast India

Ashok Kumar Kayal, Munindra Goswami, Marami Das, Lakhshya Jyoti Basumatary, Suvorit Subhas Bhowmick, Baiakmenlang Synmon

Department of Neurology, Gauhati Medical College and Hospital, Guwahati, Assam, India

Abstract

Background: The discovery of antibodies against aquaporin-4 and evolving concepts of noncompressive myelopathies in the 21st century have made a major impact on the etiological profile of these diseases, with few cases turning out to be idiopathic. **Objective:** To find causes of noncompressive myelopathy in a tertiary care hospital of Northeast India. **Materials and Methods:** An observational study was carried out in the Neurology Department of Gauhati Medical College, Guwahati, from September 2013 to February 2016. Patients of noncompressive myelopathies who underwent magnetic resonance imaging (MRI) of the spine were segregated into two categories: acute-to-subacute myelopathy (ASM) and chronic myelopathy (CM). In addition to routine blood tests, chest X-ray, urinalysis, and visual evoked potentials, investigations included MRI of the brain, cerebrospinal fluid analysis, and immunological, infectious, and metabolic profile based on the pattern of involvement. **Results:** The study had 151 patients (96 ASM and 55 CM) with a median age of 35 years and male: female ratio 1.4:1. The causes of ASM were neuromyelitis optica spectrum disorder (23), multiple sclerosis (MS) (8), systemic lupus erythematosus (1), Hashimoto's disease (1), postinfectious acute disseminated encephalomyelitis (6), postinfectious myelitis (8), infections (9), spinal cord infarct (5), and electrocution (1). The causes of CM were MS (1), probable or possible sarcoidosis (7), mixed connective tissue disease (1), Hashimoto's disease (2), infections (9), Vitamin B_{12} deficiency (4), folate deficiency (2), hepatic myelopathy (2), radiation (11), and paraneoplastic (1). No etiology could be found in 48 (31.8%) patients (34 ASM and 14 CM). In 21/96 (21.9%) patients of ASM, acute transverse myelitis was idiopathic based on current diagnostic criteria. **Conclusion:** Underlying etiology (demyelinating, autoimmune, infectious, vascular, metabolic disorder, or physical agent) was found in 68% patients of noncompressive myelopathy.

Key Words

Neuromyelitis optica, noncompressive myelopathies, transverse myelitis

For correspondence:
Dr. Suvorit Subhas Bhowmick, Department of Neurology, Gauhati Medical College and Hospital, Bhangagarh, Guwahati - 781 032, Assam, India.
E-mail: tutai1985@gmail.com

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Introduction

Spinal cord dysfunction can result from demyelinating, infectious, autoimmune, vascular, and metabolic disorders in the absence of demonstrable compression by imaging techniques. The importance of observational studies lies in the identification of important disorders and providing impetus to future research. Although there are plenty of published data on each of the noncompressive myelopathies, there has been no Indian study on the overall etiological spectrum in the light of newer diagnostic criteria and serological tests. The previous studies from India were carried out during a period when Transverse Myelitis Consortium Working Group (TMCWG) criteria for idiopathic acute transverse myelitis (ATM) could not be applied, and serological test for neuromyelitis optica (NMO) was not available.[1,2] Herein, we attempt to determine the etiological

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profile of noncompressive myelopathies in a tertiary care hospital of Northeast India.

Materials and Methods

Study design

An observational study was carried out in the Neurology Department of Gauhati Medical College, Guwahati, from September 2013 to February 2016, and the data were collected prospectively.

Aims and objectives

(a) To determine the causes of noncompressive myelopathies; (b) to study the clinical and radiological features of noncompressive myelopathies.

Study approval and patient consent

The study was approved by the Institutional Ethical Committee of the hospital. Informed consent was taken from the patients for the necessary investigations, data collection, analysis, and publication of data and images.

Inclusion criteria

Patients with acute, subacute, or chronic neurologic dysfunction consistent with myelopathy (with or without coexisting encephalopathy, neuropathy, or radiculopathy) from the Neurology, Medicine, and Pediatric Departments of our hospital were included in the study.

Exclusion criteria

Patients were excluded from the study if they met the following exclusion criteria: (a) Patients of myelopathy who did not undergo magnetic resonance imaging (MRI) of the spinal cord, (b) spinal cord compression on MRI explaining patient's neurologic dysfunction, (c) anterior horn cell involvement in Japanese encephalitis, (d) motor neuron disease (MND), and (e) degenerative ataxias. It was not possible to include cases of encephalitis with evidence of anterior horn cell involvement because of large outbreak of Japanese encephalitis in the region.[3] Although there is significant spinal cord pathology in MNDs and some degenerative ataxias, these diseases are diffuse processes with high degree of cerebral cortex, brainstem involvement, and cerebellar involvement and hence were excluded from the study.[4]

Clinical evaluation

Patients were questioned regarding duration, onset and progression of illness, neurological symptoms, skin rash, photosensitivity, joint pain, bone pain, edema, jaundice, anemia, gastrointestinal bleeding, cough, chest pain, exposure to radiation and other toxic substances, travel history, and high-risk sexual behavior. We looked for evidence of systemic disease or malignancy in the general and systemic examinations. Skin was examined for zoster lesions, erythema migrans, erythema nodosum, etc. Eye was examined for signs of uveitis, scleritis, and conjunctival xerosis. The neurological examination included evaluation of higher functions, cranial nerves, motor and sensory systems, reflexes, and funduscopy. The level of spinal cord dysfunction was determined using American Spinal Injury Association Impairment Scale. Disability was measured using modified Rankin Scale (mRS).

Investigations

All patients underwent MRI of the spinal cord, hemogram, serum electrolytes, renal function tests, liver function tests, thyroid profile, urinalysis, chest X-ray, and visual evoked potentials (VEPs). Area of interest of MRI was determined by history and clinical examination. MRI of the brain was done in selected patients based on their clinical presentation. MRI was done using Siemens Magnetom 1.5 Tesla MRI system with a slice thickness of 4 mm. As per requirement, sequences used were sagittal and axial T_1, T_2, fluid attenuation inversion recovery, short-tau inversion recovery, diffusion-weighted imaging, and magnetic resonance spectroscopy. Gadolinium contrast was used to detect enhancement of lesions. Cerebrospinal fluid (CSF) analysis included total count, differential counts, protein, and sugar. Further investigations were based on the clinical presentation. CSF tests included immunoglobulin G (IgG) index and oligoclonal bands (OCBs); polymerase chain reaction (PCR) for varicella-zoster virus (VZV), herpes simplex virus (HSV), *Cytomegalovirus* (CMV), Epstein–Barr virus, *Mycobacterium tuberculosis,* and *Toxoplasma gondii*; adenosine deaminase; venereal disease research laboratory (VDRL) test; cryptococcal antigen; enzyme-linked immunosorbent assay (ELISA) for HSV, VZV, and Japanese encephalitis virus (JEV); and angiotensin converting enzyme (ACE). Serological tests included ELISA for human T-lymphotropic virus-1, human immunodeficiency virus (HIV), *Borrelia burgdorferi,* and *T. gondii*; VDRL and *Treponema pallidum* hemagglutination assay. Immunological tests included antibody against aquaporin-4 (AQP4-IgG), antithyroid peroxidase (anti-TPO) antibody, antinuclear antibodies, anti-dsDNA, anti-Smith, anti-Ro, anti-LA, APLA, anti-tissue transglutaminase, and ACE levels. Metabolic profile included serum Vitamin B_{12}, folate, Vitamin E, and copper levels. Investigations in suspected paraneoplastic myelopathy included antibodies against amphiphysin, collapsin response mediator protein-5, Ma, Ri, Yo, and Hu. Optical coherence tomography was done in patients with optic nerve involvement. Ultrasound abdomen and computerized tomography scans of thorax and abdomen were done in patients suspected to have systemic disease or malignancy. Electrophysiological studies in patients having coexistent neuropathy or radiculopathy were done using Recorders and Medicare Systems (RMS) – Aleron 201 (2 channel) EMG/NCV/EP system (RMS Private Limited, Chandigarh, India).

Case definitions

Acute-to-subacute myelopathy (ASM) was defined as spinal cord dysfunction lasting at least 48 h and reaching nadir within 21 days of symptom onset.[5] Chronic myelopathy (CM) was defined as spinal cord dysfunction of insidious onset and progressing gradually over months to years. ATM was diagnosed as per criteria proposed by TMCWG.[6] Acute disseminated encephalomyelitis (ADEM) was diagnosed as per criteria proposed by International Pediatric Multiple Sclerosis Study Group.[7] Postinfectious myelitis (PIM) was labeled in the presence of clear history suggestive of infection preceding onset of neurological symptoms within 30 days. The diagnosis of multiple sclerosis (MS) was based on 2010 Revised McDonald Criteria.[8] NMO spectrum disorder (NMOSD) was diagnosed based on 2015 International Panel for NMO Diagnosis criteria.[9] Neurosarcoidosis (NS) was diagnosed as per 1999 Zajicek criteria.[10] Patients with consistent neurologic features and elevated CSF ACE levels were labeled as possible NS. Infectious myelopathy (IM) was diagnosed based on

positive serology, evidence of intrathecal specific antibody synthesis, detection of pathogen in CSF, or evidence of other organ involvement with temporal relationship. Paraneoplastic myelopathy was labeled in the presence of malignancy or paraneoplastic antibody after exclusion of other causes. Acute complete transverse myelitis (ACTM) was defined as relatively symmetric moderate or severe loss of motor and sensory modalities caudal to the level of the lesion. Acute partial transverse myelitis (APTM) was labeled when there was incomplete or patchy involvement of at least one spinal segment with mild to moderate weakness and asymmetric or dissociated sensory symptoms and occasionally, bladder dysfunction.[11]

Treatment and follow-up

Patients of ATM were treated with intravenous methylprednisolone 1 g (or 25 mg/kg) for 5 days followed by oral prednisolone 60 mg (or 1–1.5 mg/kg) per day tapered over 1 month. Interferon-β, dimethyl fumarate, azathioprine, or mycophenolate mofetil was used in immune-mediated myelopathies based on final diagnosis. Patients with infectious myelopathies were treated with specific antibiotics or antivirals. Patients with nutritional deficiency were supplemented. Patients were followed up for examination of residual deficits and disability. Good outcome was defined as partial or complete recovery, ability to walk without aid, isolated urinary disturbances, or mRS ≤2. Poor outcome was defined as death, inability to walk unassisted, or mRS ≥3.

Data collection and statistical analysis

Basic demographic data and data regarding clinical, radiological, and laboratory profiles were collected in a predesigned pro forma. Demographic data included native place, age, sex, and socioeconomic status of the patients. Socioeconomic status was determined as per revised Kuppuswamy scale.[12] Comparison of data was done using the Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA). Fisher's exact test was used for comparison of proportions. Student's *t*-test and Mann–Whitney U-test were used for normally distributed and nonnormally distributed numerical data, respectively. Kolmogorov and Smirnov method was used to determine if the data followed Gaussian distribution. $P < 0.05$ was considered statistically significant.

Results and Observations

During the study period, 179 patients were clinically diagnosed with noncompressive myelopathy. Patients who had an alternative diagnosis after investigations (four patients of compressive myelopathy, three patients of spinocerebellar ataxia, two patients of Friedreich's ataxia, and one patient of MND) and patients who did not undergo MRI of the spine (18) were excluded from the study. The demographics and clinical features of the final 151 patients are summarized in Table 1.

ASM was diagnosed in 96 (63.6%) patients. The median age was 29 years (range, 2–71 years). Male:female ratio was 1.1:1. The common causes of ASM were NMOSD, clinically definite MS, postinfectious ADEM, IM, PIM, and spinal cord infarct (SCI) [Table 2 and Figure 1]. No etiology was found in 34/96 (35.4%) patients. Comparison of major causes of ASM is shown in Table 3.

CM was diagnosed in 55 (36.4%) patients. The median age was 45 years (range, 3–70 years). Male:female ratio was 1.9:1.

Table 1: Demographic and clinical profile

Characteristics	*n* (%)*
Age (years)	
0-20	30 (19.9)
21-40	63 (41.7)
41-60	49 (32.5)
61-80	9 (5.9)
Sex	
Male	87 (57.6)
Female	64 (42.4)
Socioeconomic status	
Upper	6 (3.9)
Middle	74 (49.0)
Lower	71 (47.0)
Motor manifestations	
Quadriparesis	81 (56.0)
Paraparesis	58 (38.4)
Hemiparesis	5 (3.3)
Bibrachial weakness	3 (1.9)
Monoparesis	3 (1.9)
Spasticity	87 (57.6)
Flexor spasms	9 (5.9)
Tonic spasms	12 (7.9)
Dystonia	3 (1.9)
Sensory manifestations	
Paresthesia	105 (69.5)
Posterior column sensory loss	117 (77.5)
Spinothalamic sensory loss	107 (70.9)
Sphincter involvement	109 (72.2)
Brainstem involvement	9 (5.9)
Radiculopathy	12 (7.9)
Peripheral neuropathy	15 (9.9)
Optic neuritis/atrophy	20 (13.2)
Other cranial nerve involvement	3 (1.9)
Encephalopathy	9 (5.9)
Type of myelopathy	
Acute to subacute	96 (63.6)
Chronic	55 (36.4)
Relapsing myelopathy	32 (21.2)

*Total number of patients (*n*=151)

The causes of CM were progressive MS, other autoimmune disorders, infections, metabolic, vascular, radiation, and paraneoplastic [Table 4 and Figure 2]. No etiology was found in 14/55 (25.5%) patients. Comparison of major causes of CM is shown in Table 5.

Cord signal changes (hyperintensity on T_2-weighed images) on MRI were found in 122 (80.8%) patients [Figure 3]. Contrast was used in 126 (83.4%) patients, of which 38 (30.2%) patients had enhancement of cord lesions. Cord swelling was seen in 56 (39.4%) patients. T_1 hypointense lesions were found in six patients of NMOSD, three patients of radiation myelopathy, two patients of unknown ASM, and one patient of SCI. Vertebral signal changes were seen in all patients of radiation myelopathy. Diffusion restriction was seen in five patients of SCI and one patient each of NS and ADEM. Syrinx was found in four patients of NMOSD and one patient each of unknown ASM and tuberculous radiculomyelitis. Intradural

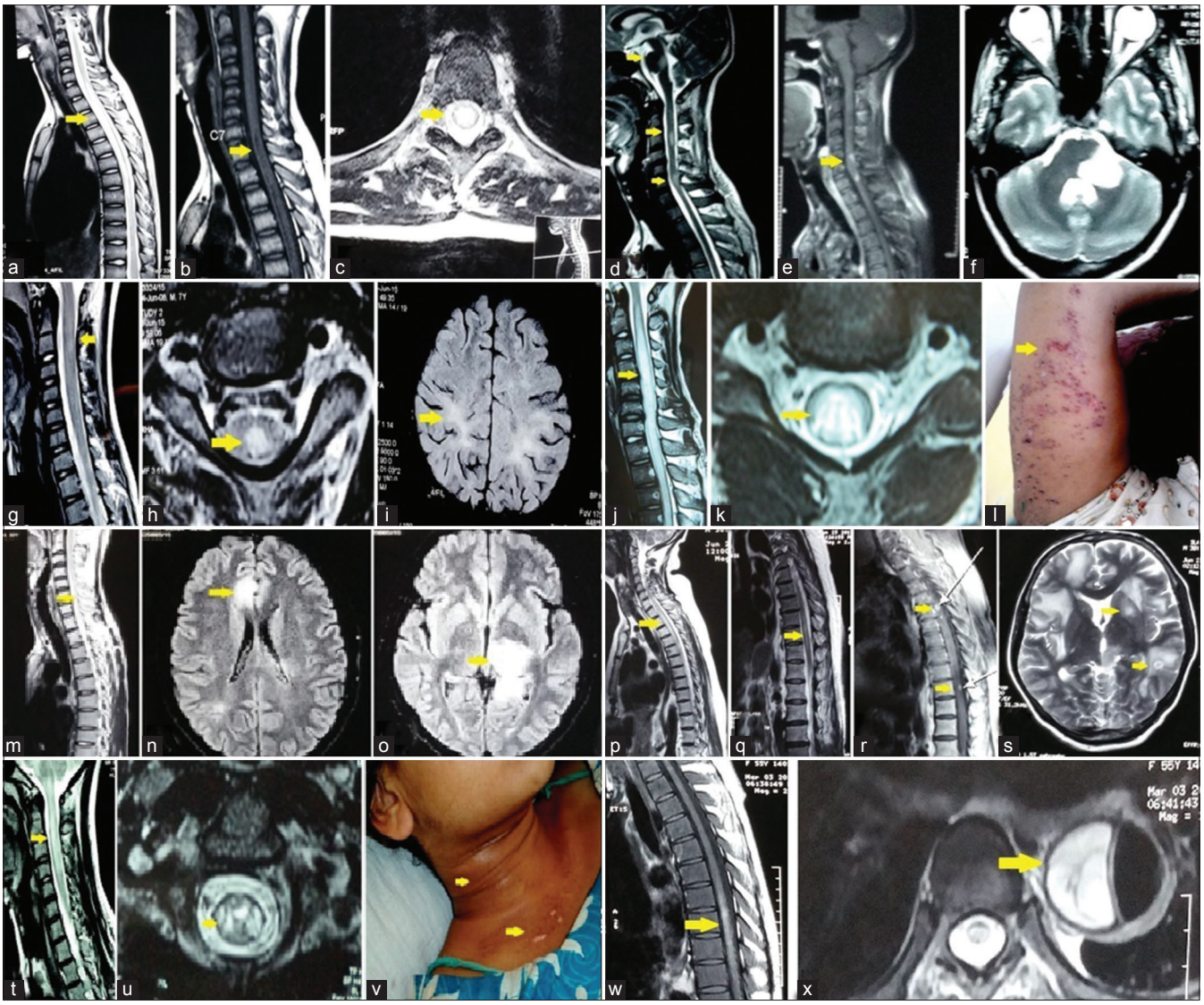

Figure 1: Acute to subacute myelopathy. (a-c) Neuromyelitis optica: Longitudinally extensive transverse myelitis. (d-f) Multiple sclerosis: Short segment lesions and brainstem lesions. (g-i) Acute disseminated encephalomyelitis: Cervical cord lesions and subcortical hyperintensities. (j-l) Varicella zoster virus myelitis: Longitudinally extensive transverse myelitis with preceding herpes zoster lesions. (m-o) *Toxoplasma gondii* myelitis: Longitudinally extensive transverse myelitis and brain lesions. (p-s) Cysticercosis: Enhancing cord lesions and brain lesions with dot-like scolex. (t-v) Postinfectious myelitis: Longitudinally extensive transverse myelitis with preceding neck swelling and skin rash. (w and x) Spinal cord infarct: Enhancing dorsal cord lesion with dissecting aortic aneurysm

extramedullary granulomatous lesion was found in one patient of tuberculous radiculomyelitis, at a site distinct from cord lesion. There was no cord signal change in 29 (19.2%) patients. Isolated root enhancement was seen in two patients (NS, HIV-associated radiculomyelitis). Cord atrophy without cord signal change was seen in four patients (one unknown ASM and three unknown CM).

The patients lost to follow-up included three patients each of NMOSD and unknown ASM and one patient each of PIM, HIV-associated radiculomyelitis, SCI, hepatic myelopathy, radiation myelopathy, and unknown CM. Outcome of the rest 139 (92.1%) patients is shown in Figure 4. The median duration of follow-up was 12 months (range, 1–24 months). By the end of the study, 14/139 (10.1%) patients expired including two patients each of NMOSD, NS, radiation myelopathy, and unknown ASM and one patient each of MS, VZV myelitis, and hepatic myelopathy. None of these patients showed improvement by two mRS grades till they lived. Relapses were seen in 32 (21.2%) patients (8 MS, 17 NMOSD, 1 ADEM, 1 PIM, 1 NS, and 4 unknown ASM). Additional details are provided in supplementary files.

Discussion

This study is the largest from India on the etiological profile of noncompressive myelopathies in the post-MRI era. The ethnic composition and lifestyle of the people of Northeast India, where this study was carried out, is unique partly because of the migration of people and past invasions from

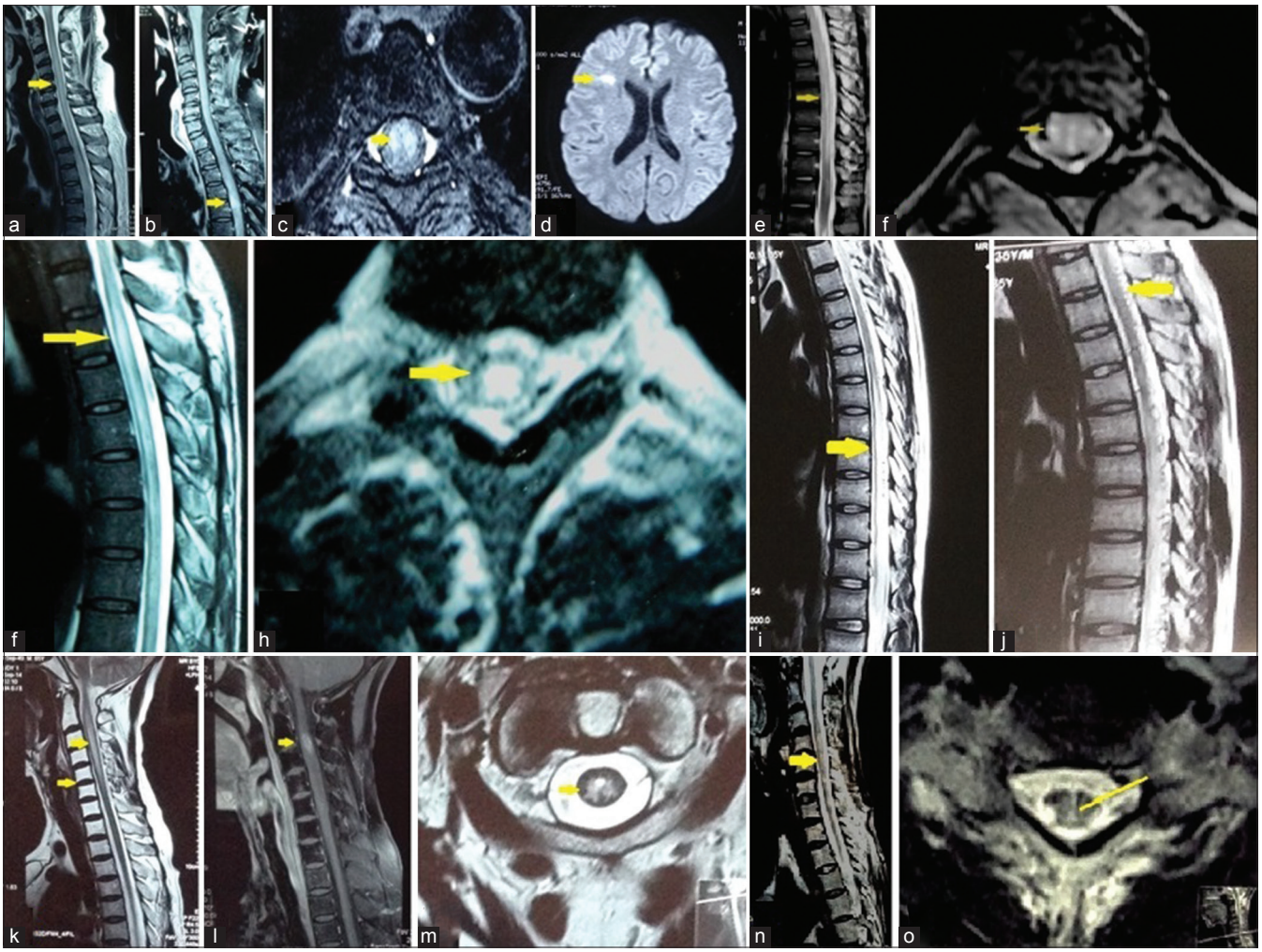

Figure 2: Chronic myelopathy. (a-d) Possible neurosarcoidosis: Longitudinally extensive transverse myelitis with focal enhancement and subcortical lesion. (e and f) Cryptococcal myelitis: Longitudinally extensive transverse myelitis. (g and h) Syphilitic myelitis: Longitudinally extensive transverse myelitis. (i and j) Spinal dural arteriovenous fistula: Longitudinally extensive lesion with flow voids at a higher level. (k-m) Radiation myelopathy: Longitudinally extensive lesion with focal enhancement and vertebral signal changes defining the radiation portal. (n and o) Vitamin B_{12} deficiency: Long segment lesion in the posterior aspect of cord with inverted V-shaped lesion in axial section

surrounding countries. Here, the population is formed of several racial stocks including principally the Mongoloids, the Indo-Aryans, the Australoids, and the Dravidians.[13] The study showed that noncompressive myelopathies commonly affected people in the prime of their lives. About 42% of the patients presented in the third and fourth decades of life. There was a slight male preponderance of patients, the male:female ratio being 1.4:1. Similar age and gender profile were observed in previous studies from other parts of India and in a study from Cameroon.[1,2,14]

A study from East India had 82 patients between July 1994 and June 1996.[1] The causes of myelopathy were MS, heredodegenerative, systemic lupus erythematosus (SLE), electrocution, SCI, and clioquinol. Etiology could not be established in 23 (28.0%) patients. ATM was diagnosed in 24 (29.3%) patients, and it was presumed postinfectious. History of antecedent fever was present in only 16 of these patients. Another study from North India had 57 patients

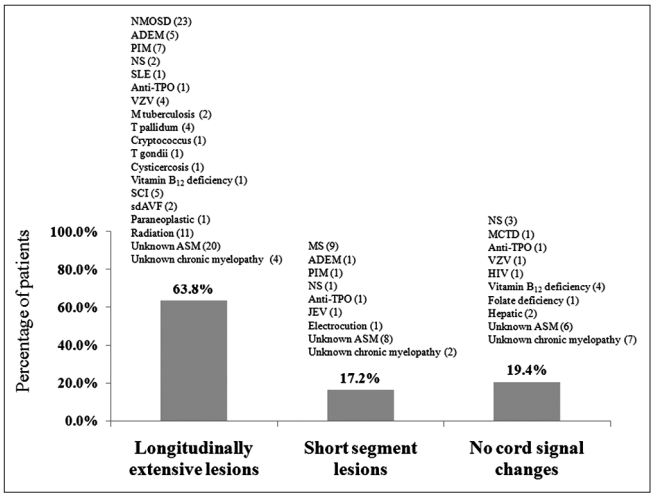

Figure 3: Cord signal changes in patients of noncompressive myelopathy

between 1997 and 1999.[2] The causes of myelopathy included Vitamin B_{12} deficiency, primary progressive MS, hereditary spastic paraplegia, tropical spastic paraplegia, syphilitic myelitis, VZV myelitis, subacute necrotizing myelitis, and radiation myelopathy. Myelopathy could not be classified in four patients. Thirty-one (54.4%) patients were labeled ATM. Etiology of ATM was not clearly known in these patients. Antecedent events in the form of febrile illness, chicken pox, and vaccination were present in 13 patients of ATM. CSF specific OCBs were present in four patients and two patients reported a recurrence of symptoms. Some of these cases could have been MS or NMOSD. The previous Indian studies were carried out during a period when serological test for AQP4-IgG was not available. MRI of the spine could not be done in all patients. MRI of the brain was done in few patients. Specific serological tests for postinfectious ATM were probably not possible due to technical reasons.

Diagnosis of ATM requires evidence of inflammation within the spinal cord, demonstrated by CSF pleocytosis, elevated IgG index, or gadolinium enhancement. The TMCWG has classified ATM into idiopathic and disease-associated (connective tissue disorders, infections, MS, and NMO).[6] As the treatment approach and prognosis differ based on etiology, ATM was not presumed postinfectious in our study. Postinfectious ATM was diagnosed if patients had a clear history of febrile

Table 2: Etiology of acute to subacute myelopathy

Etiology	*n* (%)*
Multiple sclerosis	8 (8.3)
NMOSD	23 (23.9)
SLE†	1 (1.0)
Hashimoto's disease	1 (1.0)
Varicella-zoster virus‡	5 (5.2)
Japanese encephalitis virus	1 (1.0)
Treponema pallidum	1 (1.0)
Toxoplasma gondii‡	1 (1.0)
Cysticercosis	1 (1.0)
Postinfectious myelitis	8 (8.3)
Postinfectious acute disseminated encephalomyelitis	6 (6.3)
Spinal cord infarct	5 (5.2)
Electrocution	1 (1.0)
Unknown	34 (35.4)

*Total number of patients (*n* = 96), †Another patient of NMOSD developed SLE during follow-up, ‡Two patients of VZV myelitis and the patient of toxoplasma myelitis had HIV infection. NMOSD = Neuromyelitis optica spectrum disorder, SLE = Systemic lupus erythematosus, VZV = Varicella zoster virus, HIV = Human immunodeficiency virus

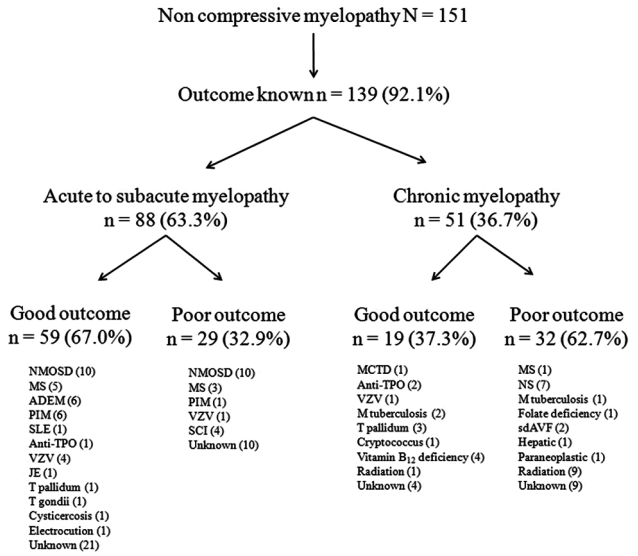

Figure 4: Outcome of noncompressive myelopathies

Table 3: Clinical, magnetic resonance imaging and cerebrospinal fluid profile of acute-to-subacute myelopathy

Characteristic	Idiopathic (*n*=21)	NMOSD (*n*=23)	MS (*n*=8)	ADEM (*n*=6)	IM (*n*=9)	PIM (*n*=8)	SCI (*n*=5)
Age in years, mean±SD	33.8±16.1	34.6±12.2	31.1±8.1	15.0±8.7	35.4±12.1	14.3±7.6	42.4±16.4
Male:female ratio	14:7	5:18	3:5	4:2	6:2	6:2	4:1
ACTM, *n* (%)	21 (66.7)	23 (100.0)	1 (12.5)	5 (83.3)	8 (88.9)	6 (75.0)	5 (100.0)
APTM, *n* (%)	7 (33.3)	0 (0.0)	7 (87.5)	1 (16.7)	1 (11.1)	2 (25.0)	0 (0.0)
Brainstem involvement, *n* (%)	0 (0.0)	7 (30.4)	3 (37.5)	3 (50.0)	1 (5.6)	1 (12.5)	1 (20.0)
Bladder involvement, *n* (%)	17 (80.9)	22 (95.7)	4 (50.0)	4 (66.7)	9 (100.0)	6 (75.0)	5 (100.0)
Severe at onset (AIS < D), *n* (%)	16 (76.2)	23 (100.0)	3 (37.5)	6 (100.0)	9 (100.0)	7 (87.5)	5 (100.0)
Relapsing myelopathy, *n* (%)	2 (9.5)	17 (73.9)	8 (100.0)	1 (16.7)	0 (0.0)	1 (12.5)	0 (0.0)
MRI, *n* (%)							
Short segment myelitis	8 (38.1)	0 (0.0)	7 (87.5)	1 (16.7)	2 (22.2)	1 (12.5)	0 (0.0)
LETM	9 (42.9)	23 (100.0)	0 (0.0)	5 (83.3)	7 (77.8)	7 (87.5)	5 (100.0)
Gadolinium enhancement	3/14 (21.4)	9/16 (56.2)	3 (37.5)	1/5 (20.0)	5/6 (83.3)	3/8 (37.5)	2/4 (50.0)
No signal change	4 (19.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CSF, *n* (%)							
Pleocytosis‡	7/19 (36.8)	11/18 (61.1)	2 (25.0)	0/5 (0.0)	7/8 (87.5)	5 (62.5)	0/2 (0.0)
Protein >45 mg/dL	12/19 (63.2)	12/18 (66.7)	3 (37.5)	2/5 (40.0)	5/8 (62.5)	5 (62.5)	1/2 (50.0)
OCBs	0/7 (0.0)	0/5 (0.0)	5/6 (83.3)	0/2 (0.0)	0/1 (0.0)	0/2 (0.0)	0/2 (0.0)

‡Pleocytosis: > 10 cells/mm^3. ACTM = Acute complete transverse myelitis, ADEM = Acute disseminated encephalomyelitis (postinfectious), AIS = American Spinal Injury Association Impairment Scale, APTM = Acute partial transverse myelitis, IM = Infectious myelitis, LETM = Longitudinally extensive transverse myelitis, MS = Multiple sclerosis, NMOSD = Neuromyelitis optica spectrum disorder, OCBs = Oligoclonal bands, PIM = Postinfectious myelitis, SCI = Spinal cord infarct, SD = Standard deviation, MRI = Magnetic resonance imaging, CSF = Cerebrospinal fluid

illness within 30 days preceding onset of myelitis and negative serological tests for NMO and systemic autoimmune diseases. Specific serological tests for all infections were not done because of technical limitations. Furthermore, detection of specific infectious agent is not always possible. In a study of 176 patients with postinfectious neurologic syndromes, serological evidence of specific infection was found in 5.7% patients.[15] ADEM was diagnosed only if the patients had encephalopathy and brain lesions on MRI in addition to spinal cord involvement. The authors who proposed the IPMSSG criteria for ADEM have emphasized that polyfocal central nervous system (CNS) event without encephalopathy is inconsistent with ADEM and should lead to alternative diagnosis of MS or NMO.[6]

The mean age of presentation of NMOSD was 34.6 years. There was strong female preponderance (P = 0.0007). AQP4-IgG seropositivity was found in 18/23 (78.3%) patients. All the patients presented with severe ACTM at onset. The cervical or the cervicodorsal cord was affected in 16/23 (69.6%) patients. A retrospective Indian study had 44 patients of NMOSD between January 2010 and April 2014. The most common location of myelitis was cervicodorsal cord (77.5%), but the patients presented at an earlier age (median age, 26.5 years).[16] In contrast to patients of NMOSD, the patients of MS were slightly younger (mean age 31.1 years, $P = 0.4667$) and presented with milder APTM. CSF OCBs were found only in the patients of MS. The patients of postinfectious ADEM and PIM were younger ($P < 0.0001$) than other patients and commonly had severe myelitis at onset. Three patients of ATM had underlying autoimmune disorder (SLE 2, Hashimoto's disease 1). One patient of SLE had IgG-AQP positive NMOSD. Patients of NMOSD have predisposition to multiple autoimmune diseases, both organ specific and nonorgan specific. The immunopathological features of the spinal cord lesion in NMOSD are well characterized in contrast to that of other autoimmune disorders.[17]

Table 4: Etiology of chronic myelopathy

Etiology	*n* (%)*
Multiple sclerosis	1 (1.8)
Mixed connective tissue disorder	1 (1.8)
Neurosarcoidosis†	7 (12.7)
Hashimoto's disease	2 (3.6)
Varicella zoster virus	1 (1.8)
Human immunodeficiency virus-1	1 (1.8)
Mycobacterium tuberculosis	3 (5.5)
Treponema pallidum	3 (5.5)
Cryptococcus	1 (1.8)
Vitamin B_{12} deficiency	4 (7.3)
Folate deficiency‡	1 (1.8)
Chronic liver disease	2 (3.6)
Spinal dural arteriovenous fistula	2 (3.6)
Radiation	11 (20.0)
Paraneoplastic	1 (1.8)
Unknown	14 (25.5)

*Total number of patients ($n = 55$), †Only one case was probable neurosarcoidosis (hepatic biopsy showed noncaseating granuloma); all other cases were possible neurosarcoidosis, ‡One more patient had both Vitamin B_{12} and folate deficiency

The most common infectious cause of ASM was VZV. These patients presented with neurological deficits after a latency of 7–12 days from the onset of rash, but the latent period can extend up to several months.[18] Other infectious agents included JEV, *T. pallidum*, *T. gondii,* and cysticercosis. Involvement of anterior horn cells of the spinal cord is known in JE.[19] Isolated involvement of the spinal cord in the form of acute flaccid paralysis and urinary retention has been observed in Vietnam.[20] Acute myelitis has been reported as a rare manifestation of neurosyphilis.[21] *T. gondii* is a ubiquitous intracellular protozoan that can cause myelitis and intramedullary abscess in patients with AIDS, usually with concurrent brain involvement.[22] Isolated involvement of the spinal cord has been reported in the Indian literature.[23] Our patient had both brain and spinal cord involvement.

All the patients of SCI had severe neurologic deficits in less than four hours of onset. Clinical examination was consistent with anterior spinal artery infarct. SCI was caused by aortic dissection in one patient and cerebrospinal air embolism during percutaneous nephrolithotomy in another. Two patients had evidence of atherosclerotic vascular disease. Fibrocartilaginous embolism was suspected in one young patient.

Table 5: Clinical, magnetic resonance imaging, and cerebrospinal fluid profile of chronic myelopathy

Characteristic	Autoimmune* (*n*=10)	IM (*n*=9)	Metabolic (*n*=7)	Radiation (*n*=11)	Unknown (*n*=14)
Age in years, mean±SD	40.6±11.9	41.2±20.7	41.9±15.2	53.7±7.8	37.5±14.9
Male:female ratio	6:4	7:2	5:2	8:3	7:7
Bladder involvement, *n* (%)	5 (50.0)	5 (55.6)	2 (28.6)	8 (72.7)	6 (42.9)
PNS involvement, *n* (%)	6 (66.9%)	4 (44.4)	7 (100.0)	0 (0.0)	5 (35.7)
MRI, *n* (%)					
Short segment lesion	2 (20.0)	1 (11.1)	0 (0.0)	0 (0.0)	4 (28.6)
Long segment lesion	3 (30.0)	6 (66.7)	1 (14.3)	11 (100.0)	4 (28.6)
Gadolinium enhancement	2/4 (50.0)	1/6 (16.7)	0/1 (0.0)	3/6 (50.0)	1/6 (16.7)
No signal change	5 (50.0)	1 (11.1)	6 (85.7)	0 (0.0)	5 (35.7)
CSF, *n* (%)					
Pleocytosis‡	1 (10.0)	4 (44.4)	0/3 (0.0)	1/7 (14.3)	0 (0.0)
Protein >45 mg/dL	8 (80.0)	8 (88.9)	2/3 (66.7)	3/7 (42.9)	6 (42.9)

*Autoimmune disorders including sarcoidosis, mixed connective tissue disorder and Hashimoto's disease (multiple sclerosis not included). ‡Pleocytosis: > 10 cells/mm^3. IM = Infectious myelitis, PNS = Peripheral nervous system, SD = Standard deviation, MRI = Magnetic resonance imaging, CSF = Cerebrospinal fluid

ASM has been investigated thoroughly in France. In a single-center study of 79 patients between 1994 and 1999, the causes included MS (43.0%), systemic diseases (16.5%) such as Sjögren syndrome (SS), SLE, and antiphospholipid syndrome (APS), parainfectious (6.3%), and SCI (13.9%). The cause of myelopathy remained unknown in 13 (16.5%) patients.[24] In a subsequent multicenter study of 288 patients between 1994 and 2004, the causes of acute myelopathy were NMO (17.0%), MS (10.8%), SS (9.7%), SLE (3.5%), sarcoidosis (5.9%), APS (1.4%), SCI (18.8%), and parainfectious (17.3%). Idiopathic ATM was labeled in 45 (15.6%) patients based on the 2002 TMCWG criteria.[25] A follow-up study of the patients admitted in one of the centers between 1994 and 2004 showed that over half of the patients initially diagnosed with ASM of unknown cause subsequently developed MS, NMO, or a systemic autoimmune disorder. In about 29% of the patients, the cause remained unknown.[6] There are four important observations from these studies. First, the etiological profile was dominated by immune-mediated myelopathies. The diagnostic criteria proposed by Wingerchuk *et al*. in 1999 led to better identification of NMO in the subsequent studies. However, the serological test for AQP4-IgG was not commercially available till 2004. Some cases of ASM caused by SS and SLE in the first two studies could be related to NMO. Second, a high proportion of patients had SCI. The authors diagnosed SCI in all patients who reached the nadir of spinal cord dysfunction by four hours, by default as per the 2002 TMCWG criteria. Third, the proportion of unknown ASM in a study depends on the duration of the study. Follow-up of patients may reveal the true nature of the disease. Finally, despite long-term follow-up, the cause of ASM may remain unknown in more than one-fourth of the patients.

Some cases of CM were seen with autoimmune disorders (sarcoidosis, mixed connective tissue disease [MCTD], and Hashimoto's disease). Spinal cord sarcoidosis usually affects the cervicodorsal cord. MRI of the spinal cord may be normal or show linear signal abnormality on T_2-weighted imaging associated with patchy gadolinium enhancement, cord swelling with T_2 hyperintensity without enhancement, subpial enhancement, or thickening with enhancement of the cauda equina. Isolated spinal cord sarcoidosis is extremely rare. Serum ACE level is raised in only 50% of the patients.[26] CSF ACE is less sensitive but relatively specific (94-95%) for CNS sarcoidosis.[27] Only one patient had elevated serum ACE (98.0 U/L; reference range 12–68 U/L). He had multiorgan involvement, and his liver biopsy showed noncaseating granulomas. Other patients had normal serum ACE levels but elevated CSF ACE levels (4.0 U/L, 4.8 U/L, 2.7 U/L, 11.4 U/L, 3.5 U/L, and 3.4 U/L; reference range 0–2 U/L). In the absence of evidence of extra-CNS involvement, these patients were labeled as possible NS. Gallium-67 or fluorodeoxyglucose positron emission tomography scan was not possible in our institution. Very few cases of myelopathy have been described with MCTD and Hashimoto's thyroiditis (anti-TPO related myelopathy).[28,29] The pathogenic role of anti-TPO in spinal cord disease is not known and its presence might simply indicate the patient's general tendency to develop autoimmune disease.

The cases of tuberculous radiculomyelitis had meningeal enhancement and preceding chronic meningitis or lymphadenitis. PCR and culture for *M. tuberculosis* were negative. The diagnosis was aided by favorable response to anti-tubercular therapy. Currently, meningomyelitis is the most common form of spinal syphilis.[21] We have reported ATM, CM, and amyotrophy as manifestations of spinal syphilis from our institution previously.[30] The patient of cryptococcal myelitis had close contact with pigeons and hens. Although we considered the possibility of viral (CMV, VZV), tuberculous, and fungal infection in a patient of radiculomyelitis with HIV infection, CSF analysis was not confirmatory. Involvement of lumbosacral roots has been reported in HIV infection in the absence of CMV infection.[31]

The causes of Vitamin B_{12} and folate deficiency in our patients were combination of strict vegetarian diet, malnutrition, alcohol consumption, and phenytoin therapy. The patients of hepatic myelopathy had decompensated alcoholic liver disease with encephalopathy. The cause of spinal cord dysfunction could have been multifactorial (toxic effect of adulterated alcohol, nutritional deficiency, nitrogenous breakdown products by-passing the liver through shunt, and venous hypertensive myelopathy).[32]

In a patient of cancer, myelopathy can be paraneoplastic or can be caused by metastases, vascular phenomenon, complications of therapy (radiation, chemotherapy), nutritional deficiency, and infection.[33] A patient of longitudinally extensive myelopathy had underlying squamous cell carcinoma of lung. He received cisplatin which could have contributed to spinal cord dysfunction. However, the patient's symptoms progressed despite treatment with corticosteroids and withdrawal of chemotherapy. The hallmark tract-specific signal changes characteristic of paraneoplastic myelopathy was lacking. The patients of radiation myelopathy had received external beam radiotherapy with photons in fractionated doses over 1–3 months for carcinoma of pyriform sinus, larynx, or esophagus. The total dose (45–60 Gy) exceeded the accepted tolerance limit of the spinal cord. The median interval between the last dose of radiation and onset of neurologic symptoms was 8 months (range, 6–12 months). It has been hypothesized that radiation causes death of glial precursor cells and changes in the structure and permeability of the microvasculature lead to necrosis and secondary damage to glial cells. Loss of oligodendrocytes ultimately culminates in demyelination.[34]

MRI of the spine in the patients of spinal dural arteriovenous fistula showed longitudinally extensive T_2 hyperintense cord signal changes bordered by hypointense rim, cord swelling, and tortuous and dilated pial vessels. The shunting of arterial blood leads to venous congestion, venous hypertension, and progressive myelopathy.[35]

At the end of the study, cause of myelopathy remained unknown in 48 (31.8%) patients including 34 patients of ASM and 14 patients of CM. Nine patients of ASM had abnormal VEP or lesions on MRI of the brain. Two patients did not undergo MRI brain. One patient had ankylosing spondylitis (AS). ATM has been reported with AS, but the mechanism of spinal cord involvement is not known.[36] Another patient of aplastic anemia following hepatitis A infection was on therapy with cyclosporine and antithymocyte globulin when he developed acute myelopathy. Unfortunately, he succumbed to his illness before investigations for an infectious cause. Idiopathic ATM

was labeled in 21/96 (21.9%) patients of ASM. One patient had chronic myeloneuropathy following renal transplant. He was on multiple immunosuppressive drugs (mycophenolate mofetil, tacrolimus, and corticosteroid) and prophylactic antimicrobial therapy (co-trimoxazole, isoniazid, and valganciclovir). MRI showed mild atrophy of the dorsal spinal cord. CSF and metabolic profiles were normal. Although the patient improved by two mRS grades at 1 year follow-up after withdrawal of co-trimoxazole and folate supplementation, we are unable to say with uncertainty that the spinal cord dysfunction was caused by functional folate deficiency.

Poor outcome was seen in the patients of NS, vascular myelopathy, radiation myelopathy, hepatic myelopathy, and paraneoplastic myelopathy. The patients of NS had a poor response to corticosteroids and could not afford other immunosuppressive drugs. Poor outcome was also seen in 10/20 (50%) patients of NMOSD, 4/9 (44.4%) patients of MS, and 9/13 (69.2%) patients of unknown CM. In contrast, only 5/21 (23.8%) patients of idiopathic ATM had a poor outcome. Favorable prognosis of idiopathic ATM has been seen in studies from other countries. In the France study, about two-thirds of the patients had a good outcome after a mean follow-up of 3.6 ± 3.1 years.[25] In another study from Spain, 9.4% of the patients had a poor outcome after a median follow-up of 2.9 years.[37]

Conclusion

This study showed that noncompressive myelopathy affects people across all age groups. Most of the patients are middle-aged and many of them are active members of the family. Etiology was found in 68% of the patients. The causes of myelopathy included immune-mediated, infectious, vascular and metabolic disorders, and physical agents. Etiology remained elusive in about one-third of the patients. Examination of acute and convalescent sera for evidence of viral infection, salivary gland biopsy or serology for asymptomatic SS, and antibodies against myelin oligodendrocyte glycoprotein (anti-MOG) could have identified more causes but were not possible. As seen in other long duration studies, an underlying disease may be revealed in long-term follow-up of the patients.

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Conflicts of interest

There are no conflicts of interest.

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