REVIEW ARTICLE

Myelopathy associated with mixed connective tissue disease: clinical manifestation, diagnosis, treatment, and prognosis

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Abstract

Mixed connective tissue disease (MCTD) is a chronic autoimmune disease, which has a broad range of clinical manifestations shared by systemic lupus erythematosus, systemic sclerosis, polymyositis/dermatomyositis, and rheumatoid arthritis. MCTD is featured with high serum titers of anti-ribonucleoprotein antibodies and multiple system involvement. Its spinal cord involvement mainly manifests as transverse myelopathy (TM) and longitudinal extensive transverse myelopathy (LETM). Myelopathy in MCTD is extremely rare, and is usually characterized by serious neurological complications, such as paralysis or muscular paresis, sensory impairment, and smooth muscle dysfunction. Progressive clinical manifestations combined with laboratory examinations and magnetic resonance imaging examinations play important roles in the diagnosis of this disease. In order to prevent permanent neurological damage to the spinal cord, plasmapheresis and intravenous immunoglobulin can be performed in patients at the early disease stage. Early high-dose corticosteroids combined with cyclophosphamide, followed by low doses of immunosuppressors, can improve the long-term prognosis of patients. There are only nine global cases reported on MCTD associated with myelopathy at present. The death rate and disability rate of myelopathy in MCTD are extremely high. In this review, the pathomechanisms, clinical manifestations, auxiliary examination, diagnosis, differential diagnosis, treatment, and prognosis of myelopathy in MCTD were systematically elucidated.

Keywords Mixed connective tissue disease · Transverse myelopathy · Longitudinal extensive transverse myelopathy · Systemic lupus erythematosus

Introduction

Mixed connective tissue disease (MCTD) was first described in 1972 by Sharp et al. as a rare autoimmune disorder with multiple systems involvement [1]. Sharing some common clinical features with systemic lupus erythematosus (SLE) and polymyositis (PM), MCTD has been defined as a distinct disease [2, 3]. The involvement of the nervous system infrequently occurs in MCTD. Although the exact number remains unknown, the neurological disorder complicates the MCTD course in approximately 10% of patients [4]. The neurological manifestations of MCTD are usually mild. However, some patients with MCTD might have concurrent acute or subacute paraplegia, sensory deficits, dysfunction of the rectum and bladder sphincter, abnormal knee-jerk or tendon reflex, and other nervous system symptoms, which suggests the involvement of the spinal cord. Myelopathy can be diagnosed in these MCTD patients after excluding other diseases, such as infection, trauma, and tumor [5]. As an extremely rare complication of MCTD, myelopathy has been sporadically reported to be complicated with MCTD, and merely nine cases have been reported in the world at present. Due to the high rate of mortality and disability in MCTD complicated with myelopathy, wide attention has been given to this distinct clinical

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syndrome. In this review, the pathogenesis, clinical manifestations, laboratory and imaging examination, diagnosis, treatment, and prognosis of myelopathy in MCTD were systematically elaborated.

Mixed connective tissue disease

MCTD was first described in 1972 as a clinical syndrome with mixed features of SLE, polymyositis/dermatomyositis (PM/DM), systemic sclerosis (SSc), and rheumatoid arthritis (RA) and was identified to display high serum titers of anti-U1 ribonucleoprotein (anti-U1RNP) antibodies [1, 6].

MCTD has been considered to be the least common CTD, which is supported by a recent population-based epidemiology study conducted in Norway [7]. This study estimated a mean annual incidence of 2.1 per million per year and a point prevalence of adult-onset MCTD of 3.8 per 100,000 [7, 8]. The female-to-male ratio was 3.3 [7]. The observed female-to-male ratio in a large Hungarian cohort study reported a ratio of 12.3 [9].

Over the last years, significant advances have been made in disease pathogenesis understanding, and a central pathogenetic role of anti-U1RNP autoantibodies has clearly emerged [10–12]. It is believed that MCTD is mediated by the autoimmune response under the stimulation of external environmental factors on the basis of individual genetic background [13, 14]. Physiological stress factors, such as virus infection or ultraviolet radiation, lead to the release of a large number of apoptotic substances–containing RNP. In individuals with defects in eliminating these apoptotic particles, these particles encounter circulating immunoglobulin and dendritic cells; then after a series of immune processes, B lymphocytes are activated to secrete autoantibodies. These autoantibodies can recognize intact or modified individual U1 RNP proteins as well as structures composed of multiple subunits of the U1 RNP macromolecule and directly provoke the anti-RNP responses that lead to a series of related clinical manifestations [11, 15].

MCTD has a clinical spectrum including Raynaud's phenomenon, swelling hands with sausage-like fingers, sclerodactyly, interstitial lung disease, esophagus dysmotility, and myositis [1, 16]. In addition, lymphadenopathy, malar rash, kidney damage, or alopecia are less common [6]. Other common and unspecific constitutional symptoms include myalgias, arthralgias, fatigue, and fever [17]. However, the above clinical manifestations are not unique to MCTD and can also occur in SLE, SSc, RA, and PM.

The diagnosis of MCTD is often not easy, because MCTD has a broad range of symptoms and signs. MCTD may be initiated with any clinical manifestations of SLE, SSc, PM, or RA during the disease progression. Clinical manifestations or laboratory alterations usually occur sequentially. Therefore, many patients do not meet the classification criteria for MCTD at the beginning of the disease, or only meet the classification criteria for other autoimmune diseases, such as SLE, SD, PDM, or RA.

In view of the heterogeneity of clinical manifestations, several MCTD classification proposals have been made [18–20]. At present, there are four coexisting diagnostic criteria for MCTD, including the criteria of Alarcon-Segovia and Villarreal, Kahn and Appelboom, Sharp, and Kasukawa, which are distinctly different and make the diagnosis of MCTD more difficult. In a recent study, Capelli S. et al. compared three different classification criteria for the diagnosis of MCTD (Kasukawa, Alarcón-Segovia, and Sharp) with defined predictors, including clinical features and autoantibody levels, which are potential shared by other CTDs [20, 21]. Their results revealed that the criteria from Kasukawa were more sensitive (75%), when compared with those from Alarcón-Segovia (73%) and Sharp (42%) [21]. To date, the concordance of clinical findings, serologic features, and alterations from close clinical follow-up is the strategy to approach a more accurate diagnosis of MCTD.

At present, although most investigators have considered MCTD as a distinct disease, some researchers still consider that MCTD belongs to subgroups of certain definite connective tissue disease (CTDs) or a transient phase before developing into another CTD, or in fact, overlap syndromes [3]. However, recent genetic studies have confirmed that MCTD is an evident human leukocyte antigen (HLA)-linked disease [10, 22]. The HLA profiles of MCTD patients distinctly differ from patients with other forms of CTDs. Specifically, MCTD is predominantly associated with HLA-DR4 (especially the loci DRB1*15:01, DRB1*04, and *09:01), whereas SLE is fundamentally correlated to HLA-DR2 and DR3 [22]. As SSc shows an association with HLA-DR3 or DR5, PM/DM also shows an association with HLA-DR3. Therefore, these genetic studies support the notion that MCTD is a distinct entity independent of other identified CTDs, such as SLE and SSc.

Myelopathy in MCTD

Neuropsychiatric (NP) involvement in patients with MCTD is a severe manifestation of the disease, which drastically impacts the quality of life of patients. Due to the high mortality and disability rate, NP symptoms have been considered as one of the major manifestations of the proposed disease activity criteria for MCTD [23]. Among patients with MCTD, the prevalence of NP symptoms varied from 5 to 39% [24–26]. The most frequently reported neurological manifestations are trigeminal neuropathy [27–29], headaches [12, 30, 31], aseptic meningitis [24, 27, 32, 33], cerebrovascular disease [27, 34, 35], and peripheral neuropathy [24, 27, 28, 36, 37], while sensory-neural hearing loss [38], depression [39, 40], cognitive impairment [41], psychosis [39], optic neuritis [25, 42, 43], and transverse myelopathy [1, 4, 43–49] have been less

frequently reported. Furthermore, merely individual reports were distributed on restless leg syndrome [50], organic brain syndrome [51, 52], and posterior reversible encephalopathy syndrome [53].

Myelopathy is a rare and severe neurological complication of MCTD, in which merely nine cases have been reported at present (Table 1). MCTD complicated by myelopathy is mostly involved in young and middle-aged women, in which seven female patients in nine cases have been reported [4, 43–47, 49]. The average age of onset was 38.6 years old. Myelopathy can occur in the early stage of MCTD, since six cases (66.7%) developed myelopathy within 2 years from the onset of MCTD [4, 44, 46–49]. However, myelopathy was not identified as the first symptom in these patients with MCTD. The course of myelopathy in MCTD can be manifested as progressive aggravation, which progresses to the disease peak within several days, and sometimes even months.

Myelopathy in MCTD may present as transverse myelopathy (TM) with the involvement of less than 3 segments of the spinal cord, or as longitudinal extensive transverse myelopathy (LETM) [54], in which more than three segments (continuous or not) are involved. The main clinical manifestations include limb paralysis, muscle paralysis, sensory deficits, and sphincter-dominated smooth muscle dysfunction. In recent years, with the advancements in imaging technology, LETM was noted in one case of MCTD complicated by myelopathy through magnetic resonance imaging (MRI) examination.

Retrospective analysis revealed that all nine reported patients with myelopathy had inflammatory lesions that involved the thoracic spinal cord, and merely one case had lesions that involved both the cervical and thoracic spinal cord. This result suggests that the thoracic region is most frequently affected. Moreover, myelopathy was accompanied by other neurological manifestations in MCTD patients. For example, optic neuritis has been reported in two of nine previously reported patients [4], and depression and peripheral neuropathy have been reported in one of them [47, 48].

Myelopathy is one of 19 NP manifestations in SLE [55]. Compared with myelopathy in MCTD, more cases of myelopathy have been reported in SLE patients (Table 2). The incidence of myelopathy in SLE patients is 1–2% [55, 61], and most of these incidents occurred within 5 years after the onset of SLE [62], approximately 50% of SLE patients manifested myelopathy as the first symptom [56]. Apart from the thoracic region, almost 50% of patients with TM may have inflammatory lesions involved in the cervical spinal cord [56]. The course of myelopathy in SLE can manifest as acute aggravation, and develop to a peak in several hours or days. Complete or partial injury of the spinal cord can occur within 24 h, which results in a dramatically acute course [56–58]. LETM is more frequently reported in patients with SLE [59, 63]. In addition, more recurrences were found in SLE patients without treatments, or those treated with long-term, low or medium doses of glucocorticosteroids [64]. The episodes of at least one recurrence were noted in 21–55% of patients with myelopathy in SLE [56, 64, 65].

Taken together, compared with myelopathy in SLE, myelopathy in MCTD is relatively mild and progressively aggravated. The extent of inflammatory injury in MCTD is limited mainly to the thoracic spinal cord, and the recurrence rate is low, which may suggest that the prognosis of the myelopathy in MCTD is better than that in SLE.

Pathomechanism

As an inflammation-associated chronic disease, MCTD can be distinguished through the production of pathogenic autoantibodies that are resulted from perturbed immune responses in the host. At present, the specific pathomechanism of myelopathy in MCTD remains unclear. It is possible that multiple mechanisms are involved, including genetic factors, blood brain barrier dysfunction, vasculitis, vascular occlusion, autoantibody-mediated tissue and neuroendocrine-immune imbalance, neuronal damage, inflammatory mediators, and direct neuronal cell death, which makes the pathogenesis of myelopathy in MCTD very complex.

The autopsy results of a MCTD patient with myelopathy revealed focal infarction of the spinal cord parenchyma, glial cell proliferation, and thickening of the vascular wall, with a large amount of infiltrated inflammatory cells dominated by plasma cells [4]. The disintegration of the nerve axon and demyelination of the spinal cord were observed under a microscope [4]. Circulating anti-phospholipid antibody was also observed. Therefore, it has been postulated that the vasculitis of small arachnoid arteries of the spinal cord and arterial thrombosis may cause spinal cord micro-infarction. The involvement of the thoracic spinal cord may be due to its poor vascularization and pathological changes, such as ischemia and necrosis, would more likely occur when vasculitis happens.

Accumulating evidence has indicated that MCTD patients may have higher titers of anti-endothelial cell antibodies (AECA) and antibodies against phospholipid structures, such as cardiolipin (anti-CL) and β2-glycoprotein I (anti-β2GPI) [66, 67]. MCTD patients complicated with CVD were found to have increased titers of anti-U1RNP, IgG and IgM anti-CL, and AECA [67]. Some MCTD patients have also been diagnosed as bearing immune-mediated endothelial dysfunction and accelerated atherosclerosis. Therefore, endothelial dysfunction, which is an early marker of both vasculitis and premature atherosclerosis, may be exacerbated by those endothelium damaging antibodies present in MCTD patients.

Classical atherosclerosis accelerating factors, such as lipid abnormalities, were also observed in MCTD patients. The levels of total cholesterol and low-density lipoprotein cholesterol in MCTD patients were elevated, while the levels of

Table 1 The list of nine cases of myelopathy in mixed connective tissue disease in the world

Report's first author (year published)	Age	Gender	Duration (y)	Onset	Serologies	CSF	Involvement	Other NP involvement	Imaging	Treatment	Prognosis
Hao YL (2018) [48]	31	M	0.5	Progressive	ANA, RNP	Increased protein level, pleocytosis	Thoracic	Peripheral neuropathy	Spinal MRI Normal	Pred/HCQ	Improved. Sequela: urinary incontinence and grade 4/5 lower-extremity muscle strength.
Bhinder (2007) [47]	70	F	1	Progressive	ANA, RNP	Normal	Thoracic T2–T9	Major depression	Spinal MRI contrast enhancement of the cord	Pred/Aza /monthly IVIG	Improved. Sequlae: left proximal lower extremity was slightly weak
Weatherby (2000) [49]	46	M	2	Progressive over 3 months	ANA, RNP	Normal	Thoracic T9–T10	None	Spinal MRI cord atrophy	Pred/Aza	No change
Mok (1995) [46]	46	F	2	Progressive	ANA, RNP, Ro	Increased protein level	Thoracic	None	Spinal MRI Normal	Pre/Aza/anticoagulation	Improved. Lower-extremity muscle strength increased to grade 4/5 over 4 months
Flechtner (1994) [43]	19	F	5	Progressive with a relapsing course	ANA, RNP	Normal	Thoracic Cervical	Optic neuritis	Spinal MRI high signal intramedullary lesion	Pre/Aza/Plasmapheresis	Each relapse resolved. Sequlae: mild sensory disturbances
Obara (1991) [45]	42	F	n/k	Progressive	ANA, RNP	Pleocytosis	T4	None	Spinal MRI Abnormal	Pred/Aza	Resolved. Sequelae: painful tonic spasm
Yamaguchi (1991) [47]	53	F	n/k	Progressive	n/k	n/k	Thoracic	None	n/k	Pred	Improved
Pederson (1987) [44]	16	F	2	Progressive in 1 week	ANA, RNP, ds-DNA	n/k	Thoracic	None	CT brain normal, no spinal CT	Pred/Aza	Resolved. Sequelae: urge incontinence
Weiss (1978) [4]	24	F	1	Progressive over 4 weeks	ANA, ENA	Increased protein and glucose level	Thoracic	Optic neuritis	n/k	Pred/Aza	No change

ANA antinuclear antibody, *RNP* anti-ribonucleoprotein antibody, *Ro* anti-Ro antibody, *ds-DNA* anti-double-stranded DNA antibody, *ENA* extractable nuclear antigen, *CSF* cerebrospinal fluid, *MRI* magnetic resonance imaging, *CT* computed tomography, *Pred* prednisolone, *Aza* Azathioprine, *IVIG* intravenous immunoglobulin, *HCQ* Hydroxychloroquine Sulphate, *NP* neuropsychiatric, *n/k* not known

Table 2 Comparisons of myelopathy in MCTD and myelopathy in SLE [41, 56–60]

Items	Myelopathy in MCTD	Myelopathy in SLE
Morbidity	Rare, only eight cases reported	1–2%
Duration (year)	62.5% occurred within 2 years	Mostly within 5 years
Mode of onset	Progressive aggravation develops to peak in a several days, and even months	Acute aggravation usually develops to peak in 24 h
Whether it is a primary clinical manifestation	None	50%
The affected area of the spinal cord	Thoracic region	Thoracic and cervical region
LETM	Rare, only one case	More frequently reported
Other NP involvement	Optic neuritis, depression	Optic neuritis, depression, ophthalmoplegia, dysmnesia, convulsions, psychosis, aseptic cerebrospinal meningitis
Response to treatment	Mostly improved with mild or moderate sequelae	Therapeutic effect varies
Recurrence	Rare, only one case	21–55%

MCTD mixed connective tissue disease, *SLE* systemic lupus erythematosus, *LETM* longitudinal extensive transverse myelopathy, *NP* neuropsychiatric manifestations

high-density lipoprotein, apolipoprotein A1, and the natural antioxidant paraoxonase were clearly decreased [68, 69]. Increased C-reactive protein (CRP) levels and the presence of vascular endothelium damaging antibodies may have a direct effect on leukocyte recruitment and endothelial cell apoptosis, which might contribute to atherosclerosis in patients with MCTD [68, 70, 71]. Studies have indicated that antibodies to the family of heat-shock proteins (HSPs), for instance, the anti-HSP60 antibody, have an important effect on atherosclerosis by provoking vessel wall injury and result in early-onset atherosclerosis in MCTD patients [72].

Damage of the blood brain barrier (BBB) caused by thrombosis and vasculitis of small arachnoid arteries of the spinal cord may be the key link of myelopathy in MCTD [4]. Indeed, as an index of BBB permeability, the parameter Qalb increased in 8 of 14 (57%) patients, and appeared to inversely correlate with the anti-U1 RNP index [33]. Okada et al. also reported that 13 of 14 patients with aseptic meningitis presented with positive serum anti-U1 RNP antibodies, suggesting that anti-U1 RNP antibodies and the corresponding immune complex in cerebrospinal fluid (CSF) may function as pathogenic factors in NP involvements in SLE and MCTD [11, 15]. For patients with positive serum anti-U1 RNP antibodies, the sensitivity and specificity of CSF anti-U1 RNP antibodies for determining NP involvements were found to be 81.8% and 90.0%, respectively [33]. Therefore, BBB dysfunction significantly contributes to the pathogenesis of myelopathy in MCTD.

Clinical manifestations

Excessive damage to the spinal cord is the fundamental clinical manifestation of myelopathy in MCTD, and this damage progressively aggravates within several hours to weeks, and even months. Normally, a short period of nonspecific prodromal symptoms can be followed by bilateral lower limb paresthesia, accompanied by the sensation of numbness and reduction in muscular power [45–48]. These symptoms include fever, malasia, dizziness, nausea, vomiting, neck pain, and back or girdle pain of the trunk [45–48]. Progressively, the clinical manifestation evolves into a complete or partial paraplegia, or less frequently, tetraplegia, accompanied by sensory impairment, retention of urine, and fecal incontinence.

Motor dysfunction in patients with myelopathy is usually bilateral, but not necessarily symmetrical. Patients have been found to have multiple levels of motor dysfunction, such as complete paralysis, various levels of paresis, and a minor reduction in muscular power [44, 46–49]. In addition, patients with prominent gray matter signs can be clinically distinguished from those with white matter involvement. Usually, lower motor neuron syndrome with flaccidity and hyporeflexia is presented in patients with gray matter involvement. The symptom onset of motor dysfunction can be vigorous and is inclined to persist a long period with little or no recovery, which might reflect a possible irreversible injury to the medulla. Fever and urinary retention prior to irreversible paraplegia have been found to be associated with high disease activity [4, 47, 48]. Therefore, the signs of fever and urinary retention should be alerted in MCTD patients. The prompt diagnosis of this subtype is mandatory, but symptoms might be misrecognized due to the nature of the complexity of the disease. White matter myelopathy mainly manifests as upper-motor neuron syndrome with spasticity and hyperreflexia. Myelopathy with white matter involvement is less serious, and the course is more indolent with preserved strength. Intriguingly, the white matter involvement group is more often associated with optic neuritis. The prognosis is relatively good, although a higher risk of recurrence exists.

Consistent with the most commonly involved spinal segment, sensory impairment is usually found in the thoracic

section. The area of sensory impairment is usually clearly limited to the same spinal segment indicated by motor dysfunction. Similarly, sensory impairment can also be identified with various intensities, which range from a complete lack of sensitivity to a selective analgesia and thermesthesia with preserved deep and vibratory sensibility [43, 44, 46–49].

Almost all patients with myelopathy in MCTD have autonomous nervous system dysfunction. Urine retention and intestinal peristalsis with the retention of gases and feces are the initial symptoms [46–48]. Progressively, urinary incontinence develops, and intestinal peristalsis returns, but fecal incontinence persists [4, 44]. Hence, patients gradually develop neurogenic bladder. Moreover, followed by trophic changes in paralyzed limbs, vasomotor dysfunction and perspiration disorders occur below the border of the region of sensory impairment. Subsequently, the limbs become cool and livid, and distal edema may appear.

Laboratory tests

Serologically, the presence of high titers of antinuclear antibodies (ANA) with a mottled pattern and antibodies targeting the U1-RNP (usually the IgG isotype) are sine qua non for the diagnosis of MCTD. Moreover, other antibodies, such as antidouble-stranded deoxyribonucleic acid antibodies, antism antibodies, anti-aPL antibodies, and antiribonucleoprotein antibodies, can also be tested to support the diagnosis [4, 43, 44, 46–49].

The frequently reported hematological features include low-grade anemia or leukopenia, and sometimes thrombocytopenia and hemolytic anemia with positive Coomb's test [4, 47, 48]. In the acute stage, the increasing rate of erythrocyte sedimentation, elevated values of CRP, and reduced levels of complement constituent can also be observed [48].

Apart from these serological and hematological tests, CSF examination is another fundamental tool for diagnosis confirmation in myelopathy, and excluding possible infection. A variable finding in CSF may be identified, ranging from normality to pleocytosis with lymphocyte predominance, and an increase in protein content [4, 45, 46, 48]. Unfortunately, the results of the CSF general tests and sediment test, which demonstrated as pleocytosis, high protein levels, and low glucose levels, could not distinguish patients with myelopathy from patients with myelitis in the course of bacterial infections. Therefore, additional adequate culturing experiments are required to exclude possible infections.

Imaging

MRI is highly sensitive in evaluating injuries to the spinal cord. In clinical examinations, the protocol for MRI images is to cover the level corresponding to the clinically observed neurological damage. However, researchers strongly recommend this examination to include the entire cord.

Inflammatory changes in the spinal cord are visible in T2weighted MRI [43, 45, 47]. With or without an edema, the intensification of a signal from the central part of the spinal cord can result in an increase in spinal cord thickness by several millimeters. As observed in several cases, the contrast uptake can be observed to determine the occurrence of spinal cord injuries [47]. Particularly, in patients with longer durations, these affected spinal cord segments may merely become thinner [49].

It is worth noting that MRI results may be normal in some cases, especially for patients in the early stages [46, 48]. The interpretation of MRI findings depends on the timing of the examination, as well as the stage of the disease. Another reason for this is possibly related to the utilized magnetic field strength. Hence, a magnetic field strength not lower than 1.5 T (Tesla units) is recommended to increase the yield. For patients with normal contrast MRI, a repeat examination at 2–7 days after the initial manifestation is recommended.

Computer tomography (CT) should not be used for the diagnosis of myelopathy due to its low sensitivity. This technology should only be used for cases where the MRI instrument is unavailable, and for the sake of excluding compressive causes of the spinal cord.

General diagnosis

Clues to the exact diagnosis of myelopathy in MCTD can be obtained from the CSF analysis, MRI examination, neurophysiological features, and immunological studies. Disease possibility should be considered when the MCTD patient progresses to one or more of the following signs/symptoms: sensory, motor, or autonomic dysfunction attributable to the spinal cord, and a clearly defined sensory level and peaking of symptoms within hours to several days, or even weeks, with or without bowel or bladder involvement. Furthermore, evidence of inflammation of the spinal cord is required, such as CSF pleocytosis, elevated protein content and IgG level, or MRI with gadolinium consistent with myelopathy. The diagnosis of myelopathy cannot be ruled out in patients without signs of any abnormalities of the spinal cord by MRI examination.

Differential diagnosis

Spinal cord transverse damage is resulted from multiple etiological causes [57, 73–76]. The key features giving most differential diagnostic value include speed of symptom onset (hyperacute, acute, subacute, or chronic), disease course (monophasic or relapsing or progressive, complete partial or no recovery, stable or fluctuating), lesion characteristics on MRI (the length and position, along with the cross-sectional pattern of involvement such as gray or white matter, anterior or posterior or lateral locations, symmetrical or asymmetrical
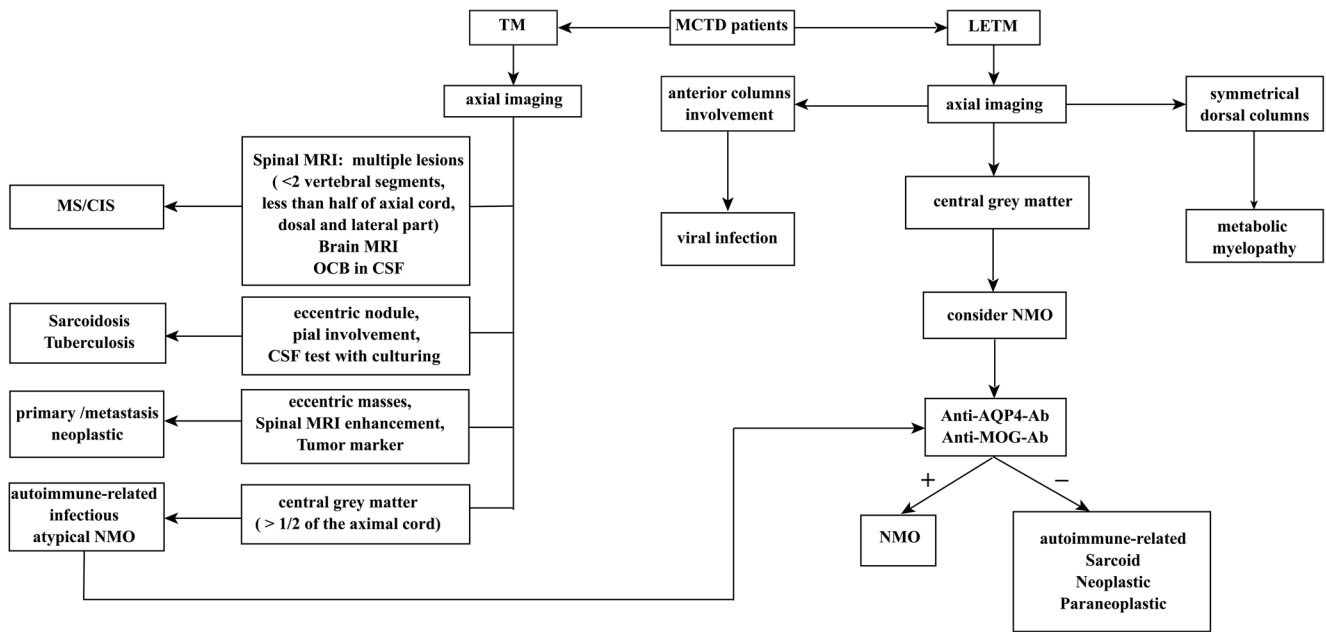
Fig. 1 Flow diagram approach to MCTD patient presenting acute/subacute myelopathy. AQP4, aquaporin-4; MOG, myelin oligodendro-cyte glycoprotein; MS, multiple sclerosis; NMO, neuromyelitis optica; CIS, clinically isolated syndrome; OCB, oligoclonal bands; MCTD, mixed connective tissue disease; LETM, longitudinal extensive transverse myelopathy; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging

and gadolinium enhancement pattern), and other additional clinical features. Myelopathy in MCTD usually manifests as acute or subacute course, so it is particularly important to differentiate it from diseases presenting as an acute or sub-acute onset (Fig. 1).

In MCTD patients with abnormal CSF test results and fever, a possible concurrent neural infection must be considered. Since patients with diagnosed MCTD usually receive immunosuppressive agents, they are at higher risk of pathogenic infection. Therefore, the careful examination of the patient's history and a thorough analysis of all clinical manifestations, especially additional adequate CSF culturing experiments are required to exclude possible infections. Acute to subacute infective myelitis is most commonly viral and detecting the viral DNA in the CSF may help.

The etiology of vascular myopathy mainly includes arteriovenous malformations, cavernomas, systemic hypoperfusion, vasculitis, and embolism [77]. The symptom onset is usually abrupt (within minutes), but the time from onset to nadir may be a few hours. The clinical symptom of spinal ischemia can cover many manifestations, such as dissociation of sensation, spastic paraparesis or tetraparesis, and the perseveration of proprioception, which are typical for vascular lesions of the spinal cord [78]. The MRI results are featured by pencil-like lesions in the anterior part of the spinal cord with typical hyper-intense long lesions. Diffuse weight imaging is promising in the diagnosis of spinal ischemia.

Notably, patients with myelopathy are inclined to be erroneously diagnosed as isolated nervous system diseases with multiple sclerosis (MS) and neuromyelitis optica (NMO) [75]. Therefore, the definite identification of these three diseases (NMO, MS, and myelopathy in MCTD) is particularly important (Table 3). As mentioned above, some patients may present with optic neuritis at the same time. In particular, for MCTD patients complicated with myelopathy who also have optic neuritis, other diseases, such as MS and NMO, should be excluded first, and then the simultaneous involvement of optic nerve and spinal cord should be considered.

MCTD patients with less than 3 spinal segments involved should be differentiated from MS or clinically isolated syndrome (CIS). The diagnosis of MS can be confirmed by past demyelination history combined with multiple demyelination lesions in brain and spinal cord MRI, and positive oligonucleotide band in CSF [84]. CIS refers to the first episode of isolated central nervous system demyelinating disease, which mainly includes optic neuritis, isolated brain stem damage, or spinal cord injury [82, 85]. CIS of the spinal cord is featured with dominant and asymmetrical sensory signs and symptoms, including mostly paraesthesias which usually slowly spread from the legs to the upper part of the body, are more pronounced on one side, and often presents with a band-like sensation, or pressure around the abdomen or chest [85]. MRI in patients with CIS is also typical with small demyelinating lesions, which involve less than two segments, and are most often located in the posterior or lateral part of the spinal cord [82]. Acute or subacute onset with main cervical spinal cord involvement and incomplete spinal cord injury involving less than two segments in MRI can help confirm the diagnosis of

Table 3 Comparisons of optic neuromyelitis [79–81], multiple sclerosis [82, 83], and myelopathy in mixed connective tissue disease

Diseases	NMO/NMOSD		MS	Myelopathy in MCTD
	Anti-AQP4-Ab (+)	Anti-MOG-Ab (+)		
Disease onset	About 40 years on average	In their 3rd or 4th decades	Young adults	Young and middle-aged adults
Female ratio	>90%	No difference	75%	87.5%
Optic neuritis	poor visual outcome; bilateral and > half the length of the optic nerve; more optic chiasmal involvement	good visual outcome; much longer; canalicular and intracranial (>90%) not in optic chiasma	Unilateral and short-segment involvement; less chiasm involvement	
Other clinical manifestation	>94% LETM (>3 vertebral segments, central gray matter); Frequently coexisting autoimmune disease	2/3 LETM, 1/3 TM (central/lateral); Brain stem symptoms; Rarely coexisting autoimmune disease	isolated brain stem damage spinal cord injury; cerebellar ataxia	Transver myelopathy involving 1–3 vertebral segments or LETM (>3 vertebral segments involving the central part of the spinal cord)
Specific antibodies	Antibody to aquaporin-4	Serum antibody to MOG	Antibody to myelin basic protein and MOG	Serum anti-RNP antibody
CSF test	OCB negative (<15%) IL-6 high GFAP high a raised protein (>2.1 g/L) sometimes mild pleocytosis	OCB negative (6–13%) IL-6 high GFAP negative sometimes mild pleocytosis	OCB positive (>80%) IL-6 low GFAP low CSF IgG index high Pleocytosis ($<15 \times 10^6$/L, mainly lymphocytes)	OCB negative Varying from normality to pleocytosis with lymphocyte predominance and an increase in proteins.
Spinal MRI	Cervical–upper thoracic cord (central gray matter) Acute phase: distinct and prominent; LETM; Contrast enhancement (+); Swelling in spinal cord Chronic phase: spinal cord atrophy (++); MR imaging abnormalities could remain	Cervical and/or lower spinal cord (central gray matter?) Acute phase: no swelling in spinal cord; contrast enhancement (±); H-shaped in the cross section Chronic phase: spinal cord atrophy (±); MR imaging abnormalities usually shrink	acute phase: small lesions (2 vertebral segments, less than half of the transverse section of the spinal cord) chronic phase: rare atrophy	Acute phase: varies from normal to swelling, T2-hyperintense, and gadolinium enhancement Chronic phase: atrophy
Brain MRI	Hypothalamic Periventricular Basal ganglia Brainstem (area postrema) Corpus callosum Cerebellum	Juxtacortical/subcortical (rare in the cerebral cortex) Pulvinar Paralimbic system Brainstem Cerebellum	Juxtacortical/subcortical (could involve the cerebral cortex) Periventricular, subcortical white matter, cerebellum, brain stem Dawson's sign open-ring sigh	Nonspecific change
Therapy	Prednisolone, rituximab, immunosuppressive drugs	Prednisolone, rituximab, immunosuppressive drugs	Disease-modifying treatments, including interferon beta, fingolimod, rituximab, natalizumab	Prednisolone, immunosuppressive drugs, plasmapheresis, IVIG
Prognosis	Poor prognosis	Better prognosis	Favorable prognosis with mild or moderate sequelae	improved with mild or moderate sequelae

NMO/NMOSD neuromyelitis optica/neuromyelitis optica spectrum disorders, MS multiple sclerosis, AQP4 aquaporin-4, MOG myelin oligodendrocyte glycoprotein, MCTD mixed connective tissue disease, LETM longitudinal extensive transverse myelopathy, CSF cerebrospinal fluid, OCB oligoclonal bands, IL-6 interleukin − 6, GFAP glial fibrillary acidic protein, MRI magnetic resonance imaging, IVIG intravenous immunoglobulin

spinal cord CIS. Particularly, for patients who have experienced CIS and have an abnormal MRI scan, a second episode (or relapse) would appear, and they would manifest the onset of clinically definite MS.

Another diagnostic problem is posed by MCTD patients who manifest as LETM. Of note, LETM can be the first presentation of NMO, and thus all such patients need to have their serology for AQP4-Ab and myelin oligodendrocyte glycoprotein (MOG) antibody tested [74, 86]. Recent studies have confirmed that AQP4 antibodies and NMO-IgG are highly specific and sensitive in NMO patients, making them part of the diagnostic criteria for NMO [79]. Its clinical features are recurrent optic neuritis and transverse spinal cord injury. The typical imaging findings are bright spotty lesions on T2-weighted images and corresponding dark lesions on T1-weighted images with central gray matter or holocord involvement, usually including the thoracic cord [79, 87]. However, AQP4-Ab positive NMO can present with short lesions in up to 14% of initial TM attacks [88]. The lesions can be eccentric, and some are asymptomatic. Ring-enhancing lesions develop in about one-third of these patients [80]. These imaging features have been described as relatively specific for distinguishing NMO from other entities, including MS.

Sporadically reported cases suggest that NMO may coexist with SLE, SS, MCTD, myasthenia gravis, autoimmune thyroiditis, or other systemic autoimmune diseases [81, 89–92]. Studies conducted by Arabshahi B et al. revealed that about half of NMO patients with systemic connective tissue disease had positive serum AQP4-Ab, while the serum AQP4-Ab in SLE or systemic sclerosis patients without NMO were negative [93]. MCTD patients complicated with spinal cord white matter damage and optic neuritis and positive AQP4-Ab should be considered as cases of MCTD combined with NMO, rather than the basic pathological changes of systemic autoimmune diseases, such as nervous system complications caused by vasculitis.

For MCTD patients with LETM, clinicians may not exclude a metabolic cause. The most common metabolic myelopathy is caused by vitamin B_{12} deficiency [94]. Of note, the neurological disease may occur either with hematological manifestations or as a result of a functional deficiency without decreased serum vitamin B_{12} level, which is supported by a raised serum methylmalonic acid or homocysteine and a low concentration of transcobalamin-2 [94]. The classic MRI finding is a long cord lesion with symmetrical T2 hyperintensity in the posterior and lateral columns, which most commonly involves the thoracic cord [95]. Anterior column T2 hyperintensity and contrast enhancement of the lesion are rare but can occur in isolated cases. Furthermore, copper deficiency is another cause of metabolic myelopathy. The differences in imaging of copper deficiency cases, compared with vitamin B12 deficiency, include increased prevalence of cervical cord and central cord involvement in addition to the similar posterior column pathology [96]. A low serum copper and ceruloplasmin would be in keeping with this diagnosis.

Treatment

The optimal therapeutic strategy of myelopathy in MCTD is less well-defined, and there is no unanimous therapy due to its rarity. In order to minimize permanent neurological damage to the cord, an aggressive approach with the prompt treatment of high-dose steroids and immunosuppressors is recommended, as referred by the treatment scheme of myelopathy in SLE [57, 58, 73]. The treatment was initiated with pulse dose therapy by intravenous injection of 1 g/day of methylprednisolone for 3 days, combined with azathioprine at a dose of 1–2 mg/kg per day [47, 48]. On the 4th day after treatment initiation, azathioprine and steroids were subsequently changed to oral prednisone at 1 mg/kg bodyweight/day for 6 months to 1 year, and the prednisone dosage was slowly tapered to a maintenance dose at 10 mg per day in 3 months. However, the duration of maintenance treatment would vary in patients.

Some scholars suggest that patients in critical condition, such as poor responsiveness to hormone therapy or recurrence, can be treated with intravenous immunoglobulin injection [43, 47]. In addition, in order to rapidly clear specific autoantibodies in plasma and prevent the formation of permanent injury to the spinal cord, plasmapheresis can be conducted, although the responses vary in patients [43, 47]. Bhinder et al. [47] reported a severe case with monthly IVIG at a dosage of 0.4 g/kg per day for 5 days, which was continued for a period of 6 months apart from the high-dose steroid and immunosuppressors. After treatment, the patient's condition significantly improved, and there was no relapse during the follow-up. Flenchter et al. [43] reported a case with recurrent episodes of optic neuropathy and transverse myelopathy. At the time of the second attack, plasmapheresis performed at regular intervals of 3 days while immunosuppressive medication (azathioprine, prednisolone) was continued. The patient's symptoms significantly improved after the 6th plasmapheresis, and the time interval of the plasmapheresis was extended to approximately once a month. Thereafter, each recurrence was well-controlled with the combination of plasmapheresis and immunosuppressive medication.

In addition, some studies have also reported the use of rituximab (anti-CD20 receptor antibody), autologous bone marrow transplantation, intrathecal dexamethasone, and methotrexate to treat severe SLE neurological complications [26, 65, 97]. When the patient has contraindications, or does not respond to hormone and immunosuppressive therapy, the above treatment plans can be considered. Moreover, hydroxychloroquine would reduce the number of relapses in SLE patients [60, 98].

Symptomatic treatment is critical in the therapy of patients with ATM. When urinary retention occurs, Foley catheter

insertion to the urinary bladder is necessary in the early stage of the disease, because the overflow of the bladder caused by sphincter paralysis may lead to rupture [48]. Patients with spinal paralysis can easily develop bedsores due to immobility, sensory impairment, and damaged autonomic nervous system. Therefore, intensive anti-bedsore care is needed. Patients with myelopathy also require complex and intensive rehabilitation, which should be started at the diagnosis of the disease. Before the start of the rehabilitation training, venous thrombosis of the limbs needs to be excluded to avoid serious consequences.

Prognosis

The clinical course of myelopathy in MCTD varies. The prognosis of patients can be obvious improvement with minor sequelae, partial remissions, arrest of progress of the disease and deterioration of neurological symptoms, and sometimes relapse or death might occur [4, 43–49]. The time needed for improvements in neurological function may vary, which ranges between several days and many months [46–49]. It has recently been agreed that the early introduction of immunosuppressive therapy with intravenous azathioprine and high doses of glucocorticosteroids, followed by oral low doses of glucocorticosteroids, improves the long-term prognosis of patients with myelopathy in MCTD.

As highlighted by previous reports, serious neurological manifestations, such as myelopathy, may rarely complicate in the course of MCTD, but these appear to intrinsically have a better prognosis than a similar presentation in SLE. In addition, the prognosis of patients with MRI alterations is worse than that of patients without such abnormalities [43, 47]. The prognosis is particularly poor in patients with long extensive spinal lesions of the spinal cord [43]. When patients have obvious improvement at the onset of immunosuppressive therapy, these patients would probably also have a good prognosis, as they would respond well to the immunosuppressive therapy.

Flenchter et al. [43] reported a patient with myelopathy in MCTD, who received long-term, low-dose hormone therapy. One of the recurrences in this patient was observed right after hormone dosage reduction. In order to prevent further recurrences, a continuous maintenance immunosuppressive treatment was mandatory, as suggested by this case. In addition, hormone reduction in the patients receiving long-term low-dose hormone therapy should be performed with caution, and regular laboratory examinations should be periodically conducted.

Conclusion

Myelopathy in MCTD is extremely rare. Although its diagnosis is complex due to the heterogeneity of the pathological processes, its treatment remains challenging. Similar to MS

and SLE complicated by myelopathy, this disease often demonstrates spinal cord involvement with serious neurological complications, such as paralysis or muscular paresis, sensory impairment, and smooth muscle dysfunction. Progressive clinical manifestations combined with laboratory examinations and MRI examinations play important roles in the diagnosis of myelopathy in MCTD. CSF examination is a fundamental tool for diagnosis confirmation in myelopathy, and excluding possible infection. Although the treatment for myelopathy in MCTD might be individualized, an aggressive approach with prompt treatment of high-dose steroid and immunosuppressors is recommended to minimize permanent neurological damage to the spinal cord, and plasmapheresis can also be conducted to rapidly clear the specific autoantibodies in the plasma. The oral administration of low doses of glucocorticosteroids and other immunosuppressors can improve the long-term prognosis of patients with myelopathy in MCTD. The ongoing surveillance and more reports on this rare presentation in MCTD would greatly help in better understanding its pathomechanisms, and shed more light on the definite diagnosis and effective therapy of this disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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