REVIEW ARTICLE

Myelitis in the course of systemic lupus erythematosus

Review

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KEY WORDS

longitudinal myelitis, lupus myelopathy, systemic lupus erythematosus (SLE), transverse myelitis

ABSTRACT

Myelopathy manifested clinically as acute longitudinal or transverse myelitis constitutes one of the most severe and rare neuropsychiatric manifestations of systemic lupus erythematosus (SLE) (1–3% of patients). Myelitis has been observed less commonly in other connective tissue diseases, mostly in antiphospholipid syndrome, and rarely in Sjögren's syndrome, Behçet's disease and mixed connective tissue disease. Acute transverse myelitis (ATM) may also be present in diseases of various etiology, including multiple sclerosis, sarcoidosis, infectious diseases and malignancies.

Myelitis in SLE is manifested as a dramatic spinal cord injury leading to paralysis or muscular paresis, sensory deficits, and smooth muscle dysfunction usually in the form of sphincter dysfunction. The imaging technique of choice in case of suspected ATM is magnetic resonance imaging with intravenous contrast agent (gadolinium diethylenetriamine-pentaacid). Cerebrospinal fluid (CSF) examination in patients with ATM in the course of SLE indicate usually pleocytosis with prevalence of granulocytes, increased protein levels, low glucose levels, significantly hindering differential diagnosis in the early stage of the disease. Observations made by the authors (2 female patients with SLE) show that antibodies specific to SLE can be found in the CSF collected in the acute phase of myelitis. These observations have not yet been confirmed by other researchers.

Early introduction of intravenous immunosuppression with large doses of cyclophosphamide and glucocorticosteroids improves the long-term prognosis. Other therapeutic approaches have been also used in more severe cases. Even with appropriate therapy, prognosis in this disease is uncertain.

INTRODUCTION Acute transverse myelitis (ATM) is a consequence of inflammation of various etiologies, resulting in damage to spinal neurons and nerve tracts passing through the spinal cord. Its sequelae include paralysis or muscular paresis, sensory deficits and smooth muscle dysfunction, usually in the form of sphincter dysfunction.

Prevalence of ATM in the general population, regardless of etiology, is estimated at 1 to 4 new cases per million a year.[1] Two prevalence peaks are observed, the first one between the age of 10 and 19, and the second between the age of 30 and 39. It is believed that there is no family predisposition or sex-associated preference.[1]

ATM may occur in the course of various diseases, including systemic connective tissue diseases, sclerosis multiplex, sarcoidosis, infectious diseases (of bacterial etiology such as borreliosis, *Mycoplasma pneumoniae* infection, syphilis, tuberculosis, or caused by viruses such as measles, mumps, rickettsiosis, AIDS, diseases caused by *Coxsackie*, ECHO, *Herpes, Epstein-Barr* viruses), or as a paraneoplastic syndrome.[2-4]

It has recently been estimated that in approximately 10% of cases it is unfeasible to determine ATM etiology during the acute stage of the disease.[5] In these cases the disease is referred to as idiopathic ATM. In 2001 an international group of experts defined criteria for diagnosis of idiopathic ATM (TABLE 1).[1] Clinical symptoms or laboratory abnormalities suggesting the diagnosis of

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TABLE 1 Criteria for idiopathic acute transverse myelitis developed by the Transverse Myelitis Consortium Working Group in 2002[1]

Inclusion criteria
Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord
Bilateral signs and/or symptoms (though not necessarily symmetric)
Clearly defined sensory disorder level
Exclusion of extra-axial compresive etiology by neuroimaging (MR or myelography; computed tomography of spine not adequate)
Inflammation within the spinal cord demonstrated by cerebrospinal fluid pleocytosis or elevated IgG index *or* gadolinium enhancement. If none of the inflammatory criteria is met at symptom onset, repeat MR and lumbar puncture evaluation between 2 and 7 d following symptom onset meet criteria
Progression to nadir between 4 h and 21 d following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from the point of awakening)
Exclusion criteria
History of previous radiation to the spine within the last 10 years
Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery
Abnormal flow void on the surface of the spinal cord associated with i.e., AVM
Serologic or clinical evidence of connective tissue disease (sarcoidosis, Behçet's disease, Sjögren's syndrome, SLE, mixed connective tissue disorder, etc.)[a]
Central nervous system manifestations of syphilis, Lyme disease, HIV, human T-cell lymphotropic virus-1, *Mycoplasma*, other viral infections (e.g. *herpes simplex virus*, *varicella zoster virus*, Epstein-Barr virus, *cytomegalovirus*, *human herpes virus*, enteroviruses)[a]
Brain MR abnormalities suggestive of multiple sclerosis[a]
History of clinically apparent optic neuritis[a]

a Do not exclude disease-associated acute transverse myelitis

According to the experts' opinion, a diagnose of ATM in course of a particular disease requires also meeting all the inclusion criteria and determination of the disease in the course of which ATM occurred, mentioned in one of the inclusion criterion.

Abbreviations: ATM – acute transverse myelitis, AVM – arteriovenous malformation, MR – magnetic resonance, SLE – systemic lupus erythematosus

a connective tissue disease constitute one of the exclusion criteria for idiopathic ATM.

Among systemic connective tissue diseases, ATM is most commonly encountered in systemic lupus erythematosus (SLE), less frequently in antiphospholipid syndrome (APS) or secondary antiphospholipid syndrome (SAPS).[6] ATM was only sporadically reported in the course of other connective tissue diseases, including Sjögren's syndrome, Behçet's disease, mixed connective tissue disease.[1,2]

Pathomechanism A precise mechanism of inflammatory lesion formation in the spinal cord of patients with SLE has not yet been discovered. Based on papers published in the 1970s it is suggested that vasculitis and arterial thrombi leading to spinal cord ischemic necrosis, are responsible for pathological lesions.[7] Autopsy showed various vascular changes within the spinal cord in 11 out of 12 individuals who died because of ATM. The abnormalities included ischemic necrosis, infarction or malacia in 8 cases, vasculitis without necrotic foci in 2 cases and degenerative lesions within the white matter with adventitia thickening in small arteries in 1 patient. Vascular pathologies involved perivascular lymphocytic infiltrations, proliferation of connective tissue, thrombi in small vessels (small arteries and arterioles), micro-extravasations within the spinal cord parenchyma.[7] Autopsy performed by other authors in one patient showed perivascular cellular infiltrations, presence of inflammatory cells and colliquative necrosis of the spinal cord.[8] It is believed that autoimmunologic phenomena similar to those present in other organs involved in SLE are responsible for development of vascular lesions in the spinal cord.[7] Lack of more recent pathomorphological data is probably a result of a more favorable clinical course of the disease associated with intensive immunosuppressive therapy.

Myelopathy in patients with systemic lupus erythematosus Involvement of the nervous system is common in patients with SLE. Depending on the accepted criteria it is estimated that symptoms of nervous system involvement are present in approximately 25–80% of patients.[9,10]

In 1999 the Research Committee of the American College of Rheumatology (ACR) defined 19 neuropsychiatric syndromes that may occur in the course of SLE and determined precise criteria of their diagnosis.[10,11] The most common neuropsychiatric forms of SLE include: headaches, cerebrovascular disease, mood changes, cognitive disorders and convulsions.[9]

Myelopathy is one of the less common neuropsychiatric manifestations of SLE (1–3% of patients).[4,9,12,13] Diagnostic criteria for myelopathy in SLE according to the ACR are presented in TABLE 2. The most common form is ATM. Longitudinal myelitis is less frequently observed.[14]

Until recently, it has been believed that inflammatory lesions in the course of myelopathy in patients with SLE involve a relatively short, 1- to 4-segment-long section of the spinal cord.[15] All cases of myelitis were referred to as ATM.

TABLE 2 Diagnostic criteria for myelopathy in course of systemic lupus erythematosus proposed by the American College of Rheumatology in 1999[37]

Usually rapid onset (hours or days) of one or more of the following
Bilateral weakness of legs with or without arms (paraplegia/tetraplegia), may be asymmetric
Sensory impairment with cord level similar to that of motor weakness; with or without bowel and bladder dysfunction
Exclusion criteria
Mass lesion causing compression of or within spinal cord (e.g., prolapsed disc, tumor, hematoma, or ruptured spinal arteriovenous malformation)
Cauda equina lesion

Currently, possibly due to improvement in quality and availability of magnetic resonance imaging (MR), an increasing number of diagnoses of the so-called longitudinal myelitis is noted. The condition is associated with inflammatory changes involving spinal cord sections of more than 4-segment length, usually several segments or even the whole length of the spinal cord. Inflammatory changes are not always continuous. Sometimes they are present in 2 separate localizations at some distance from each other.[14,16,17]

The term ATM is still used by several authors to describe all cases of myelitis, regardless of the length of the spinal cord occupied by inflammation.[1,2,5] Use of the term is justified because, regardless of the number of spinal cord segments involved by inflammation, always the same clinical presentation is observed – transverse spinal cord damage. Recently a report has been published. It recommends that all cases of myelitis – both transverse and longitudinal – in patients with SLE be referred to as lupus myelopathy.[18]

In patients with myelitis in SLE, symptoms of acute spinal cord damage are usually accompanied by other neurological manifestations of SLE, most commonly by optic neuritis. Other less common symptoms include depression, dysmnesia, convulsions, psychosis, ophthalmoplegia.[4,13,19] There are also reports of single ATM cases preceded by aseptic cerebrospinal meningitis.[19-21]

ATM with associated optic neuritis is referred to as Devic's syndrome in literature and currently recognized as a separate disease belonging to demyelinating diseases.[22] Coexistence of optic neuritis and ATM has been found in 21–48% of patients with myelopathy in SLE.[4,18]

In the majority of cases, myelitis occurs shortly after SLE is diagnosed, usually within the first 5 years from the onset of the disease.[4,13] In nearly half of patients ATM is the first clinical manifestation of SLE.[4] The disease usually affects young and middle-aged females, although some males might be affected.[4,13]

Recurrence of myelitis within several months after the first episode of myelopathy is relatively frequently observed in patients with ATM in SLE. At least one recurrence of ATM in SLE is noted in 21–55% of patients.[4,13,23] Episodes of recurrence were found mainly in untreated patients and in patients receiving long-term therapy with low or medium doses of glucocorticosteroids.[13]

Clinical observations Myelopathy in SLE is manifested as a dramatic damage to the spinal cord progressing within several hours up to several days. Usually symptoms of transverse, partial or complete damage to the spinal cord develop within 24 hours.[5,7]

An episode of acute myelitis may be preceded by general symptoms, including fever, malasia, dizziness, photophobia, nausea, vomiting, neck pain, back or girdle pain of the trunk.[6,8] In cases of patients with accompanying cerebrospinal meningitis nuchal rigidity was also observed.[20,21]

Usually a short period of non-specific prodromal symptoms is followed by bilateral lower limb paresthesia with accompanying sensation of numbness and reduction of muscular power, quickly evolving into a complete or partial paraplegia, or less frequently tetraplegia, with accompanying sensory impairment, retention of urine and fecal incontinence.[7,8]

Motor dysfunction is always bilateral but not necessarily symmetrical. The level of motor dysfunction may be different, ranging from a complete paralysis, various levels of paresis, to a minor reduction in muscular power manifested by some difficulties with standing and walking.[13]

During the initial period paralysis of limbs is a flaccid paralysis with abolition of deep reflexes and reduced muscular tonus. Spastic paralysis develops in several days or weeks. Sometimes, flaccid paralysis persists.[3,5]

Myelitis may be ascending. Initially paresis/paralysis involves only lower limbs and gradually covers also upper limbs and finally it may lead to paralysis of respiratory muscles with resulting respiratory failure.[7,21] The level of inflammatory changes occurrence in the spinal cord and extent of the inflammatory process are factors deciding on the scope of motor dysfunction and the level of sensory impairment.

The area of sensory impairment is usually clearly limited.[3] Similarly to motor dysfunction, sensory impairment may be of various intensity, from a total lack of sensitivity below the level corresponding to the spinal cord damage, to a selective analgesia and thermesthesia with preserved deep and vibratory sensibility.[24] Sensory impairment is commonly found in the thoracic section of the trunk, which is explained by poor vascularization of the corresponding section of the spinal cord.[4]

Autonomous nervous system dysfunction is observed in all patients with ATM. Initial symptoms include urine retention with overfilling of the urinary bladder and paralysis of intestinal peristalsis with retention of gases and feces. Several days later, in the next stage, urinary incontinence develops, intestinal peristalsis returns but fecal incontinence persists. Neurogenic bladder is gradually developed.[13] Moreover, vasomotor dysfunctions and perspiration disorders appear below the border of the region of sensory impairment, followed by trophic changes in paralysed limbs. Limbs become cool and livid. Distal edema may appear.[3]

Imaging The imaging technique of choice in cases of suspected ATM is MR with intravenous contrast agent (gadolinium diethylenetriamine-pentaacid). The imaging should cover at least the area corresponding to the level of damage evaluated based on a neurological examination. It has been recently recommended that the whole length of the spinal cord be included in the image. MR of the brain is also recommended in patients with diagnosed myelitis in order to exclude the presence of demyelinization foci. The recommendation is particularly valid for patients with the inflammatory process confirmed by lumbar puncture.[1]

Inflammatory changes in the spinal cord are visible in T_2-weighted MR images as intensification of a signal from the central part of the spinal cord and as an edema increasing the spinal cord thickness by several millimeters. In the majority of patients intensification of signal in T_2-weighted images becomes more pronounced following administration of the contrast agent.[1,15,25,26] It should be noted that as much as 30% of patients with diagnosed ATM in SLE presented normal image of the spinal cord in MR.[4] If initial MR does not reveal any inflammatory changes within the spinal cord intensifying after introduction of the contrast medium it is recommended to repeat MR 2–7 days after the onset of the disease.[1]

The reduction in inflammatory lessions visible in MR is observed in successfully treated patients. On the other hand, MR of patients in whom inflammatory lesions sustained may show atrophy within the spinal cord.[8]

It has recently been agreed that computed tomography (CT) is not sufficiently sensitive to be a rationale for the diagnosis of myelitis. Therefore the technique is not recommended in patients with symptoms of transverse spinal cord damage. Use of CT should be only considered if MR is unavailable and in order to exclude compression of the spinal cord.[1]

Laboratory tests An increasing erythrocyte sedimentation rate from a low to a three-digit value, increased C-reactive protein values and a reduction in complement constituent levels are observed in the majority of patients in the acute stage of the disease.[4,13,14,21] Other alterations of laboratory test results may also be present in active SLE (leucopenia, lymphopenia, anemia, activated partial thromboplastin time elongation, false positive VDLR). Moreover, antibodies characteristic of active SLE are present in serum: antinuclear antibodies, anti-double-stranded deoxyribonucleic acid antibodies, anti-Sm antibodies, anti-ribonucleoprotein antibodies and antiphospholipid antibodies (APA).

Some authors suggest that there is a relation between myelitis and APA antibodies presence in patients with ATM.[6,27] This is not confirmed by other authors.[4,18] According to Covacs et al.[4] the APA occurrence rate in patients with ATM in SLE is just slightly higher compared to the total population of patients with SLE (64% vs. 30–50%). Moreover, there are reports describing patients with ATM and present APA antibodies who did not meet diagnostic criteria for SLE.[6,12,27]

According to some investigators, analysis of the cerebrospinal fluid does not show any alterations.[13,27,28] Other authors, including the authors of this report, claim that pleocytosis with prevalence of granulocytes, increased protein levels, low glucose and positive protein reactions are observed in cerebrospinal fluid (CSF) of patients with ATM in SLE.[17,18,21,24] A number of cells may be variable and may sometimes exceed a thousand in a microliter, glucose levels may be reduced to several milligrams per deciliter. It is suggested that a low glucose level in CSF is present on the first days of the disease, and then it returns to normal.[7] It should be noted that low CSF glucose levels are not observed in other neurological manifestations of SLE, or in idiopathic ATM.[24]

In the light of scarce observations made by the authors of this report (2 cases) which have not been confirmed by others yet, antibodies characteristic of SLE may be found in CSF of patients with acute ATM in SLE.[21] Only a few similar observations have been published and they confirmed the presence of antibodies in CSF of patients with other neurological manifestations in the course of SLE.[29,30] However, results reported by other authors do not support this concept.[31,32] A suggested mechanism responsible for presence of antibodies in CSF involves intrathecal synthesis of immunoglobulins in patients with SLE involving the central nervous system.[30]

Differential diagnosis Transverse myelitis should be differentiated from spinal cord transverse damage resulting from compression by various pathological structures, for example tumor masses, inflammatory granulation tissue of bacterial etiology, vascular malformations, and secondary changes to a previous injury or spinal cord radiotherapy.

A possible concurrent neural infection in the course of viral, bacterial or parasitic infection must be considered in patients with fever who have abnormal CSF test results. Careful history taking and analysis of the whole clinical presentation is necessary, because patients with diagnosed SLE usually receive immunosuppressive agents,

and are at higher risk of coexisting infection. Unfortunately, results of CSF general tests and sediment test may be identical in patients with myelitis in SLE and patients with neural infection in the course of bacterial infections (pleocytosis, high protein levels, low glucose levels). Therefore, an adequate culture is necessary to exclude a possible infection. This may delay the appropriate immunosuppression therapy. Clinical observations made by the authors of this report suggest that the presence of SLE-associated antibodies in CSF favors the diagnosis of ATM in SLE.[21]

Differential diagnosis should also consider sclerosis multiplex. An earlier clinically evident demyelinization episode in history, MR of the spinal cord and the brain suggesting multiple sclerosis (demyelinization changes disseminated in space and time occupying not more than 2 segments of the spinal cord and less than 50% of its diameter) and presence of bands of oligoclonal antibodies in the CSF test indicate the disease.[1,5,33]

Moreover, ATM should be differentiated from Devic's syndrome currently most frequently referred to as neuromyelitis optica (NMO). It is an idiopathic demyelininating disease involving recurrent episodes of optic neuritis and transverse myelitis. Precise criteria for the diagnosis of this disease have been recently developed based on a modern, highly sensitive and specific NMO-IgG antibody.[22, 33] Aquaporin 4 – a protein forming one of the main water channels within the central nervous system – is a target antigen for NMO-IgG.[22]

Idiopathic myelitis should be diagnosed in patients who do not meet diagnostic criteria for SLE and in whom no symptoms suggestive of another disease are observed.

Therapy Because of low prevalence of myelitis there are no precise and unanimous recommendations for standard therapy of ATM in SLE.

Currently, use of glucocorticosteroids and cyclophosphamide is a standard therapy of SLE involving the central nervous system, including myelopathy in SLE.[6] It is postulated that therapy of patients with SLE and ATM symptoms should be started with intravenous 1 g methylprednisolone for 3 days, followed by cyclophosphamide (1 g/m^2 of body surface area), and continued with oral glucocorticosteroids. In more severe cases additional plasmapheresis for 5 days with complete plasma exchange is recommended. However, there is no unanimous evidence of effectiveness of this therapy.[4] Some authors postulate repeated cycles of immunosuppression in therapy-resistant cases.[28] However, duration and frequency of the repeated cycles have not been determined. Sole infusions of glucocorticosteroids were effective in some cases of ATM.[4] In severe cases some authors additionally used intravenous immunoglobulins.[23,34]

There are controversies as to whether antithrombotic therapy is appropriate. Some authors postulate the need of this therapy based on the hypothesis that inflammatory lesions in the spinal cord are a result of thrombosis in the medullary vessels.[4,7] Addition of antithrombotic therapy is especially recommended in patients with APA antibodies present in serum.[6]

Single reports on positive effects of therapy with rituximab (anti-CD20 receptor antibody)[34] and of autologous bone marrow transplantation[23] have been published recently. After 2 infusions with rituximab given to a patient with contraindications to therapy with cyclophosphamide and uneffective glucocorticosteroid therapy, a distinct and rapid improvement in neurological condition was observed.[34] Autologous bone marrow transplantation was performed in a patient with recurring severe neurological symptoms in the course of SLE that persisted despite therapy with cyclophosphamide and glucocorticosteroids, which resulted in remission of SLE-related symptoms and a reduction in paresis.[23]

Single reports have also been published on successful intrathecal therapy with dexamethasone and methotrexate. In some patients this intrathecal administration of immunosuppressants has been repeated several times.[18,35,36]

Symptomatic treatment is also of importance in therapy of patients with ATM. Foley catheter insertion to the urinary bladder is necessary in the early stage of the disease, when urinary retention occurs, because overflow of the bladder caused by sphincter paralysis may lead to rupture.[3] Intensive anti-bedsore care is needed. Patients with spinal paralysis easily develop bedsores due to immobility, sensory impairment and damaged autonomic nervous system.[13, 21] Patients with ATM also require a complex and intensive rehabilitation which should be started already in the first days of the disease.[13]

Prognosis Data on long-term prognosis of the disease are conflicting. Complete recovery, partial remissions, arrest of progress of the disease, and deterioration of neurological symptoms, including death of a patient might occur.

It has recently been agreed that early introduction of immunosuppressive therapy with intravenous cyclophosphamide and high doses of glucocorticosteroids, followed by oral glucocorticosteroids improves the long-term prognosis of patients with ATM in SLE.[4,8,24,28] The earlier immunosuppressive therapy is introduced and the more aggressive it is, the better the long-term prognosis is.[6,18] Considering lack of sufficiently large sample sizes of patients with myelopathy there are no unanimous results of studies on effectiveness of ATM therapy based on reliable results of clinical tests.[14]

Prognosis in patients with MR alterations is poor compared to those patients with no such abnormalities.[4] Prognosis is particularly poor in patients with extensive spinal lesions involving the whole length of the spinal cord.[16] Patients with inflammatory lesions visible in the MR of the spinal cord that resolve after the first, preliminary

intravenous immunosuppressive therapy have better prognosis.[25]

There is also poor prognosis in patients with a dramatic clinical course of myelitis, encountering the so-called, medullary shock phase and whose initially evaluated deficit in muscular power is very large.[8,18,19] An association between the initial high SLE activity and the long-term prognosis has not been confirmed.[4,18]

The time of complete or partial improvement in neurological function may be variable, ranging between several days and many months.[5,7,34]

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