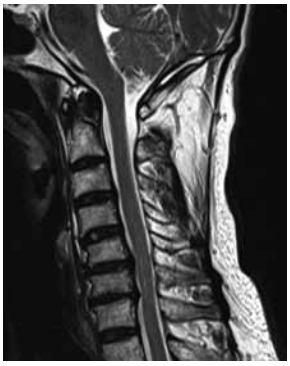

DIAGNOSTIC APPROACH TO MYELOPATHIES

ENFOQUE DIAGNÓSTICO DE LAS MIELOPATÍAS

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Key words (MeSH)
Spinal cord
Spinal cord diseases
Magnetic resonance imaging

Palabras clave (DeCS)
Médula espinal
Enfermedades de la médula espinal
Imagen por resonancia magnética

SUMMARY

Myelopathy is a broad term that refers to spinal cord involvement of multiple etiologies. Spinal cord diseases often have devastating consequences, ranging from quadriplegia and paraplegia to severe sensory deficits due to its confinement in a very small area. Many of these diseases are potentially reversible if they are recognized on time, hence the importance of recognizing the significance of magnetic resonance imaging when approaching a multifactorial disease considered as one of the most critical neurological emergencies, where prognosis depends on an early and accurate diagnosis.

RESUMEN

Mielopatía es un término general que hace referencia a la afectación medular por múltiples etiologías. Las enfermedades de la médula espinal tienen con frecuencia consecuencias devastadoras: pueden producir cuadriplejía, paraplejía y déficits sensitivos graves debido a que la médula espinal está contenida en un canal de área pequeña. Muchas de estas enfermedades de la médula espinal son reversibles si se reconocen con oportunidad, por ello los radiólogos deben sensibilizarse sobre la importancia de las imágenes por resonancia magnética en el enfoque de una patología multifactorial en la cual el pronóstico depende del diagnóstico precoz y preciso, y por ello constituyen una de las urgencias neurológicas más importantes.

Introduction

The term *myelopathy* describes pathologic conditions that cause spinal cord, meningeal or perimeningeal space damage or dysfunction. Traumatic injuries, vascular diseases, infections and inflammatory or autoimmune processes may affect the spinal cord (1) due to its confinement in a very small space. Spinal cord injuries usually have devastating consequences such as quadriplegia, paraplegia and severe sensory deficits.

The history, an adequate neurological examination and the study of the cerebrospinal fluid (CSF) guide the diagnosis of spinal cord injuries. However, imaging is of great importance in order to home in on the diagnosis and classify the etiology appropriately (2-3).

Many of the processes affecting the spinal cord may be reversible if recognized and treated early. The vast majority of spinal cord diseases may be treated medically, with surgical treatment reserved for compressive disorders, which constitute a neurological emergency (2). This paper reviews the different etiologies, divided into compressive and non-compressive.

Definition and clinical picture

It is important not to mistake *myelopathy* for *myelitis*. Although both terms refer to spinal

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cord compromise due to a pathological event, myelopathy has multiple etiologies, while *myelitis* is used to refer to inflammatory or infectious processes (1,4). *Acute transverse myelopathy* (includes non-inflammatory etiologies) and *transverse myelitis* have been used as synonyms in the published literature (5).

Findings of spinal tract injuries, a certain degree of sensory dysfunction, or urinary retention, point to a spinal cord injury. There are certain conditions that may mimic myelopathy, such as myopathy or disorders of the neuromuscular junction, but the absence of a sensory deficit rules them out. On the other hand, bilateral frontal mesial lesions may mimic myelopathy but they are associated with abulia or other signs of frontal dysfunction (6).

Myelopathies may have a variable course and may manifest as a single event or as a multi-phasic or recurrent disease. The latter is rare and is usually secondary to demyelinating diseases, vascular malformations of the spinal cord, or systemic diseases (4,5). The central nervous system (CNS) damage may be monofocal as in transverse myelitis and optic neuritis, or multifocal as in acute disseminated encephalomyelitis (ADEM) (brain and spinal cord), neuromyelitis optica (optic nerve and spinal cord) and multiple sclerosis (MS) (any area of the neural axis) (4).

Spinal cord pathologies may be classified as acute, subacute/intermittent (6) or chronic, depending on the time course, the extent of the involvement, the clinical picture or syndrome, or the etiology (2-4,6,7). Patients with myelopathies but no evident lesions, or who present with multiple lesions of chronic appearance on magnetic resonance imaging, must be questioned about prior subtle symptoms (6).

Acute onset that worsens within hours or days points to a spinal cord infarct or hemorrhage. When symptoms are recent, it is of paramount importance to rule out a surgical emergency. This requires immediate imaging work-up, ideally total spine magnetic resonance (MR). If there is evidence of spinal cord compression due to an acute lesion (epidural metastasis or abscess), definitive management is required in order to avoid damage or to adequately manage all other potential diagnoses. If the symptoms progress for more than three weeks, transverse myelitis is improbable, and other conditions must be considered, such as a spinal tumor, chronic compressive disease, dural arterio-venous fistula, metabolic disorder, sarcoidosis, or a degenerative process (6).

Spinal cord syndromes present with typical signs and symptoms caused by a lesion of a specific tract in a specific location that may lead to the etiological diagnosis. They are classified as follows (2,6,8):

- Complete spinal cord: involvement of all the tracts (trauma, compression or acute transverse myelitis).
- Brown Séquard or hemi-spinal cord syndrome: ipsilateral cortico-spinal tract, posterior columns and contralateral spinothalamic tract (multiple sclerosis and compression).
- Anterior spinal cord syndrome: anterior horns, cortico-spinal, spinothalamic and autonomic tracts (anterior spinal artery infarct and multiple sclerosis).
- Posterior spinal cord syndrome: posterior columns (vitamin B12 or copper deficiency).
- Central syndrome: spino-thalamic crossing, cortico-spinal and autonomic tracts (syringomyelia, neuromyelitis optica).
- Medullary cone: sacral emerging fibres (post-viral myelitis).
- Cauda equina: cauda equina nerves (acute cytomegalovirus infection, polyradiculits and compression)
- Tractopathies: selective disorders (vitamin B12 deficiency, paraneoplastic myelopathy and multiple sclerosis).

There are cases where the etiology is never identified, and they are classified as idiopathic myelopathy. In 2001, De Seze *et al*. found that 43% of acute myelopathies were secondary to multiple sclerosis; 16.5% were due to a systemic disease; 14% to a spinal cord infarct; 6% to an infectious disease; 4% were secondary to radiation; and 16.5% were idiopathic (9). Moore *et al.* found that in cases of non-traumatic injury, 23.6% were due to cervical spondylolysis; 17.8% to multiple sclerosis; 16.4% to a neoplastic lesion; 4.1% to motor neuron disease; and 18.6% were idiopathic or of unknown etiology (10). Chronic myelopathies include, among others, spondylotic myelopathy, vascular malformations, retrovirus-associated myelopathy (human immunodeficiency virus), syringomyelia, chronic myelopathy due to multiple sclerosis, combined subacute degeneration (vitamin B12 deficiency), tabes dorsalis, and familial spastic paraplegia.

Based on the Sicard and Forstier classification that divides the disease into compressive and non-compressive, in relation to subarachnoid space obstruction, Table 1 shows a list of the different etiologies (2-3,11).

Compressive myelopathies

Compressive diseases of the spinal cord are divided into acute and chronic, including degenerative changes, trauma, tumor infiltration, vascular malformations, infections with abscess formation, and syringomyelia (Table 1). Patients with clinical findings of compressive myelopathy that show extensive (more than three vertebral segments) fusiform spinal cord hyperintensity in T2 weighted sequences, are often mistakenly thought to have optic neuritis, or classified as idiopathic. This delays surgical treatment when other causes such as stenosis of the spinal canal are not taken into consideration (9).

Compressive disease is the main cause of myelopathy in older patients. It has a chronic course and usually does not recur (7). High intensity signals in T2 images is explained by myelomalacia, gliosis, tethering damage, vascular or inflammatory edema, demyelination and vacuolar changes. Gadolinium enhancement is limited to the region of maximum compression (12). Kelley *et al.* found that none of the patients with compressive myelopathy improved with intravenous corticosteroids, while patients with inflammatory myelopathies did improve, invalidating the hypothesis of traumatic inflammatory demyelination.

Surgery improved or stabilized all patients with compressive disease, consistent with the hypothesis of spinal cord edema or reversible ischemia in compression. These findings support the argument that the clinical and imaging findings may differentiate those patients who will benefit from surgical decompression (12). In 2007, Yukawa *et al.* found that the signal intensity in the pre-operative T2 image correlates with patient age, chronicity of the disease, and post-operative recovery. Patients with greater signal intensity in T2 weighted images recover poorly. Consequently, this parameter may be used as a predictor of surgical prognosis (13). Matsumoto *et al.* found no relationship between hyperintense signals and prognosis (14).

Table 1. Etiologies

Compressive	Non-compressive
Degenerative	Infectious transverse myelitis: • Viral: Zoster, Ebstein-Barr, herpes simplex, cytomegalovirus, adenovirus, enterovirus, Coxsackie B, type 6 herpes virus, HIV and AIDS, HTLV I and II • Bacterial: staphylococcus aureus, streptococci, mycobacteria • Spirochetes: syphilis and Lyme disease • Fungi: cryptococcus, aspergillus Acute Disseminated Encephalitis: • Demyelinating diseases • Multiple sclerosis • Neuromyelitis optica • Eale's disease Vascular: • Spinal arterial thrombosis • Central nervous system vasculitis (lupus, Sjögren's, sarcoidosis)
Traumatic • Bone lesion • Disc herniation • Epidural hemorrhage	Toxic substances and physical agents • Lathyrism, arsenic, tri-ortho-cresyl phosphate, nitric oxide and intrathecal methotrexate • Radiation • Electric injury
Infectious (abscess)	Degenerative: • Primary lateral sclerosis • Familial spastic paraparesis • Spinocerebellar ataxia • Iron neurodegeneration • Friedriech's ataxia
Tumors: • Extradural: benign and malignant • Intradural: intra and extra medullary	Metabolic: • Vitamin B12 deficiency • Vitamin E deficiency • Chronic hepatic or renal disease • Hexosamidase deficiency
Vascular: arterio-venous malformation	Paraneoplastic
Syringomyelia	

Degenerative compressive myelopathy

Degenerative compressive myelopathy may be classified according to the compression site, as follows:

- Anterior (disc protrusion or posterior osteophytes).
- Anterolateral (Luschka joints).
- Lateral (facet joints).
- Posterior (*ligamentum flavum)*.

It may be caused by atlanto-axial instability, spinal canal stenosis due to cervical spondylolysis (15), cervical spinal fusion, myelomeningocele or epidural masses.

Atlanto-axial instability is the primary cause of degenerative compressive myelopathy. It is found mainly in rheumatoid arthritis, followed by Down's syndrome, Morquio's syndrome or type IV mucopolysaccharidosis, skeletal dysplasia, ankylosing spondylitis and Lesh-Nyhan syndrome (16). Ninety per cent of patients with rheumatoid arthritis have a cervical lesion, either an atlanto-axial subluxation, atlanto-axial impaction (basilar invagination), or Luschka joint disease, and pannus transfer to the disc or ligaments. Neurological decline may be irreversible, although the lower cervical spine is the most vulnerable to myelopathy (17) (Figure 1). Patients with compressive myelopathy due to Morquio's syndrome have cervical disease due to atlanto-axial subluxation, associated with hearing loss, joint elasticity, growth retardation and hip dysplasia (16) (Figure 2).

On the other hand, spinal canal stenosis may be caused by familial pathologies such as achondroplasia or familial lumbar stenosis, or by acquired diseases such as vertebral collapse, nucleus pulposus herniation, spondylolysis or epidural lipomatosis (18). Canal stenosis secondary to nucleus pulposus herniation is more frequently found in C6-C7, but it may occur in C5-C6 and, to a lesser extent, in C4-C5. It may be intraforaminal and produce sensory symptoms (most common), anterolateral with motor symptoms, or central with spinal cord compression resulting in myelopathy (18).

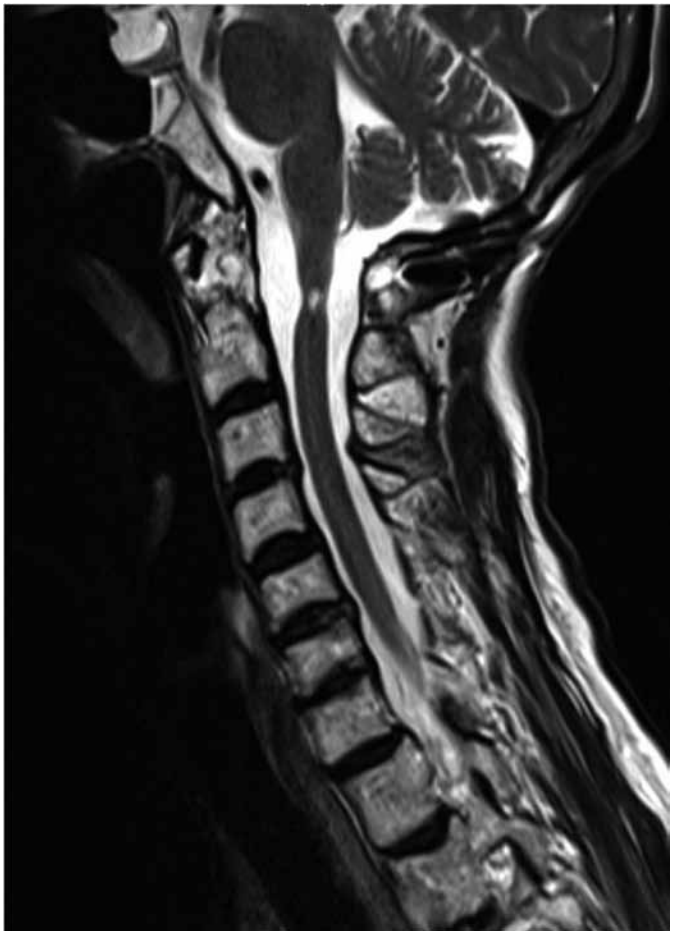


Figure 1. Increased intensity of the spinal cord in C2 in the T2 weighted sequence due to compressive myelopathy secondary to rheumatoid arthritis.

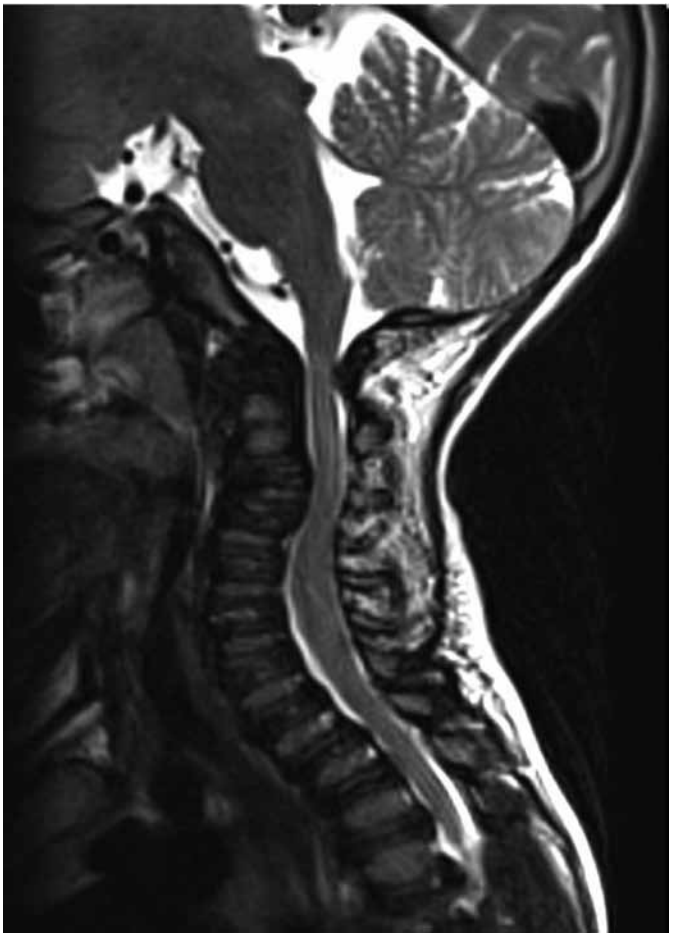


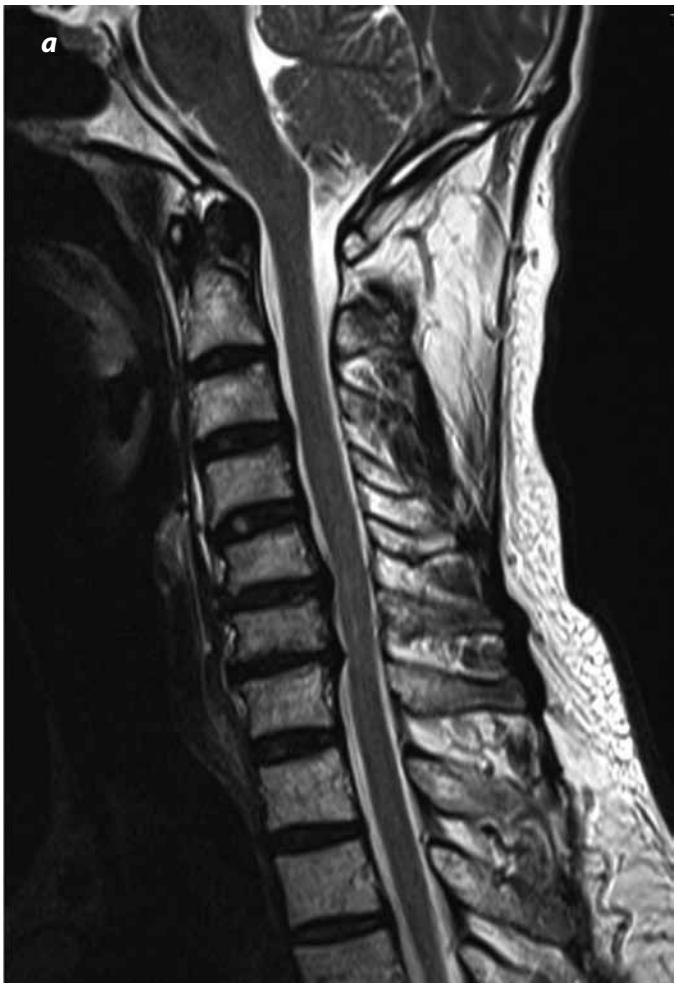
Figure 2. Increased intensity and thickening of the spinal cord from the bulbo-medullary junction down to C4 in the sagittal T2 sequence, due to compressive myelopathy in Morquio's syndrome.

On MRI, there is usually a hyperintense lesion in T2 weighted sequences close to the herniation area or the osteophyte that is giving rise to spinal cord compression, although there may be extensive increased intensity in T2 (more than three segments), leading to the suspicion of an inflammatory lesion. Gadolinium enhancement limited to the point of greatest stenosis, plus a history of progressive symptoms, contribute to the diagnosis (6) (Figures 3a and 3b).

Post-traumatic compressive myelopathy

Post-traumatic myelopathy is four times more frequent in males, in particular between 16 and 30 years of age. Motor vehicle acci-

dents are the most common cause, accounting for 50% of the events, followed by violence (firearm or stab wounds), falls from heights, and sports injuries (diving, American football and horseback-riding) (19). The most mobile segments are more often affected, in particular C5-C7 and T10-L2. Clinically, quadriplegia predominates in 30-40% of cases, and paraplegia occurs in 6-10% (16).



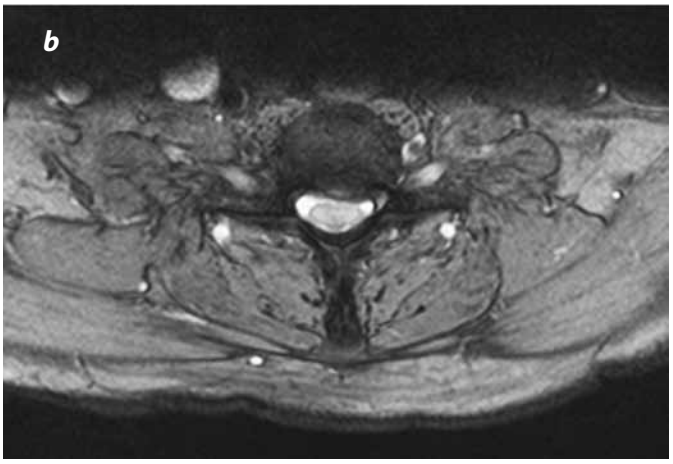


Figure 3. a) Axial sequence with T2 gradient echo information. B) Sagittal section with T2 information in C7 showing diminished height and signal intensity with annulus protrusion in C5-C6 and C6-C7; there is also central and left subarticular protrusion of the annulus associated with annulus and ligament tear in C7, giving rise to central spinal hyperintensity due to compressive myelopathy resulting from nucleus pulposus herniation.

MR imaging is of vital importance in approaching spinal cord trauma because it shows location, extension and severity very clearly, and also reveals edema and intramedullary bleeding. Some studies have shown that hemorrhage and longer hematomas are associated with a lower rate of motor recovery (20). Over the long term, CSF leaks, infections, cysts and syringomyelia may develop (16,21) (Figure 4).

Abscess-related compressive myelopathy

Epidural abscesses are uncommon but they constitute a surgical emergency because they may progress rapidly within days and early diagnosis is difficult, leading to delayed treatment. The incidence is 0.2-2 cases for every 10,000 hospital admissions. They affect mainly men, with no specific age range (22), and the incidence has been shown to have increased in recent years. Morbidity and mortality are high, between 18% and 31%. Risk factors are similar to those for spondylodiscitis, including diabetes mellitus, use of intravenous drugs, chronic renal failure,

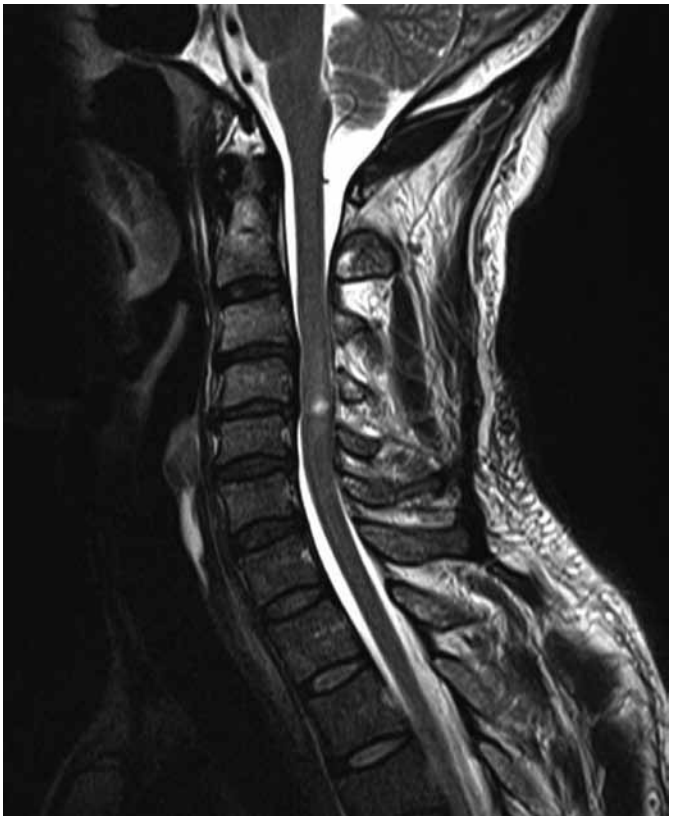


Figure 4. T2 weighted image with annulus protrusion in C4 and C5, giving rise to spinal cord hyperintensity due to traumatic compressive myelopathy.

alcohol abuse, and immune deficiency. Lumbar trauma has also been described in one third of patients, as a cause for epidural abscess. Human immunodeficiency virus has not been shown to be the cause of the increased incidence (23).

It usually presents as subacute lumbar pain, fever (may be absent in subacute and chronic stages), increased local tenderness, progressive radiculopathy or myelopathy. The second phase of radicular irritation is followed by neurologic deficit (muscle weakness, abnormal sensation and incontinence) and then by paralysis in 34% of cases, and even death. Symptoms result from mechanical compression and, in some cases, from ischemia. Any segment of the spinal cord may be affected, but the most frequent are the thoracic and lumbar segments. Numaguchi *et al.* classified the disease as focal when it involves up to five vertebral segments, and diffuse when it involves six or more (22).

Staphylococcus aureus is the main pathogen found in 67% of cases, 15% of which involve the methicillin-resistant strain (24). *Mycobacterium tuberculosis* is the second most frequent pathogen, found in 25% of cases (22). The spinal cord culture is usually sterile most of the time (25).

MRI is the diagnostic method of choice, with a sensitivity ranging between 91% and 100%. It must be selected as the first imaging technique because it is more sensitive than other imaging modalities and allows to rule out other causes. A spinal cord abscess develops by phases, starting with an infectious myelitis that appears hyperintense on T2 with poorly defined enhancement, followed by a late phase with well-defined peripheral enhancement and perilesional edema. The final phase is intraspinal abscess formation with low signal intensity in T1 images and high signal intensity in sequences with T2 information (25).

Diffusion MRI may increase diagnostic sensitivity and specificity of spinal cord diseases (acute ischemia, tumors or multiple sclerosis lesion). However, it is not performed frequently because of limitations such as movement artifacts and the small size of the spinal canal. Diffusion can help with the detection of early ischemic lesions, where conventional MRI does not show abnormalities. On the other hand, high-signal spinal areas of reduced apparent diffusion coefficient are visible in patients with spondylotic myelopathy, surrounded by a low-signal halo of edema. In cases of myelitis, there is only a small high-signal area that allows to make the distinction between infection and ischemia (26).

Tsuchiya *et al.* used diffusion MRI to assess fourteen patients between two hours and three days after cervical trauma and found that lesions that showed a high signal on MRI with diffusion restriction showed myelomalacia or exacerbation on follow-up, helping to predict the functional prognosis (27). Treatment is emergency surgical drainage and decompression, plus broad-spectrum antibiotics until the pathogen is isolated (23). The differential diagnosis includes extradural metastasis, epidural hematoma, migrated disc fragments or epidural lipomatosis (22) (Figures 5a and 5b).

Tumoral compressive myelopathy

Myelopathy may be the initial manifestation of a malignancy in up to 20% of cases where the only systemic symptom is weight loss (16). Tumors compressing the spinal cord may be divided into extradural and intradural. Extradural tumors may be classified as follows:

- Benign: synovial cyst, osteoma, osteoblastoma, giant cell tumor, hemangioma, eosinophilic granuloma, schwannoma and meningioma.
- Malignant: bone metastasis (are the cause of the most common myelopathy due to extradural spinal cord compression) (28), multiple myeloma, lymphoma and chondrosarcoma.

Intradural tumors are classified as follows:

- Extraspinal: neurofibroma, meningioma, lipoma, schwannoma and arachnoid cyst.
- Intraspinal: astrocytoma, ependymoma, hemangioblastoma and metastasis.

Forty per cent of patients present with radiculopathy and myelopathy associated with subacute dorsal pain that worsens in decubitus position. MRI may reveal the cause of the myelopathy and help guide the approach to the primary tumor (Figures 6 and 7).

Myelopathy of vascular origin

The arterial supply to the spinal cord consists of one anterior spinal artery and two posterior spinal arteries with their penetrating vessels. It is provided mainly by the anterior spinal artery that emerges from the vertebral arteries, the artery of Adamkiewicz (arteria radicularis magna) of variable origin, generally left between T9 and T12, and by anastomosis between the anterior and posterior spinal arteries, with a hypovascular area located between T4 and T8.

The spinal cord may be affected by compressive and non-compressive vascular diseases, of which the most common are malformations of the dural arteriovenous fistula type (29). In cases of vascular malformation, patients present with non-specific clinical findings, usually distal to the site of the disease. Early detection and treatment offer the best chance for neurological recovery. These diseases were classified by Riche in 1985 (29) as follows:

- Intraspinal arteriovenous malformations.
- Perispinal arteriovenous malformations.
- Spinodural arteriovenous fistulas.
- Epidural arteriovenous malformations.
- Paravertebral vascular malformations.
- Vertebral hemangiomas.
- Complex angiomatosis (Cobb's syndrome, Osler-Weber-Rendu syndrome).
- Cavernomas, telangiectasias and spinal venous angiomas (do not require endovascular treatment).

In 2002, Spetzler proposed the following new classification (30):

- Neplastic vascular lesions: hemangioblastoma and cavernous malformation.

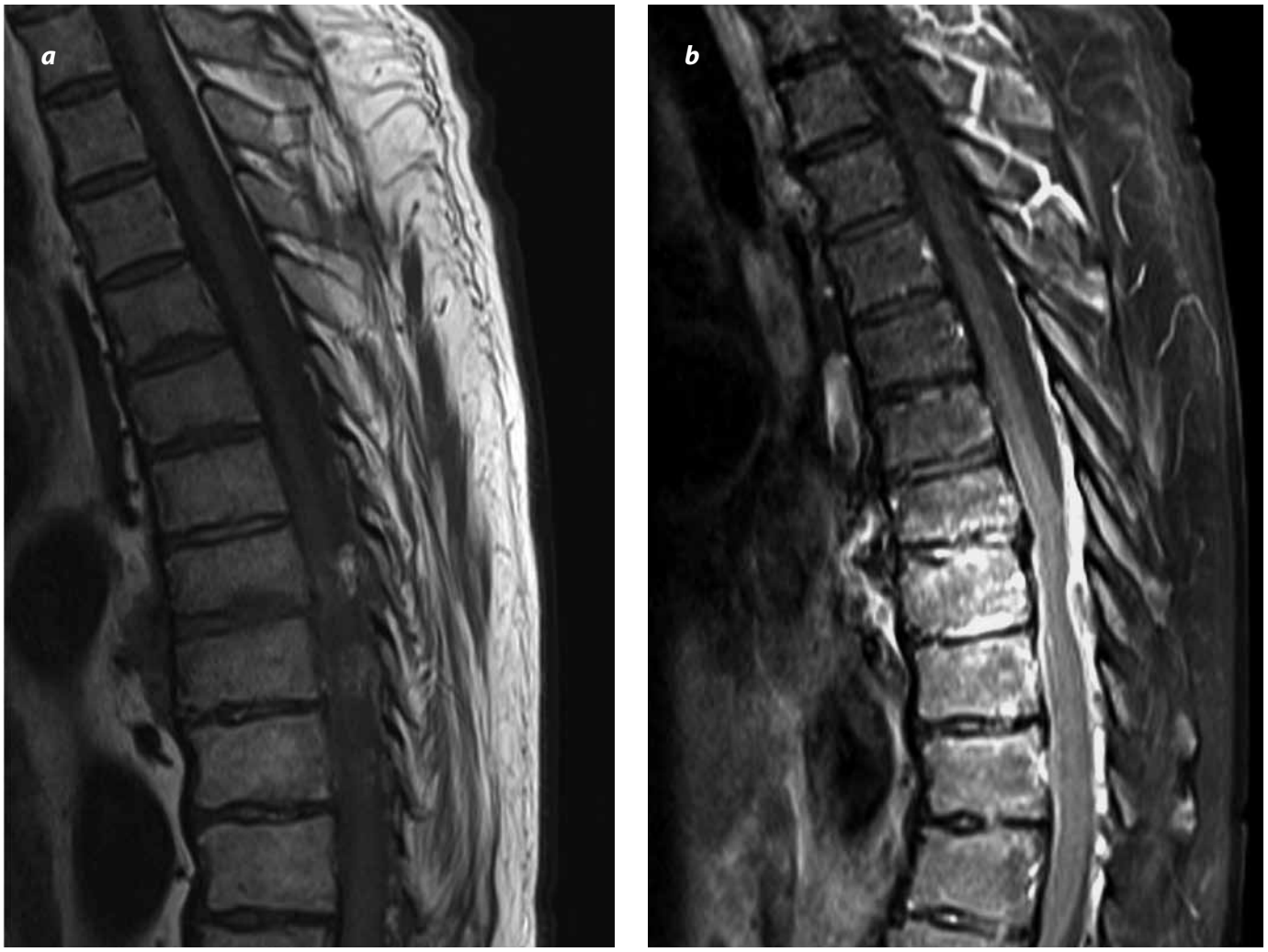


Figure 5. a) Sagittal image with T1 information showing signal-intensity changes of the lower T10 endplate and upper T11 endplate, and of the corresponding disc, associated with hyperintensity and spinal cord thickening in that segment. b) Post-gadolinium STIR image showing thickening of the prevertebral soft tissues, the vertebral bodies and the disc from T10 to T11. These enhance with contrast, together with the thickened spinal cord due to myelopathy resulting from an epidural abscess.

- Spinal aneurism.
- Arteriovenous fistula: extradural and intradural. The latter includes ventral (small, medium and large) and dorsal (one or several feeding vessels) fistulas.
- Arteriovenous malformations: extra-intradural and intradural (intraspinal, compact, diffuse and of the medullary cone).

Arteriovenous malformations may be dural or Type I (extraspinal, accounting for 75%) (31). Ninety per cent are found in the low thoracic or lumbar regions, and in a lesser proportion, in the sacral and cervical regions. They are four times more frequent in men, with a mean age at onset of 58 years. Initial symptoms include gait disorders, paresthesias or numbness, lumbar or radicular pain, asymmetric weakness of the legs, and bleeding in up to 25% of cases. Arteriovenous fistulas may be differentiated from other causes of myelopathy because symptoms are triggered by walking or standing for long periods of time (6). Eighty per cent present with bladder dysfunction, when the malformation involves the cone (32). The disease may progress over a period of months and even years, and may become exacerbated with exercise (33). Findings on MRI include serpent-like images with absence of flow signals in most patients; these structures appear enhanced in T1 images with gadolinium (34).

Intraspinal arteriovenous malformations account for 10% of cases and include dural sinus drainage or Type II malformations, and subarachnoid venous drainage or Type III malformations. They are localized in the cervical spine in 46% of cases and in the thoracolumbar spine in 44% of cases. The age of onset is under 40 years, when hemorrhage is the main symptom, and aneurisms are present in 20% of cases. There is progressive myelopathy in up to 60% of cases.

Cavernous malformations account for 5% of the 12% of spinal malformations and are associated with bleeding in 0.8% of cases. On MRI, they show intermediate signal in T1 and T2, with presence of hemosiderin (Figures 8a and 8b).

Another cause of myelopathy of vascular origin of the non-compressive type is acute vascular occlusion, which is less frequent and may lead to an infarct that mimics myelitis (8).

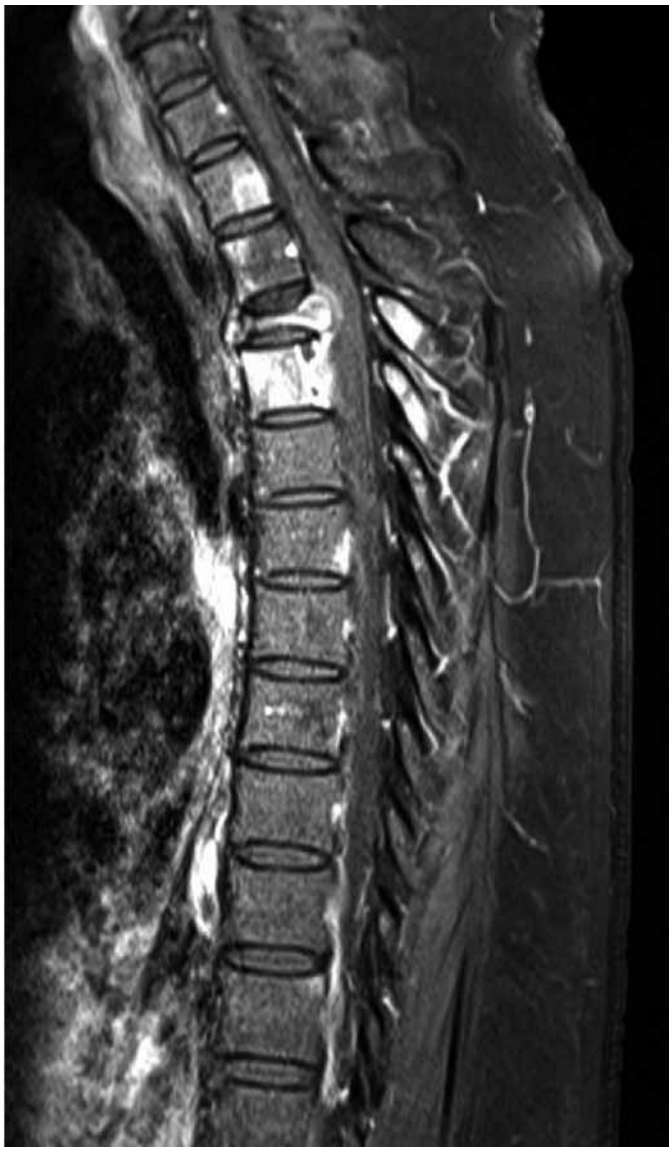


Figure 6. Post-gadolinium sagittal STIR image showing abnormal signal intensity of the bodies of T3 and T4, with a pathological fracture of T3 involving the epidural component and which compresses the spinal cord. There is gadolinium enhancement of T1, T3 and T4 and of the spinous processes, but no enhancement of the spinal cord due to metastatic disease. This causes tumor compression myelopathy.

The diagnosis of myelopathy secondary to spinal cord ischemia is difficult because of the lack of diagnostic criteria in the acute stage. It has been found generally in patients over 50 years of age (9,35). The initial symptoms usually present within less than four hours and include severe motor and sphincter dysfunction, temperature and pain alterations, with no alterations to vibration or proprioception. The etiologies include the following:

- Arterial thrombosis: aortic surgery, spinal angiography, vasculitis, embolism, arterial dissection, hypotension, and prothrombotic states.
- Anterior spinal artery lesion: anterior spinal syndrome
- Posterior spinal artery lesion: posterior column syndrome
- Subcommisural artery lesion: Brown Séquard syndrome
- Arteriovenous fistula

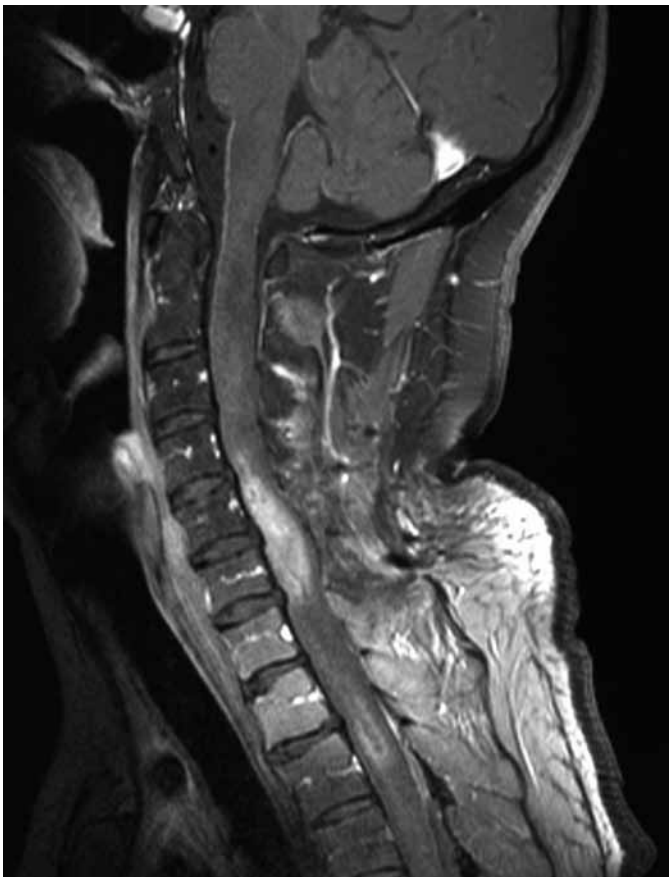


Figure 7. Postgadolinium sagittal STIR image showing spinal widening in C5 and C6, with enhancement of the spinal cord and the bodies of C7 and T1. There is also enhancement of the prevertebral soft tissues and of the cervical muscles due to myelopathy secondary to a high-grade glioma.

- Venous infarct

CSF is normal, although in arteriovenous fistulas there may be higher protein concentrations without pleocytosis (8). Spinal MRI shows single central hyperintensity. The CSF analysis reveals absent or low cell content, without oligoclonal bands (Figure 9).

Compressive myelopathy due to syringomyelia

Syringomyelia is a rare neurologic disorder, characterized by the slow development of fluid-filled areas extending along the spinal cord, and causing symptoms such as pain, weakness and stiffness of the back, shoulders and limbs. The prevalence is 3.3 to 8.5 cases for every 100,000 people and it varies depending on the ethnic background. In the United States, it is more common among African-Americans. It may be related to congenital or acquired malformations. Chiari's malformation is a congenital abnormality in which cerebellar amygdalas herniate through the foramen magnum in the spinal canal, with altered CSF flow. This causes headache, double vision, dizziness and muscle weakness of the upper limbs. Most non-traumatic forms of syringomyelia are due to Chiari malformation (36,37). The acquired causes of syringomyelia include trauma, tuberculosis-associated chronic arachnoiditis, and intraspinal tumors (38) (Figures 10a and 10b).

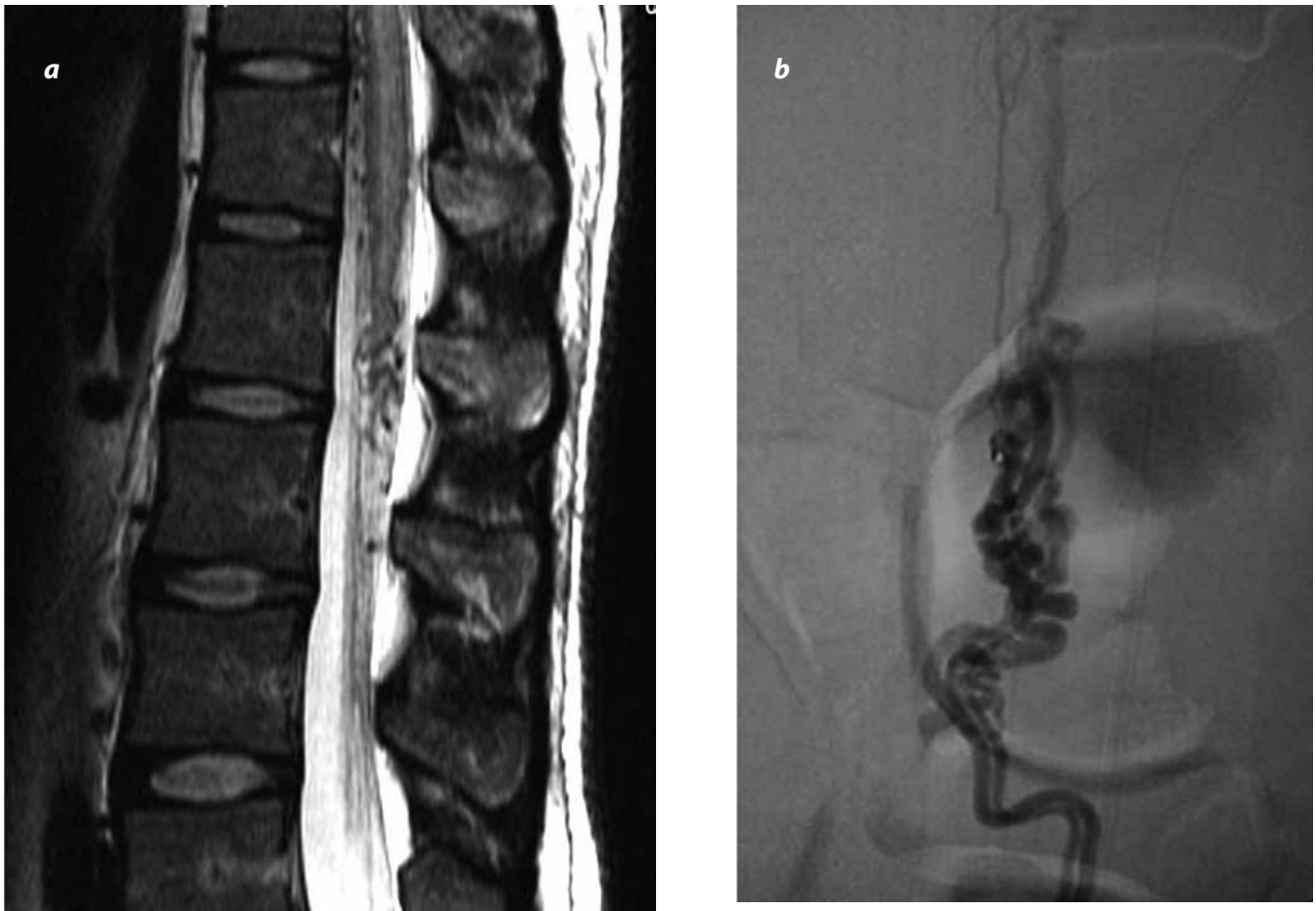


Figure 8. a) Sagittal sequence with T2 information of the medullary cone, showing serpent-like, tortuous intra and extraspinal images with absence of flow signal, associated with dorsal spine hyperintensity. b) Arteriogram confirming the presence of dural arteriovenous malformation with myelopathy of vascular origin.

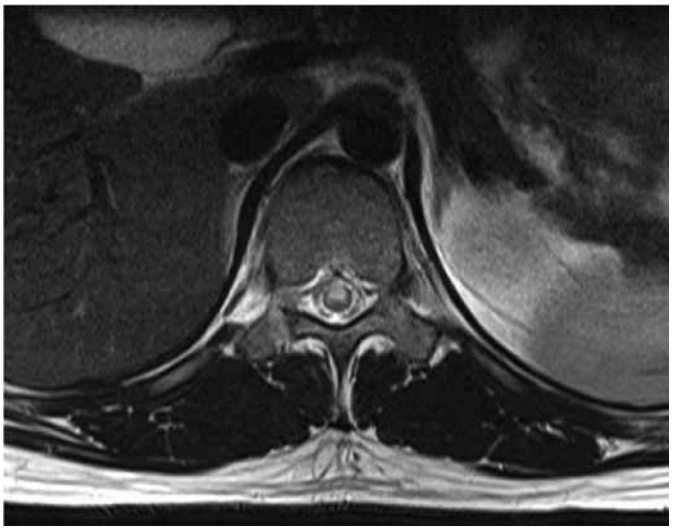


Figure 9. Fifteen-year old patient with neurologic deficit of sudden onset and normal laboratory tests. The sagittal sequence with T2 information shows a high-intensity signal anterior to the spinal cord suggesting a diagnosis of myelopathy due to ischemia.

Non-compressive myelopathies

Once compression is ruled out as the etiology of myelopathy, the clinical history is analyzed in depth and a careful clinical examination is performed in order to look for an inflammatory cause. The diagnosis of an inflammatory myelopathy requires evidence of spinal cord inflammation. At the present time, MRI and CSF analysis are the only tools available for determining the presence of inflammation. There needs to be gadolinium enhancement of the spinal cord, pleocytosis in the CSF or a high immunoglobulin G index in the CSF, with a time course ranging between four hours and four weeks. If none of these findings are present at the time of onset of symptoms, MRI and lumbar taps must be repeated two to seven days later (39).

Transverse myelitis

Acute transverse myelitis is a spinal disorder characterized by bilateral motor, sensory and autonomic abnormalities because it involves the spinothalamic and pyramidal tracts, the posterior columns and the anterior funiculus of one or more levels (25). Close to one third of the patients recover with mild or no sequelae, one third have a mild degree of disability, and yet another third have a serious disability. Middle-aged adults are most frequently affected.

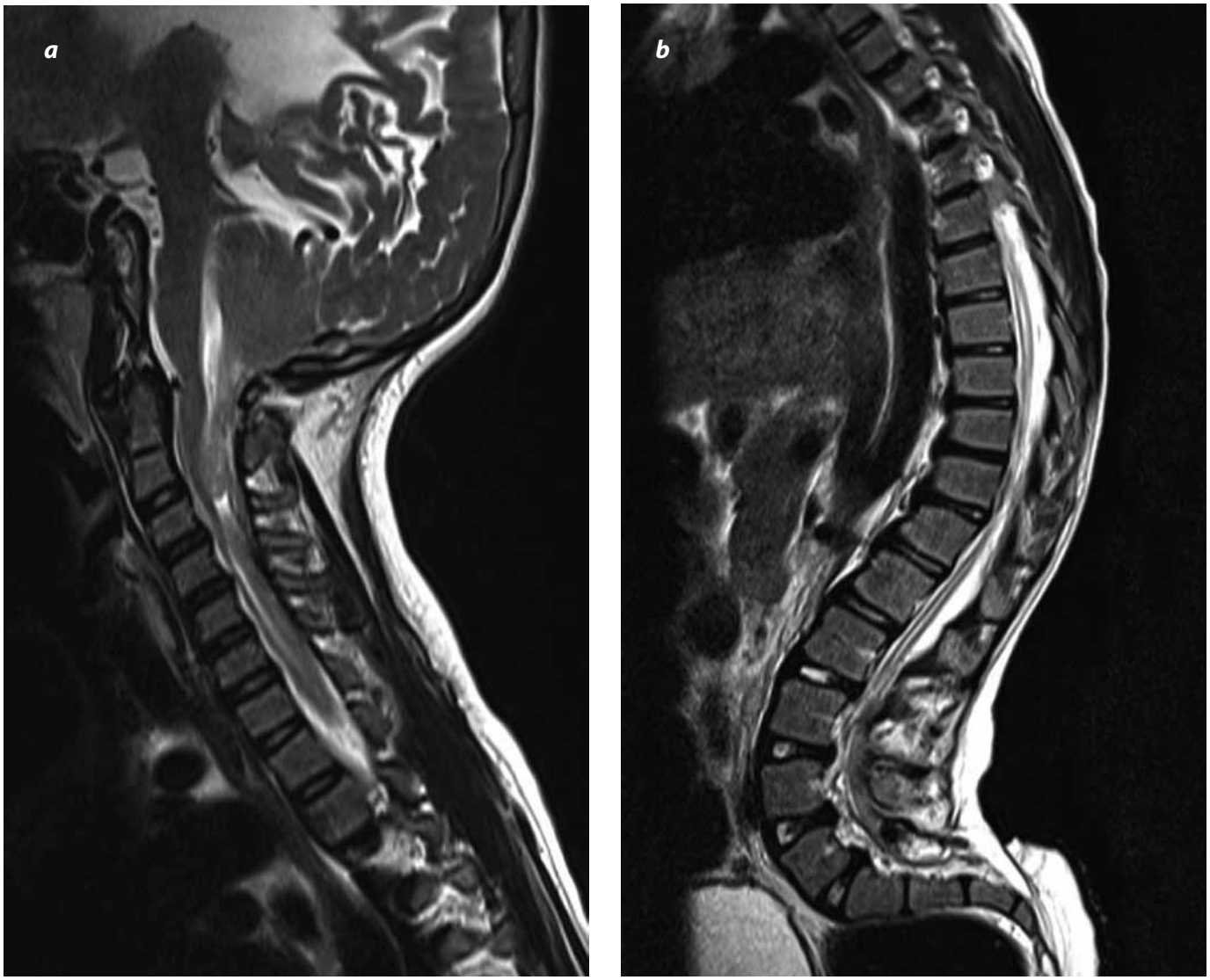


Figure 10. a) Sagittal sequence with T2 information of the cervical spine showing Chiari malformation type II, absent corpus callosum and a tubular zone of high signal intensity in the spinal cord down from the bulbo-medullary junction, involving all the segments. b) Sagittal sequence with T2 information of the dorso-lumbar spine with myelopathy secondary to syringomyelia.

A publication established the following criteria for transverse myelopathy: bilateral spinal cord dysfunction during a four-week period with a well-defined sensory level and no history of disease, where compression has been ruled out. Other criteria are proposed later for the differentiation between inflammatory and non-inflammatory transverse myelitis, and between idiopathic transverse myelitis and myelitis associated with a systemic or nervous system disease. These criteria are the following (5):

- Sensory, motor or autonomic dysfunction of spinal origin.

- Bilateral signs and symptoms.
- Clearly defined sensory level.
- Spinal inflammation (CSF pleocytosis or high immunoglobulin G levels, or gadolinium enhancement).
- Maximum progression during a period ranging between four hours and four weeks.

In 2002, the Transverse Myelitis Consortium Working Group proposed CSF and MRI criteria for the diagnosis of idiopathic transverse myelitis, including the following: 1) spinal bilateral motor, sensory or autonomic dysfunction; 2) bilateral sensory level signs and symptoms; 3) evidence of spinal inflammation on MRI or CSF tests; 4) symptoms with a duration ranging between a few hours and 21 days, from onset to maximum deficit; and 5) extra-axial compression ruled out (40).

In acute cases, the histopathology shows medullary and perivascular focal infiltration of monocytes and lymphocytes with astroglia and microglia activation. In subacute phases, the finding is macrophage infiltration (5). MRI findings include focal and central high signal areas in T2 sequences, occupying more than two thirds of the spinal cord axially, and extending over three to four segments, generally in the thoracic spine. Spinal expansion may or may not be found and, in general, there is contrast medium enhancement, usually patch-like or diffuse. MRI findings are usually normal in 40% of cases. There is growing evidence that the length of the lesion may be important from a prognostic standpoint. Lesions extending less than two segments involve the risk of developing MS (40) (Figures 11a and 11b).

Inflammatory transverse myelitis, in the absence of a specific cause (idiopathic), is the main cause of acute myelitis. It varies significantly in frequency (from 9% to 60% according to some studies) (9). There are two incidence peaks – the first between 10 and 19 years of age, and the second between 30 and 39 (8). The diagnosis is made by exclusion and it has a course of progression between four hours and four weeks. Clinical and MRI follow-up of these patients has led to a diagnosis in approximately 50% of cases (9).

The ability to differentiate transverse myelitis from other intramedullary diseases, in particular spinal tumors, is critically important because it may help differentiate between surgery, post-operative complications and radiotherapy. The use of gadolinium has made it possible to detect spinal tumors and delimit their location and extension in relation to the perilesional edema (41) (Figure 12).

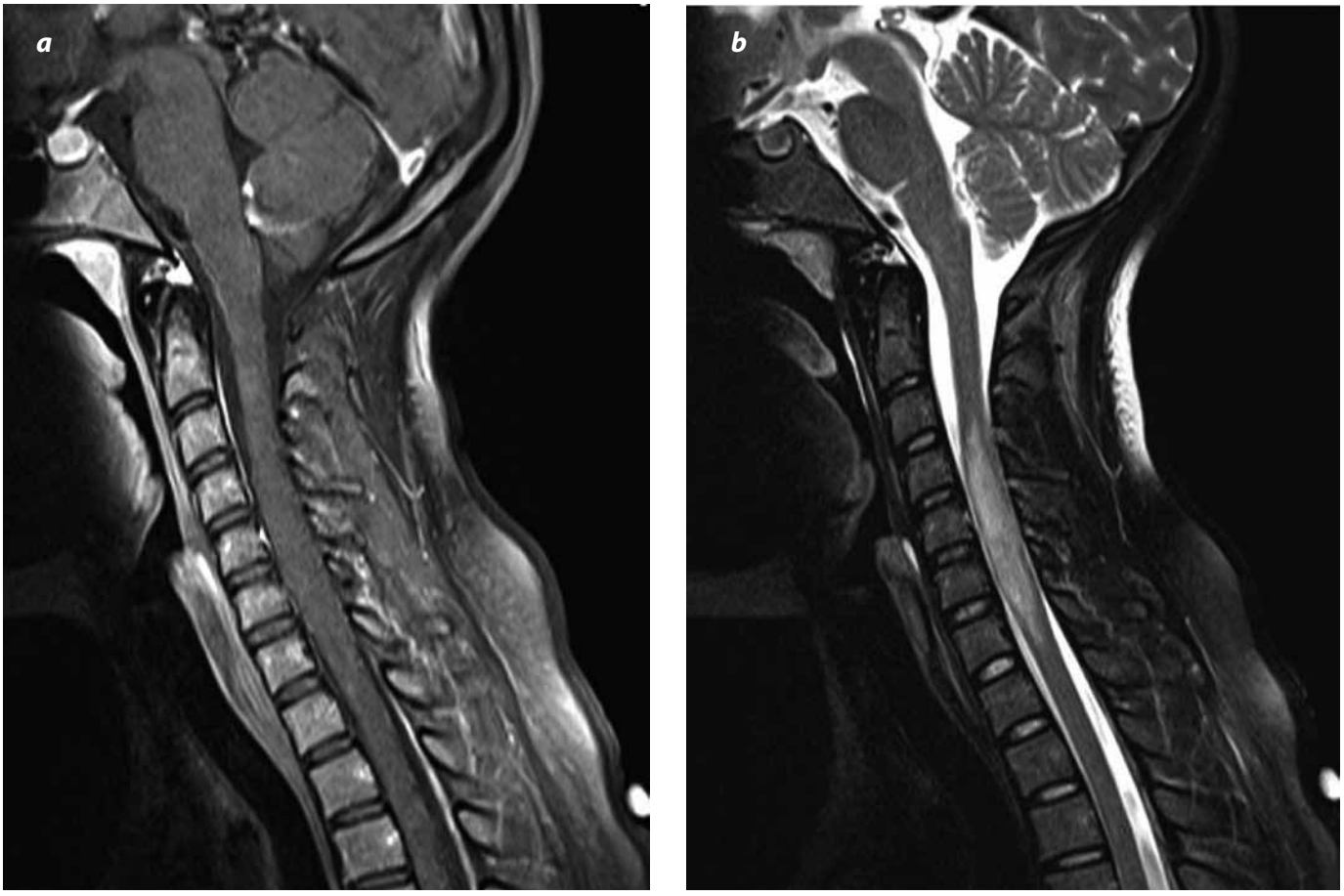


Figure 11. Twenty-year old patient with suspected multiple sclerosis. a) The sagittal sequence with T1 information shows widening of the spinal cord from C3 down to C7, with no other abnormal findings. b) Central high-signal area in T2 sequences due to acute transverse myelopathy.

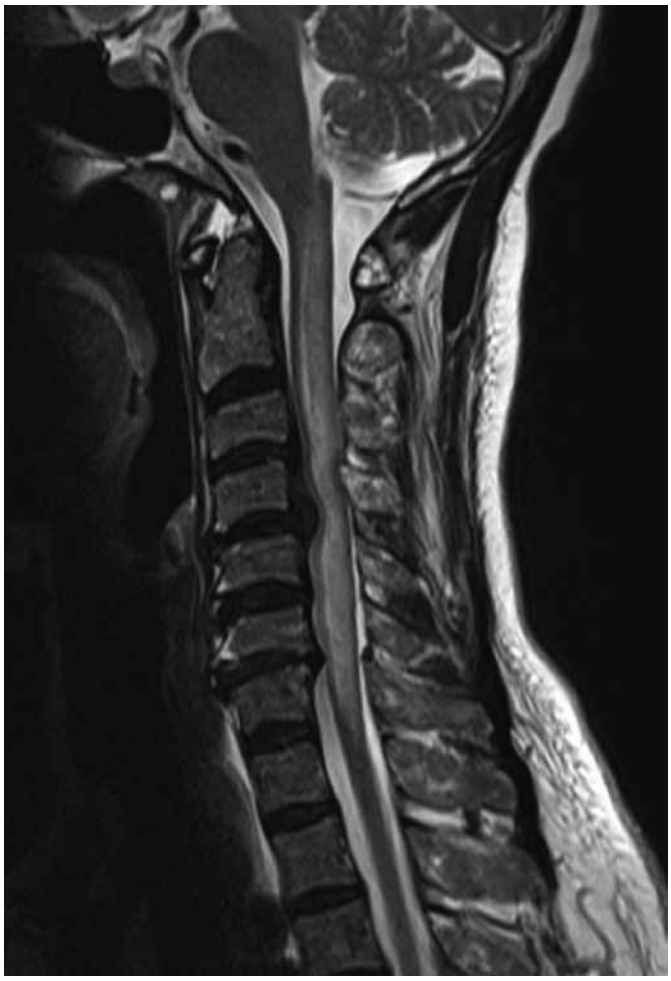


Figure 12. Sixty-one-year-old female patient with neurological abnormalities over the past three days, but no significant history. Laboratory tests and the medullary biopsy were all normal. The sagittal sequence with T2 information showed discal and osteophytic changes of the vertebral bodies associated with bulging of the inferior annulus and thickening and hypersensitivity of the cervical spinal cord from the craniocervical junction down to C7. The clinical findings and the additional studies established the diagnosis of idiopathic myelopathy.

Parainfectious myelopathy

Neurological damage in parainfectious myelopathy is caused directly by the infection, the immune reaction against the agent, and the reaction of the immune system. It is usually due to a blood-borne infection originating in the lungs, the skin, the skeletal, genitourinary or digestive systems. It presents with severe motor and sphincter dysfunction associated with fever, meningism and skin exanthema. The time period for the onset of myelitis after the infection is no different between infectious and post-infectious myelitis: five days for small-pox myelitis, ten days for mycoplasm and twelve days for herpes zoster myelitis (43,44). Possible etiologies include the following (3):

- Viral: herpes, varicella zoster, EBV, CMV, HIV, dengue, influenza, measles, mumps, HTLV-1, enterovirus, Coxsackie B, hepatitis A and C, and polio.
- Bacterial: mycoplasm, treponema pallidum, brucella, mycobacterium tuberculosis and borrelia.
- Fungi: actinomyces, blastomyces, coccydiodes and aspergillus.
- Parasites: schistosoma, cysticercus, echinococcus and toxoplasma.

There is CSF pleocytosis, generally neutrophilia with increased protein concentrations and no oligoclonal banding (8). Spinal MRI findings include extensive central high signal areas in T2 sequences, associated with spinal edema, mainly cervicodorsal. Brain MRI is usually normal; however, abnormalities have been described, including white matter changes very similar to those found with acute demyelinating encephalopathy.

Syphilitic myelopathy is a rare manifestation of neurosyphilis. It appears as a high-signal image in T2 sequences, with enhancement mainly on the spinal surface that disappears, suggesting its reversible nature. Intraspinal tuberculosis is rare. Intraspinal tuberculomas are found in 0.002% of cases of tuberculosis, and in 0.2% of cases of CNS tuberculosis. MRI is the method of choice for detecting spinal tuberculomas. Fusiform spinal edema is found, with areas of intermediate or high signal intensity in T1 sequences. In T2 sequences there are central low signal areas with surrounding edema. A high-signal center in T2 may be present due to the lower degree of caseification or liquefaction. The solid or ring enhancement is present in contrast images (40) (Figures 13 and 14).

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an uncommon inflammatory disease of the central nervous system, characterized by diffuse demyelination of the cerebral white matter and the spinal cord. It is more frequent in children and young adults. It has been associated with infection or vaccination, but this is not considered a criterion in clinical consensus (45). It is believed to be a single-phase disease with a good prognosis; however, recurrent forms make differentiation from MS difficult (22).

ADEM has clinical manifestations that usually include encephalopathy but may also include focal or multifocal demyelinating inflammatory syndromes of the CNS such as optic neuritis and myelitis. For that reason, ADEM is a differential diagnosis for isolated demyelinating syndrome, which is a more common precursor of MS in adults (45). ADEM symptoms include rapidly progressing encephalopathy associated with seizures or multiple neurologic deficits. The spinal cord is affected in 11% to 28% of patients, generally in the thoracic and cervical segments. CSF findings are non-specific and oligoclonal bands are found in 65% of patients (8).

MRI shows bilateral symmetric multifocal white matter lesions, with or without damage of the grey matter, and extensive disease of several spinal segments with expansion. These lesions appear with low signal in T1 sequences, and well defined with a high signal in T2 sequences; gadolinium enhancement is variable. All patients with spinal involvement have brain damage (8,22). These findings do not differentiate it from MS; the only characteristics that help with the differentiation are the single-phase occurrence and the complete spinal cord involvement

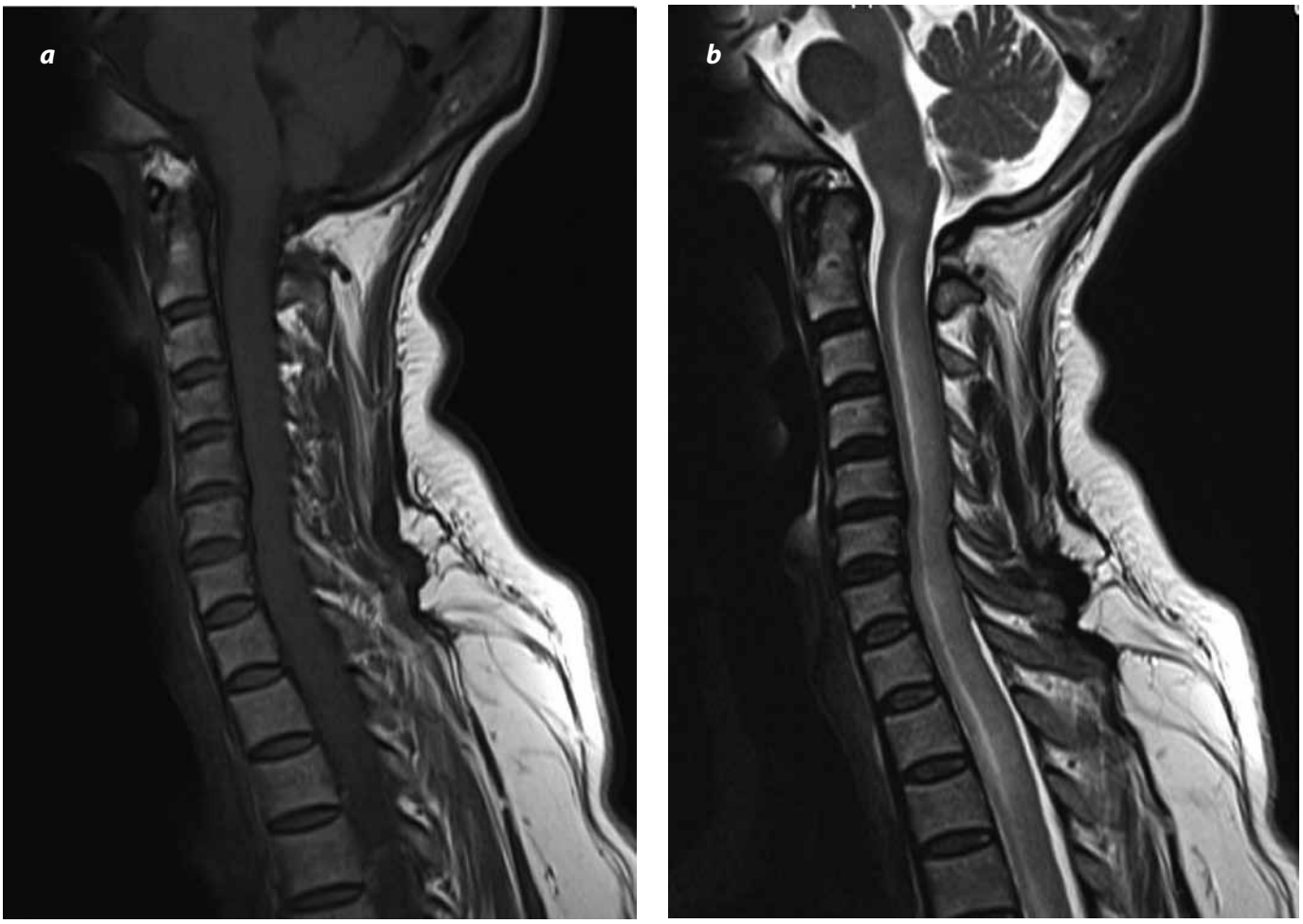


Figure 13. a) Sagittal sequence with T1 information showing thickening of the spinal cord from the craniocervical junction down to the thoracic region. b) Sagittal sequence with T2 weighted image showing high central spinal signal. HTLV-1 infection is confirmed later by positive serology.

in ADEM. ADEM differentiation from MS and neuromyelitis optica is important for prognosis and treatment, because patients with MS and neuromyelitis optica benefit from early treatment as a way to avoid relapses. Up to 35% develop MS in the course of follow-up (22). There are no diagnostic criteria, but ADEM must be suspected when one or more of the following are present (45):

- Initial multifocal presentation with multiple symptoms.
- Less than 10 years of age.
- Signs and symptoms of meningoencephalitis.
- Encephalopathy.
- Bilateral optic neuritis.
- CSF pleocytosis without oligoclonal banding.
- MRI shows lesions in areas not affected by MS, such as the grey matter or the cortex.
- Lesions on MRI appear larger with poorly defined edges that enhance with gadolinium.

Advanced neuroimaging such as diffusion tensor and magnetization transfer imaging may help identify the involvement of the apparently normal white matter, which is abnormal in MS and normal in ADEM (45) (Figure 15).

Myelopathies due to demyelinating diseases

The onset of neurologic symptoms occurs over a period of days as a result of demyelination, although necrotizing myelopathies, like neuromyelitis optica, may sometimes progress in a matter of hours. They usually occur in patients with prior non-specific viral infection (8).

Multiple sclerosis

MS is a chronic demyelinating inflammatory CNS disease. It is common in Europe, the United States, Canada, New Zealand and Australia, but it is rare in Asia, the tropics and the subtropical regions. It is estimated to affect between 250,000 and 350,000 individuals in the United States and more than 2,500,000 in the world (40,46). In high-risk populations, the incidence is one out of every 200 women. The female-to-male ratio varies between 1.5 and 2.5. The age of onset of symptoms varies by region; however the incidence is low in children, increases in adolescence and peaks between 25 and 35 years of age, after which it starts to decline (47). The etiology remains unknown, although

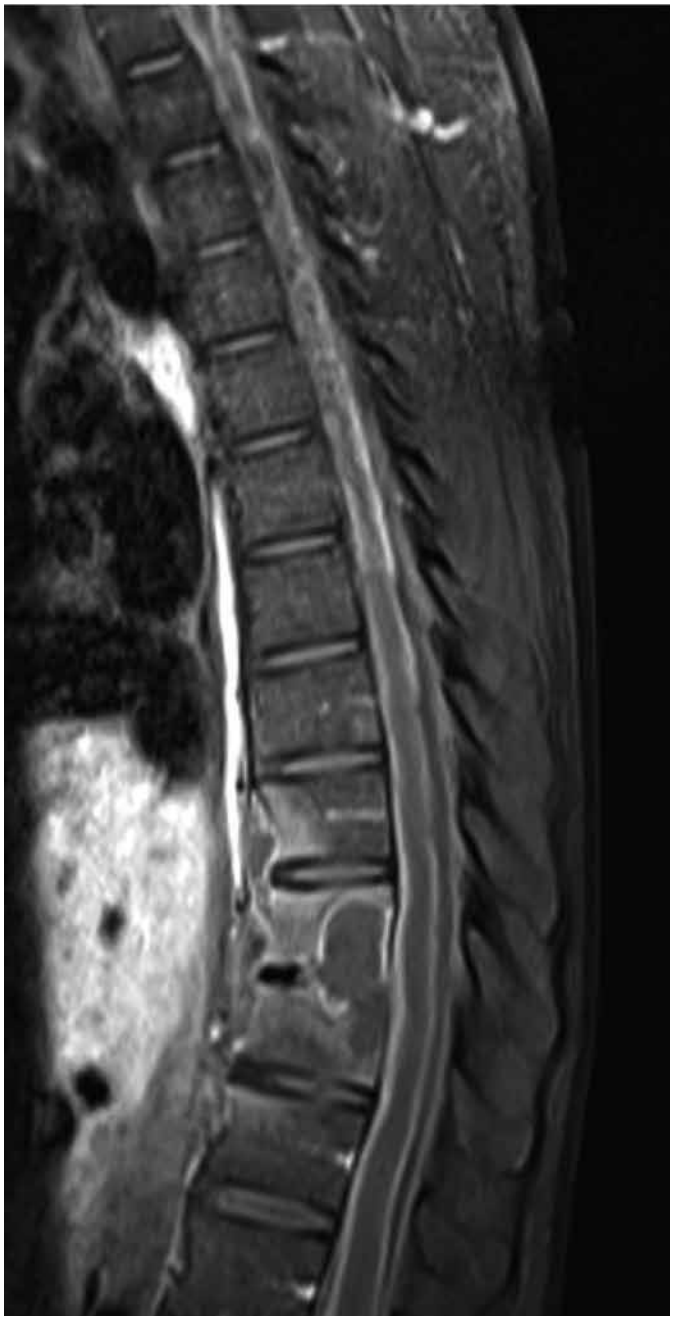


Figure 14. Twenty-four-year old patient with congenital HIV and tuberculosis. The image shows alteration in the shape and signal intensity of the vertebral bodies of T10 and T11, of the disc and of the prevertebral soft tissues. It is associated with widening of the spinal cord with edema and contrast enhancement, and with fluid accumulations near the spinal canal in the post-gadolinium sagittal STIR sequence due to tuberculous myelopathy.

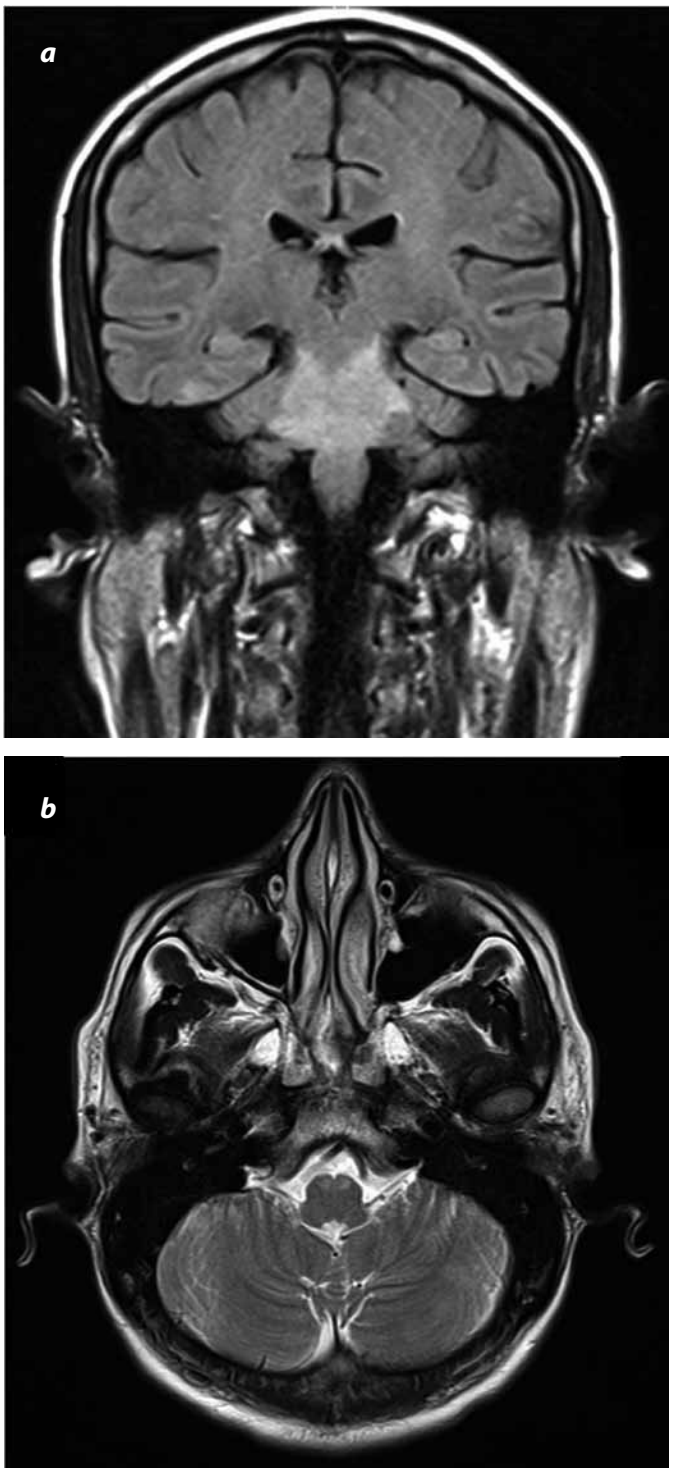


Figure 15. Twenty-eight-year old patient presenting with sudden neurologic decline. a) Coronal FLAIR sequence of the brain showing hyperintensity in the bulbo-medullary junction. b) Axial image with T2 information in the bulbo-medullary junction with anterior hyperintensity related to myelopathy due to acute disseminated encephalopathy.

environmental, viral and immune-mediated factors in genetically susceptible patients are thought to be the culprits (40,46).

The strongest risk factor is family history. Approximately 80-85% of patients present with a relapsing picture, with symptoms that last for several days and improve over the course of weeks. In 15% of patients, the disease is progressive from the start (40,46). It is the most studied of all acute myelopathies, and its effects range from irreversible tissue loss to partial demyelination where there can be remyelination and repair (40). There is spinal cord involvement in more than 90% of patients. It may present in the form a cervicodorsal asymmetric transverse myelitis with sensory symptoms.

On MRI, lesions are low signal in T1 sequences and high signal in T2 sequences, and they are visible in 95% of patients, generally in the cervical spine, and on occasions they show gadolinium enhancement, even in asymptomatic patients (48). Lesions may be focal, diffuse with axonal loss, and spinal atrophy. Focal lesions are peripheral, asymmetrical and may involve from a few millimeters up to a couple vertebral segments. They localize to the posterolateral region of the spinal cord.

On the sagittal plane, the plaques may be anterior, central or posterior. Acute lesions enhance with gadolinium, due to rupture of the blood-brain barrier. This enhancement is less in cerebral lesions. Unlike neuromyelitis optica, viral or idiopathic myelitis, in MS no black holes are visualized in the spinal cord (40, 46).

Diffuse lesions are more frequent in primary MS, and they appear as a slightly higher intraspinal signal in T2 sequences. It has been shown that 70% of chronic lesions present with axonal loss. NAA has been found to be reduced on spectroscopy, in spinal cord areas that appear normal on conventional MRI (40). A relationship has been found between low-signal lesions in T1 sequences and the degree of disability, whereas no association has been found between high-signal and enhancing lesions in T2 sequences. This dissociation between MRI and clinical disability has prompted the search for other markers that may provide information about the natural history of the clinical compromise (48). Polman *et al.* reviewed McDonald's diagnostic criteria in 2010 and proposed the following (49):

- Space: one or more lesions with and without gadolinium enhancement in two of the following areas: periventricular, juxtacortical, infratentorial, or the spinal cord.
- Time: one new lesion on T2 sequences or a gadolinium-enhancing lesion when compared to the previous MR image, and concomitant finding of asymptomatic lesions with or without enhancement.

The following criteria are defined for MS with progression from the start (49):

- One year of disease progression, plus two of the following: evidence of one or more brain lesions in T2 sequences, with or without enhancement in two of the characteristic sites (periventricular, juxtacortical or infratentorial); evidence of two or more spinal cord lesions in T2 sequences with or without enhancement; and positive CSF (oligoclonal bands or elevated immunoglobulin G index).

The CSF analysis shows oligoclonal bands in up to 90% of cases. During the initial phases of MS, before the development of glial scars, symptoms resolve over a period of weeks or months. Cerebral MRI shows concomitant demyelinating lesions; the presence of two or more lesions is associated with an 88% probability of conversion to sclerosis within the following twenty years. When the MRI is normal, this risk is only 19% (8). Abnormal evoked potentials do not help differentiate between multiple sclerosis and myelitis due to a systemic disease (Figure 16).

Neuromyelitis optica or Devic's syndrome

Neuromyelitis optica is defined as the concomitant presentation of myelitis and optic neuritis. This combination occurs in MS, ADEM, systemic lupus erythematosus and Sjögren's syndrome. It is also found in association with viral and bacterial infections (50).

Neuromyelitis optica is an immune CNS demyelinating condition that affects the spinal cord and the optic nerves. It is often mistaken with MS, although clinical, radiological and immunopathological tests suggest that they are different. The identification of the specific antigen of the neuromyelitis optica immunoglobulin G/aquaporin 4 antibody implies humoral immunity, which makes it different from MS (51).

It is an uncommon disorder among the Western population, with an incidence of 0.4 per million people per year, representing one out of every 200 patients with demyelinating disease. In Asia, the Caribbean and South America, the incidence is higher, pointing to genetic mechanisms. In all populations, females with a mean age of 40 are predominantly affected, in a 3:1 ratio (51). It is usually recurrent (8).

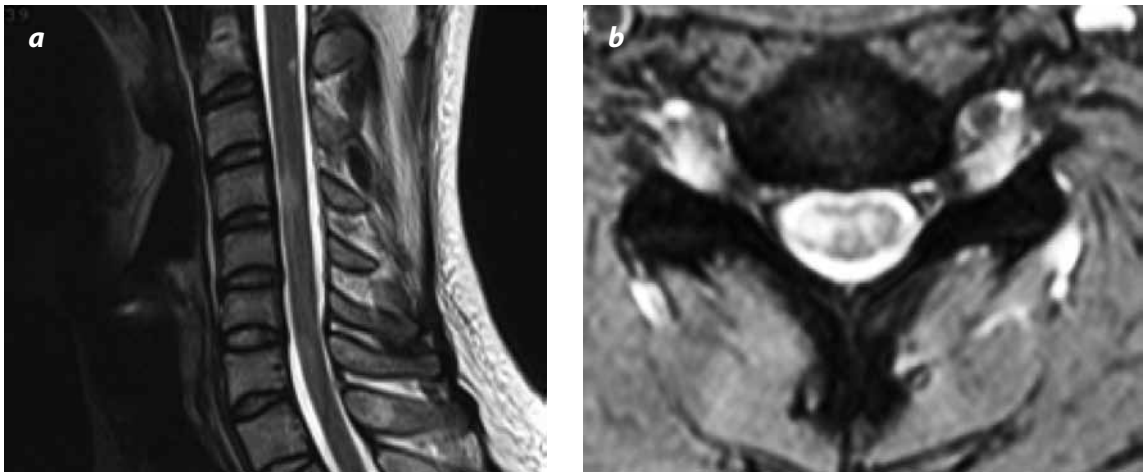


Figure 16. Twenty-eight-year old patient diagnosed with multiple sclerosis in December 2010 with progression in time and space. a) Sagittal sequence with T2 information showing high spinal signal in C4. b) High-signal area in C4 shown on a T2 gradient echo axial view due to myelopathy secondary to multiple sclerosis.

The clinical findings, which may be present at the same time or separated by several years, are transverse myelitis with longitudinal extension and optic neuritis. Optic neuritis may be unilateral or bilateral. Up to 80% of patients will experience recurrences, which are usually more debilitating than in patients with typical MS. Diagnostic criteria (8,51) include optic neuritis and acute myelitis, and at least two of the following:

- Central spinal lesions on MRI in more than three vertebral segments.
- MRI findings non-consistent with MS.
- Immunoglobuline G-positive neuromyelitis optica (S70% and E>90%).
- CSF findings of pleocytosis, elevated proteins and albumin, with no evidence of oligoclonal bands (8).

Radiological characteristics include a central longitudinal and extensive cervicodorsal lesion (three or more spinal segments) with spinal expansion, of low signal in T1 sequences and high signal in T2 sequences and patchy enhancement. Lesions of the optic nerves are found on occasions (50). Although the classical thinking was that neuromyelitis optica was not accompanied by brain lesions, it has been demonstrated that 60% of patients may have periventricular lesions (areas of high aquaporin 4 concentration, target for neuromyelitis optica-immunoglobulin G) (8). MRI may help differentiate between neuromyelitis optica and MS. In this case, neuromyelitis optica is not associated with cerebral white matter lesions, and the spinal lesions are confluent and extend to multiple segments (which is infrequent in MS); moreover, cranial nerve and cerebellar involvement is common in MS and is not present in neuromyelitis optica (21).

Recovery from neuromyelitis optica is less complete. Published studies suggest a 68% five-year survival, with mortality resulting from severe spinal compromise and respiratory failure (51). The presence of the neuromyelitis optica-immunoglobulin G antibody predicts the risk of developing recurrent myelitis. Certain autoimmune conditions may coexist with neuromyelitis optica, including systemic lupus erythematosus, Sjögren's syndrome and autoimmune thyroid disease (Figure 17).

Myelopathy due to systemic disease

Myelitis associated with a systemic disease has been rarely described in the literature. It has been associated with systemic lupus erythematosus (SLE), Sjögren's syndrome, scleroderma, Behçet disease, and sarcoidosis (25). It has been estimated that the frequency of myelitis in patients with SLE is 3%, but it is unknown in Sjögren's syndrome. Myelitis usually occurs in the first year of the disease and may be its first manifestation. The hypothesis about the pathophysiology is still a subject for debate, and the most accepted is a vascular mechanism secondary to ischemic lesions (9). Women are more frequently affected than men, in an 8:1 ratio. CNS involvement in SLE is often found in relation with the antiphospholipid syndrome with anticardiolipin antibodies (22).

The clinical symptoms often include transverse myelitis with severe motor and sensory dysfunction. CSF may be normal or show plecytosis, and although oligoclonal bands are rare, they may be present (9). MRI findings have been studied more in SLE than in Sjögren's syndrome. Moreover, it has been found that the central high-signal spinal lesion in T2 sequences, oc-

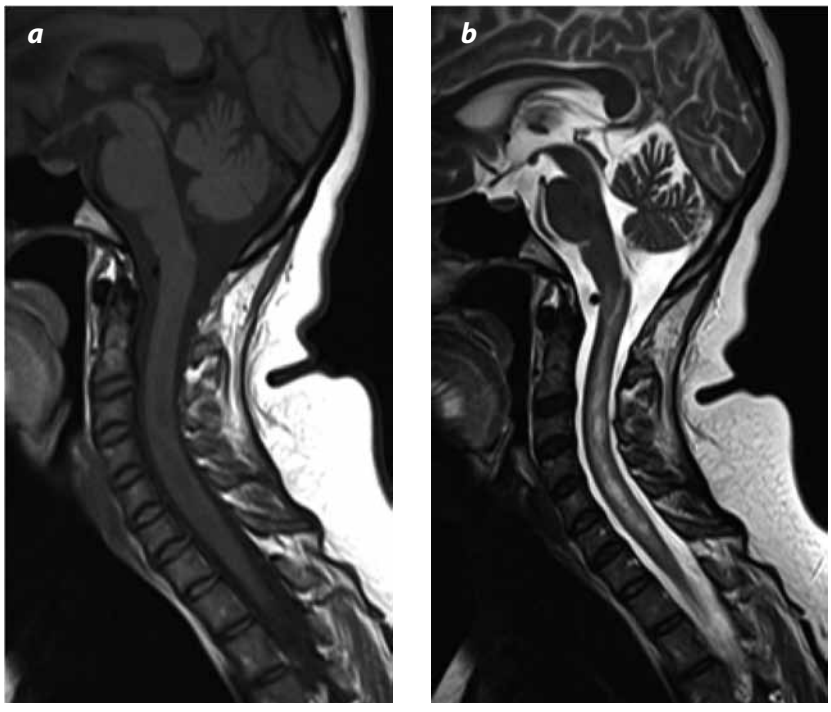


Figure 17. Forty-four-year old patient with demyelinating disease and proven neurological decline. a) Diminished signal intensity in the upper segments of the cervical spinal cord in the sagittal T1 sequence. b) Sagittal sequence with T2 information showing hyperintensity from the bulbo-medullary junction down to C6 and C7, due to neuromyelitis optica myelopathy.

cupying two-thirds of the spinal cord in axial sections, extends over three or four segments and shows variable gadolinium enhancement (22,25). Normal or mild areas of high signal have been described on MRI. In Sjögren's syndrome, spinal MRI has been studied only in isolated cases, and findings are similar to those of SLE (25) (Figure 18).

CNS sarcoidosis may occur in isolation in the form of a myelopathy. The definitive diagnosis requires biopsy evidence of non-caseifying granulomatous inflammation of the CNS or any other compromised organ. Angiotensin-converting enzyme elevation is suggestive of the diagnosis but is not specific. An isolated CNS sarcoidosis must be suspected when a slowly-progressing subacute myelopathy is present, with asymmetrical spinal cord patches and persistent gadolinium enhancement. A satisfactory response to empirical steroid treatment, during months or even years, suggests the diagnosis (6).

Post-radiation or electric damage

Neurotoxicity is a known complication of high-dose radiation. The deep white matter is the most affected since it comprises the cortex and the subcortical arcuate fibers. There are three forms of lesions: acute (weeks or months), early late and late (six months to two years). The latter may be irreversible, progressive and, on occasions, fatal; however, it may resolve spontaneously in some cases (52,53).

Radiation myelopathy is a devastating complication of radiation therapy (22). It is a rare cause of acute myelopathy, accounting for only 2% of complications, and it is suggested in cases where there is a history of exposure to head and neck

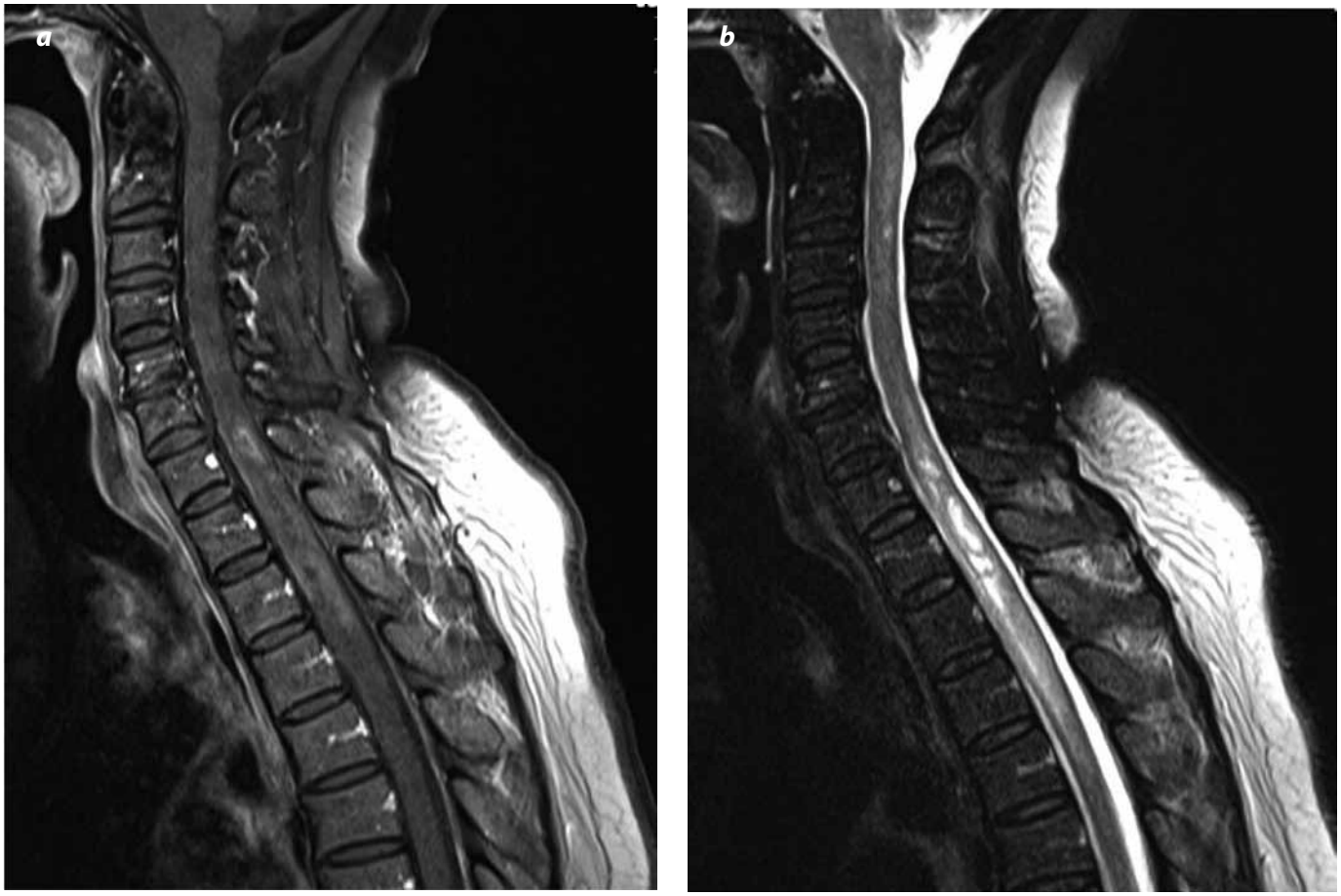


Figure 18. a) Sagittal sequence with T2 information showing spinal cord thickening and hyperintensity from C4 down to T2. b) Post-gadolinium STIR image showing enhancement due to SLE-associated myelopathy.

radiation (even longer than ten years), with a dose greater than 4,000 rads. It is an irreversible process with no effective treatment (52). It may have an early manifestation ten to sixteen weeks into radiotherapy, or a late manifestation, and may resolve spontaneously between two and nine months after onset (9). In the early stages, there is evidence of edema or spinal enhancement and, in late cases, spinal atrophy is observed (8).

It manifests as a transient sensory loss, progressive chronic myelopathy, acute transverse myelitis, or local amyotrophy. The transient sensory loss gives an electric-shock sensation when the neck is flexed forward (Lhermitte sign) and it resolves within two and thirty-six weeks. In chronic progressive myelopathy, it presents like a Brown Séquard syndrome lasting between three months and five years.

The CSF analysis is normal in most cases, with absent oligoclonal banding. There is no cellular reaction and this is how in may be differentiated from MS (8). Spinal cord MRI shows a high signal image in T2 sequences, with local spinal edema and gadolinium enhancement, during at least eight months. After this time, the signal intensity is normal and there is severe atrophy, with or without persistent enhancement that diminishes after 24 months (22) (Figure 19).

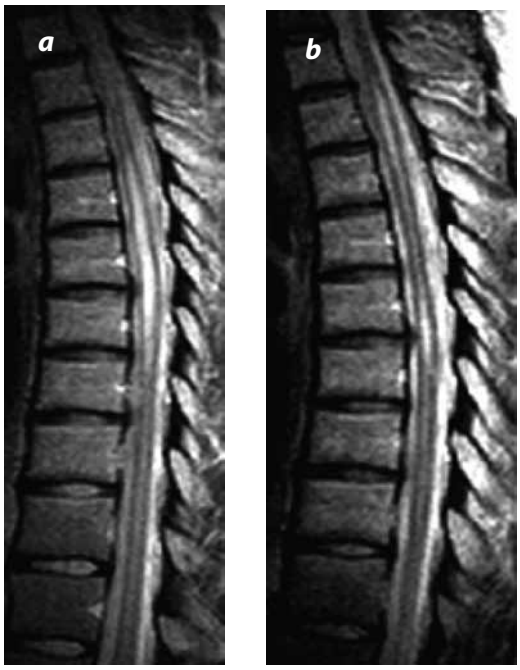


Figure 19. Patient with a history of radiotherapy due to esophageal cancer who complains of paresthesias and discreet loss of strength in the lower limbs, and Lhermitte sign. a) Sagittal T2 image of the dorsal spine with discreet fusiform thickening of the spinal cord showing high intensity signal and post-radiotherapy bone marrow changes. b) Follow-up MRI after 18 months with evidence of partial regression of post-radiation myelopathy. Courtesy of Dr. Alex Rovira Cañellas, Head of the Magnetic Resonance Unit at Vall d'Hebron University Hospital.

Subacute combined degeneration

Combined subacute degeneration is a complication of vitamin B12 deficiency, associated with pernicious anemia. This deficiency may be related to parietal-cell autoantibodies or the intrinsic factor required for vitamin B12 binding. There is a genetic deficiency of transcobalamin 2 (cobalamin transporter protein). The complete transcobalamin 2 deficiency is a recessive autosomal condition characterized by normal concentrations of vitamin B12 with severe infantile megaloblastic anemia associated with neurologic damage (54).

The clinical picture presents as a slowly-progressing spastic paraparesis with distal proprioceptive loss and symmetrical dysesthesias (54). This clinical picture is due to axonal loss and inferior cervical and thoracic spinal demyelination, generally in the posterior and anterolateral columns, that cannot be explained by compression or inflammation on MRI (22,25,54). The absence of anemia with or without macrocytosis does not rule out a vitamin B12 deficiency diagnosis.

MRI shows high signal intensity of the posterior columns in T2 sequences, without contrast enhancement (25). Imaging improvement correlates with clinical improvement (22). The mean time to diagnosis since the onset of neurological symptoms due to vitamin B12 deficiency is approximately on year, with a range that extends to four years (54) (Figure 20).

Acute paraneoplastic or necrotizing myelitis

Paraneoplastic myelopathy is a rare disease. It may occur before the cancer is detected. Several antibodies have been associated with subacute myelopathies, in general with lung, breast, thyroid, ovarian and prostate cancer, and Hodgkin's lymphoma. The lesion often involves the thoracic spinal cord that shows a high-intensity signal in T2 sequences and gadolinium enhancement. There is increased protein concentration in the CSF (8).

Myelopathy with normal MRI

In some cases of acute myelopathy, the MR image is normal. There are several explanations for this: 1) the syndrome is not a myelopathy (Guillain-Barré, inflammatory radiculopathy); 2) the picture may not be acute but rather a decompensated existing myelopathy (Friedreich's ataxia, motor neuron disease, vitamin B12 deficiency, HIV or HTLV-1 myelopathy); and 3) MRI performed during the convalescence period (8) (Figure 21).

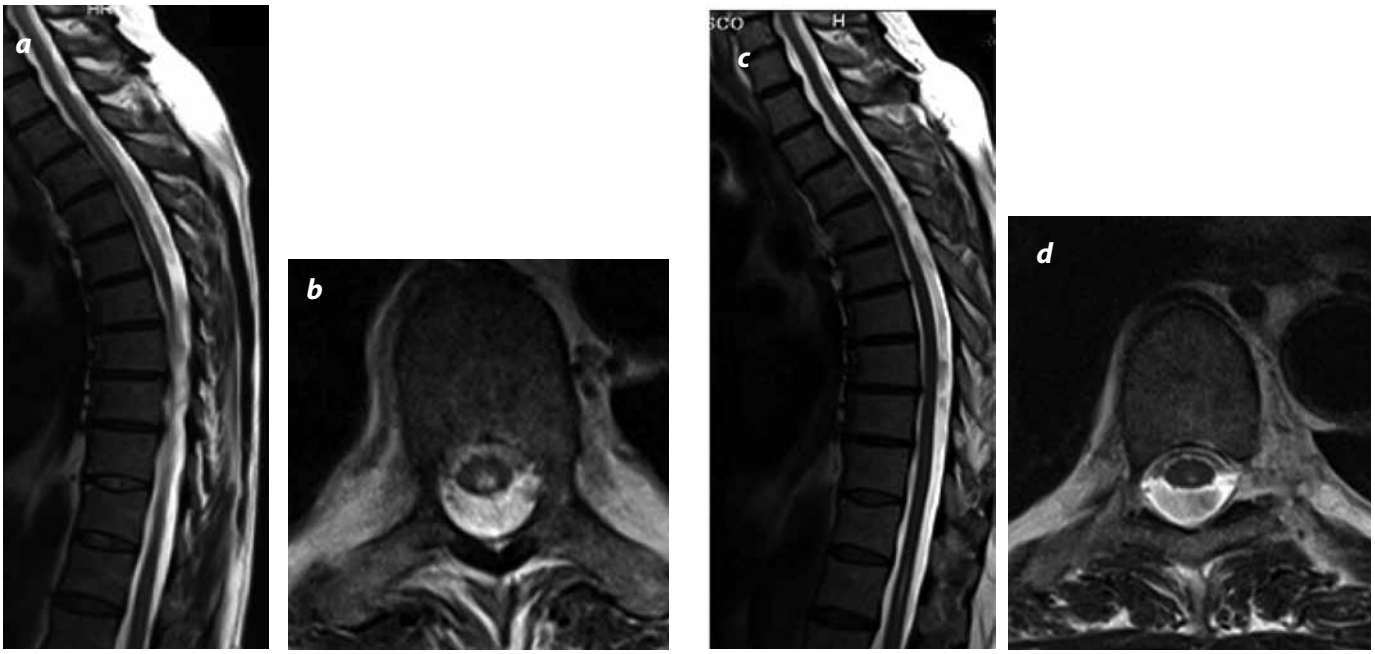


Figure 20. a) Sagittal T2 sequence showing hyperintense signal in the dorsal spine. b) Axial T2 image confirming spinal damage predominantly in the posterior horns. Low concentrations of vitamin B12 were found, pointing to the diagnosis of myelopathy due to vitamin B12 deficiency. c) and d) Follow-up MRI performed one year after the diagnosis, showing no evidence of abnormalities. Courtesy of Dr. Alex Rovira Cañellas, Head of the Magnetic Resonance Unit at Vall d'Hebron University Hospital.

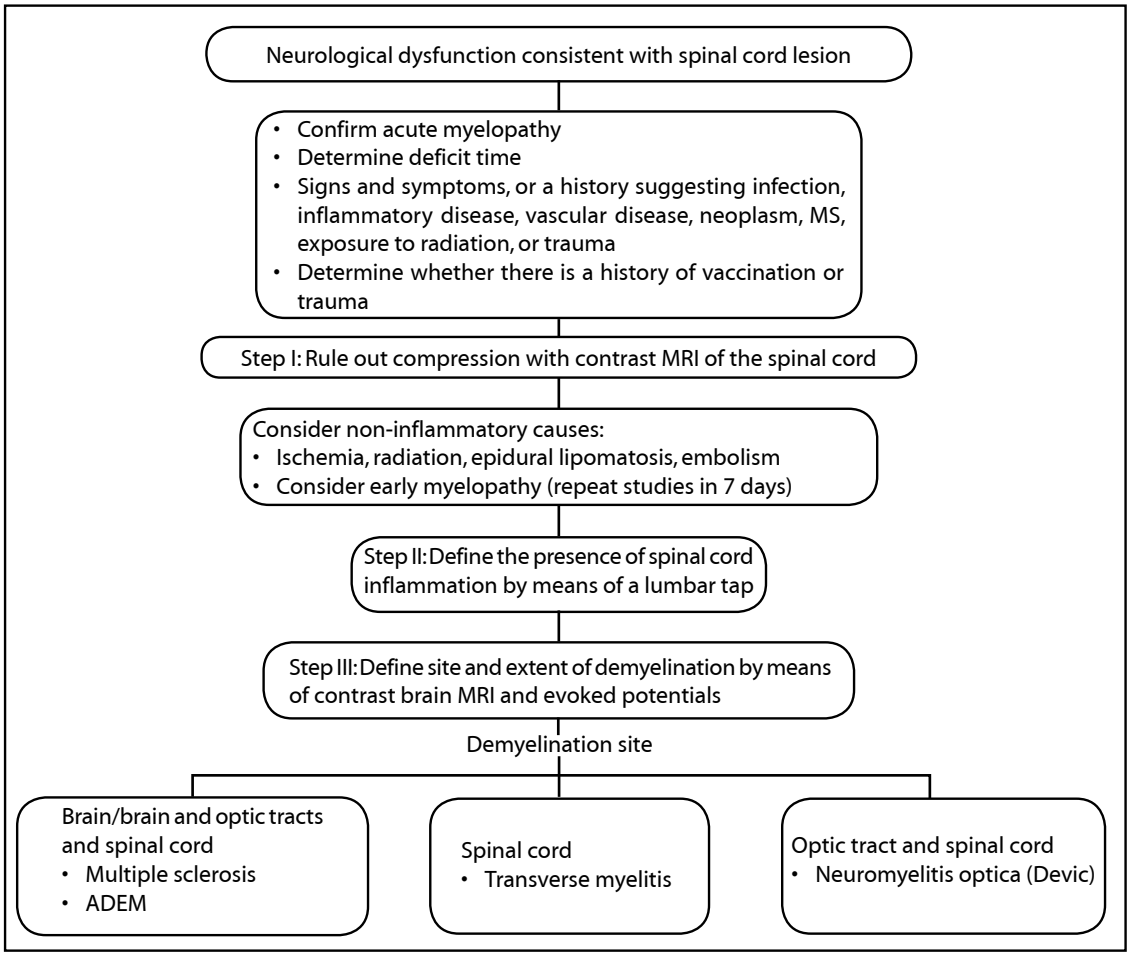


Figure 21. Diagram of the diagnostic approach to myelopathies.

Acknowledgements

We are grateful to Dr. Alex Rovira Cañellas, Head of the Magnetic Resonance Unit at Vall d'Hebron University Hospital.

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Received for evaluation: February 11, 2011
Accepted for publication: August 17, 2011