REVIEW

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Myelopathy but normal MRI: where next?

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For most patients presenting with a spinal cord syndrome MR scanning has become the key investigation in establishing the diagnosis. However, myelopathy with normal spinal imaging remains a common clinical conundrum. In this review we discuss the diagnoses to consider for the neurologist presented with a patient with "MR normal myelopathy". We will illustrate this scenario with a series of short cases and consider the further investigation of "MRI normal" myelopathy.

"So the gait is spastic, the toes go up and even general physicians think it's a cord problem—but the MRI is normal... now what to do?"

Spinal cord syndromes are common, usually quite easy to recognise, and the level and even the nature of the lesion can sometimes be defined clinically without any imaging. Nonetheless, to exclude surgically treatable lesions, most commonly extrinsic compression of the cord, an MR scan is essential; indeed, it is often undertaken early, before referral to a neurologist. However, because a range of conditions can present with a cord syndrome but with normal or near-normal MRI findings, a request to review a patient with a clinically diagnosed myelopathy but with a "normal MR scan" is not unusual. This scenario occurs in about one fifth of cases of myelopathy referred to a UK neurosciences centre.[1]

As ever, the first step for the neurologist is to re-take the history, examine the patient, and personally review the available radiology, ideally with an experienced neuroradiologist. Importantly, the clinical sensory level is quite often below the level of the lesion (and the available imaging may not have gone high enough), although with a spinal dural arteriovenous malformation, it may be many segments *above* the lesion.

THE DIFFERENTIAL DIAGNOSIS IN CLINICALLY ISOLATED MYELOPATHY WITH NORMAL SPINAL MRI

Inflammatory and autoimmune conditions

Multiple sclerosis

In the pre-MRI era, about half the unexplained progressive myelopathies were diagnosed as primary progressive multiple

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sclerosis (MS) on the basis of evoked responses, CSF oligoclonal bands and CT brain scan.[2] This increased to 85% in a later study using brain MRI.[3] Spinal MR imaging can however be entirely normal in a minority of cases, with small cord lesions often missed, particularly on older scanners or with smaller magnets. Certain MR sequences increase the chance of detecting abnormalities in spinal cord; for example, fast-STIR sequences maximise the MRI sensitivity for detecting multiple-sclerosis lesions.[4] Gadolinium enhanced MRI is recommended to exclude spinal arteriovenous malformation.[5]

The diagnostic criteria for primary progressive MS have been recently revised,[5] requiring clinical progression over more than one year, support from CSF or evoked potentials in MR negative patients, and exclusion of other conditions such as adrenoleukodystrophy, HTLV-1, syphilis, Lyme disease, and Sjögren's syndrome. CSF protein over 1 g/l, or more than 50 white cells per mm^3 suggest diagnoses other than MS.

Neuromyelitis optica

Although in episodes of myelitis spinal MR imaging is typically abnormal (indeed the presence of longitudinally extensive signal change has been added to recent diagnostic criteria[6]), such changes can be transient (fig 1). It is clearly important therefore to establish whether imaging was performed acutely at a time when it was likely to have been abnormal.

Sjögren's syndrome

Sjögren's syndrome can present with an acute transverse myelitis or, less often, with a progressive myelopathy that mimics MS.[7-9] The subacute and chronic progressive forms tend to start unilaterally with sensory symptoms and sphincter involvement.[8] There may even be optic neuropathy and other neurological symptoms outwith the cord, again mimicking MS.[8] Central nervous system involvement, however, is rare, occurring in 1% of patients with primary Sjögren's syndrome,[10] which itself has a prevalence of 3–4% of adults in the general population.[11] The myelopathy is thought to be due to either vasculitis or organ-specific immunological damage.[12] Spinal MRI may be normal in up

Think of all possible infective agents! (Illustration by S Wong.)

to 25%,[9] especially in the chronic progressive type.[13] The CSF changes may resemble those seen in MS and the visual evoked responses may be abnormal.[14] MRI of the brain tends to be equivocal or normal, compared to primary progressive MS where inflammatory lesions are generally present.[14, 15]

The diagnosis of Sjögren's syndrome can be a challenge; the European diagnostic criteria have a sensitivity of 96% and specificity of 94%.[16] Unfortunately, the symptoms of sicca may be subtle,[8] and many of these patients with chronic myelopathies have negative Ro/SS-A and La/SS-B antibodies[15] although alpha-frodin antibodies may be helpful in differentiating primary progressive MS from

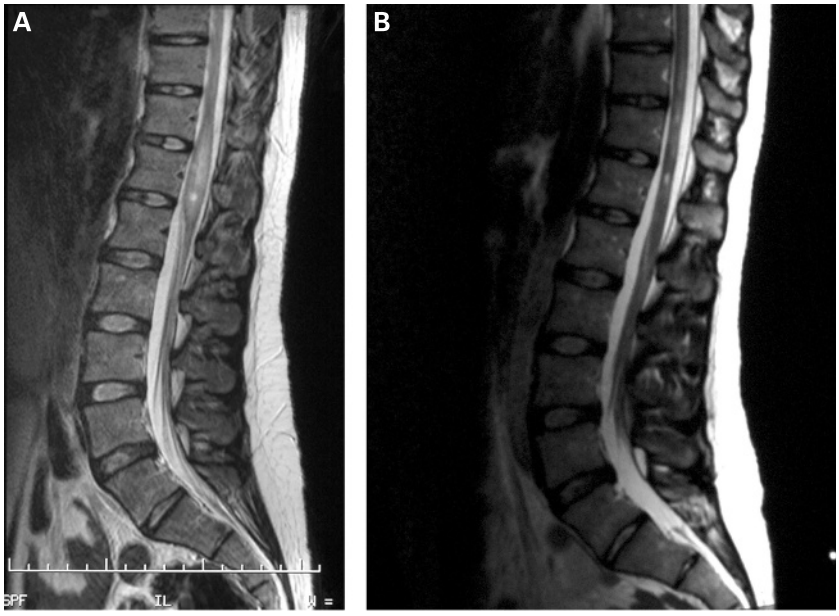

Figure 1
MRI spine of a patient with neuromyelitis optica. (A) During an acute inflammatory episode and (B) four months later, demonstrating the importance of checking the timing of imaging. Sagittal T2 (fast spin echo) image showing a bright signal within an expanded cord at T12/L1 (A). Repeat MRI four months later showing significant improvement (B). The antero-posterior diameter of the cord is normal and there is still some residual bright signal within the cord, though significantly less than previously.

Case 1

A 60-year-old man presented with sudden onset of back pain eight months previously while shovelling snow, with radiation into the right groin. His walking was affected following resolution of the pain in six weeks. This improved over the next four months but then gradually deteriorated, with progressive right leg weakness and numbness exacerbated by walking, perineal numbness and urinary difficulties. Examination showed mild wasting of right quadriceps, normal tone with mild pyramidal weakness of both legs, and reduced pin prick from L2–S4 bilaterally. The ankle jerks were absent and the plantars extensor. The spinal MRI had been reported as normal but on review there was an equivocal high signal area in the conus on the T2 images, with no gadolinium enhancement on T1. Subsequent myelography showed an extensive vascular malformation in the lumbar and thoracic regions, extending to L5, although no fistula was demonstrated on catheter angiography—a thoracolumbar spinal dural arteriovenous malformation, with probable spontaneous thrombosis of the fistula. On follow-up his condition continued to gradually deteriorate with a worsening spastic paraparesis and urinary incontinence. Spinal MRI and MR angiography (fig 2) eventually identified an arteriovenous fistula at T10 which was successfully embolised.

Sjögren's syndrome.[12] Most UK neurologists tend not to pursue more invasive investigations—for example, lip biopsy—without some clinical or serological clue to the diagnosis of Sjögren's syndrome in the setting of an otherwise unexplained myelopathy. It is therefore unknown how often we are missing this diagnosis, which is important because Sjögren's syndrome-associated myelopathy may respond to cyclophosphamide, azathioprine and corticosteroids.[8–10, 14]

Systemic lupus erythematosus

Acute transverse myelitis occurs in about 2% of patients with systemic lupus erythematosus (SLE),[17, 18] as the first manifestation or within five years of diagnosis in most patients.[17, 18] Revised diagnostic criteria for SLE have a 96% sensitivity and 96% specificity and may alert the neurologist to consider SLE as the cause.[19] The cervical or thoracic cord can be involved[17, 18] but spinal MRI, even if undertaken acutely, is not infrequently normal.[17, 18] The CSF may also be normal or only non-specifically abnormal.[17, 18] Over half of these patients have positive antiphospholipid antibodies, more in comparison to SLE patients in general.[18] The pathophysiology of the transverse myelitis in SLE is unclear, although postulated mechanisms include an ischaemic or vasculitic process. Treatments include intravenous methylprednisolone, cyclophosphamide and anticoagulation.[17, 18] Complete recovery occurs in up to 50% and those with a normal MRI may have a better outcome.[17, 18]

Sarcoidosis

Spinal cord involvement in sarcoidosis is rare, occurring in less than 0.5% of sarcoid patients.[20] A recent review summarised the features of all reported cases of sarcoidosis in the spinal cord:[21] it was the presenting manifestation in most cases (57%) and in 16% it was the only manifestation of sarcoidosis. The lungs were the most

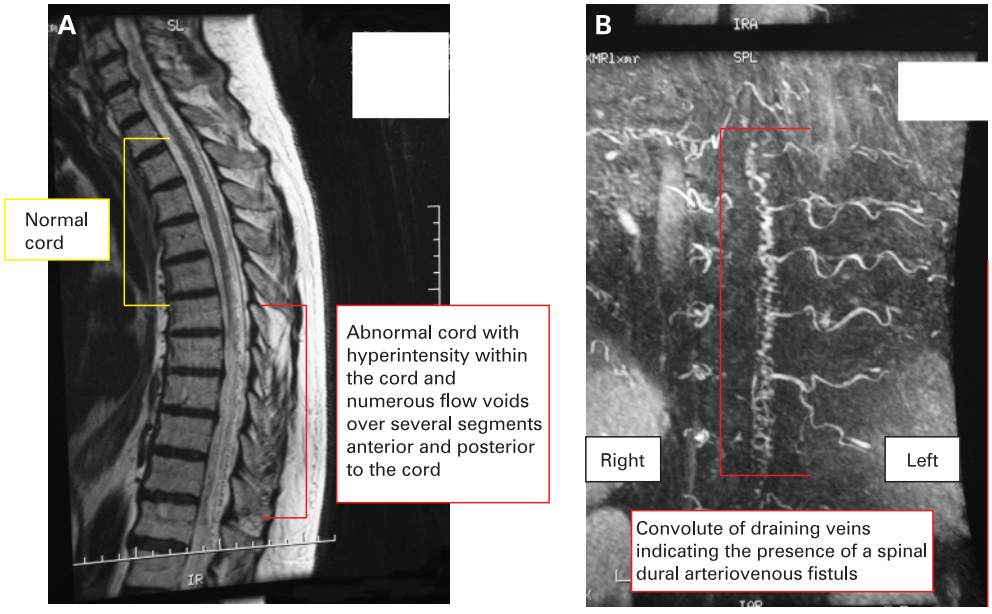

Figure 2
(A) MRI spine (sagittal T2) showing hyperintensity within the cord and numerous flow voids over several segments anterior and posterior to the cord in the thoracolumbar region, suggestive of a spinal dural arteriovenous malformation. The hyperintensity within the cord is likely secondary to ischaemic change, and the flow voids demonstrate abnormally dilated vessels. (B) Contrast enhanced spinal MR angiography (digitally reconstructed image). A convolute of draining veins is demonstrated within the spinal cord, indicating the presence of a spinal dural arteriovenous fistula, confirmed on catheter angiography.

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commonly affected extra-axial organ (58%) in patients whose first manifestation of sarcoidosis was the spinal cord. Neurosarcoid can present as a slowly progressive myelopathy, or an acute transverse myelitis.[20] Histology suggests that the damage is caused by demyelination of the lateral and posterior columns,[22] and perivascular granulomatous infiltrates.[20, 22] The proposed diagnostic criteria, management and investigations of possible neurosarcoidosis have been recently reviewed in this journal.[23] Useful investigations include chest *x* ray, CT thorax, serum calcium, ESR, gallium scan and tissue biopsy. Serum ACE is raised in only about 50% of patients with neurosarcoidosis. The CSF findings, if abnormal at all, are rather non-specific with a lymphocytic pleocytosis, a raised protein and low glucose.[21] CSF ACE is only raised in about one third of cases, but can be useful in monitoring response to treatment.[21]

Motor neuron disease

Diseases of motor neurons which can present with a progressive spastic paraparesis without any sensory involvement and a normal spinal MRI include amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS). The mean age of onset is the fifth or sixth decade, similar for ALS and PLS. Clinical and neurophysiological assessment looking for lower motor neuron features are obviously important and often repeated in trying to diagnose ALS. Differentiation is helpful for prognosis: mean disease duration is 2.5 years for ALS, but 8–15 years for PLS.[24, 25]

Primary lateral sclerosis typically presents as slowly progressive symmetrical upper motor neuron spinobulbar dysfunction, beginning in the legs, and causing sphincter and emotional instability only very late.[24, 25] The diagnostic criteria include a minimum duration of three years, no family history or CSF oligoclonal bands, and a normal CSF.[24] Brain MRI may show focal atrophy of the precentral gyrus.[24] Important negatives are the absence of sensory, bladder (except in late disease) and ocular involvement.

Although a small number of patients with ALS present with only limb upper motor neuron features, on follow-up about one half develop lower motor neuron features by three years, and three quarters by four years.[26]

Case 2

A 70-year-old woman presented in 2004 with progressive gait difficulties over two years and mild urgency of micturition. She was one of nine siblings and although the family history was initially thought to be negative for neurological problems (her mother died aged 91, and her father died aged 49 from cancer) it was later revealed that two brothers had died in childhood, one almost certainly from a "neurological illness". On examination she had a spastic paraparesis, generalised hyper-reflexia, extensor plantars and normal sensation. The spastic paraparesis progressed over the next three years with no additional signs. Routine blood tests, CSF and MRI of her brain, cervical and thoracic cord were all normal. In view of the death in childhood of her two brothers, very long chain fatty acids were requested and these showed increased C26, C26/22 and C24/C22 levels, indicating the patient was a manifesting carrier of X-linked adrenoleukodystrophy. She did not have cortisol insufficiency or any skin pigmentation to suggest Addison's disease.

Inherited disorders

Hereditary spastic paraplegias

These cause symmetrical spastic paraparesis with the upper limbs, bulbar and respiratory function remaining normal. Urinary urgency is common and may occasionally be the presenting symptom.[27, 28] There may be mild dorsal column sensory loss. In "complicated" hereditary spastic paraplegias there are additional features such as cataracts, cognitive

Case 3

A 15-year-old girl had been wheelchair-bound in the afternoons for five years, though until the previous year she could just manage to walk in the mornings. The progressive leg stiffness and weakness had begun aged seven, with no other symptoms. At the time, no other family members were affected. On examination, abnormalities were confined to marked rigidity and moderate weakness of both legs, with hyper-reflexia and big toes which were extended at rest and more so with testing the plantar response. Repeated MR scanning of her neuraxis had been normal over the years, as were all blood tests. A challenge with apomorphine (and later levodopa) led to a most dramatic effect; she was able to walk and indeed run down the ward corridor 15 minutes later. Within two weeks on continuing treatment her gait was normal. The diagnosis was Segawa's disease, dopa-responsive dystonia. For the next 16 years, she remained asymptomatic and without any signs on 100 mg levodopa every morning. In the meantime, both an older and a younger sister have developed symptoms, the former sufficiently severe to take levodopa. Our patient did not have foot dystonia, although this was present in her sisters when they became symptomatic. Genetic analysis has shown mutation of the GTPCH1 gene in these three siblings, and their mother, who has no symptoms or signs.

Case 4

A 54-year-old woman presented with a 30-year history of progressive difficulty with walking and urinary incontinence for 10 years. There were no symptoms in the upper limbs or cranial nerves, and no definite sensory symptoms in her lower limbs apart from pain, especially of her left thigh. She had not travelled abroad but may have received a blood transfusion during a routine hip replacement 25 years previously. She was married to a merchant seaman, who remained well. On examination she had a spastic paraparesis with hyper-reflexia and extensor plantars. Vibration sense was absent at the ankles but proprioception intact. Pin prick was impaired in the lower shin bilaterally.

Investigations 10 years previously included a normal myelogram, MRI brain and spinal cord. Repeat MRI brain and spine 10 years later was normal except for possible atrophy of the cervical cord. Initial cerebrospinal fluid (CSF) examination showed 10 white blood cells, and a repeat CSF later was normal except for unmatched (type 2) oligoclonal bands. Visual evoked response was delayed in the right eye (which was amblyopic). VDRL was negative and very long chain fatty acids were normal. She had also been found to have pernicious anaemia 10 years previously with vitamin B_{12} deficiency (73 pg/ml), a macrocytosis (MCV 103), positive Schilling test and positive gastric parietal cell antibody. Vitamin B_{12} replacement had been given with haematological improvement, but ongoing progression of her paraparesis. Serology was positive for HTLV-I and the diagnosis was of an HTLV-I associated myelopathy. We believe she had probably been infected by her husband (her blood transfusion occurred after the onset of the leg symptoms).

impairment, retinopathy and amyotrophy which is less likely to enter into the differential diagnosis of an "MRI negative" myelopathy.

Case 5

A 66-year-old man presented with a five-month history of progressive unsteadiness, sensory symptoms in his lower limbs, and a constant "tightness" around his upper abdomen. The only past medical history was of a myelodysplastic syndrome diagnosed two years previously. On examination, he had a broad based gait, hyper-reflexia in the lower limbs and extensor plantars. Vibration sense was absent below the iliac crests, and proprioception was impaired below the ankles. Chest *x* ray, MRI of his brain and cervical spine were normal. Serum ACE was slightly raised at 52 U/l (normal <45) and his ESR was 24. Full blood count showed a microcytic anaemia (Hb 8.4 and MCV 88.9) and a leucopenia (white cell count 1.6). Serum B12 was normal at 222 (range 150–750). The rest of the extensive investigations including serum calcium, syphilis serology, very long chain fatty acids, anti-endomysial antibodies and CSF were all normal. He was given B_{12} vitamin replacement, but continued to deteriorate. Subsequently further tests showed a low serum copper of 3.6 μmol/l (range 10–26) and caerulopasmin of 0.03 g/l (range 0.15–0.6). A diagnosis of copper-deficiency myelopathy was made, he was started on copper replacement and improved.

Transmission can be autosomal dominant (in most cases), autosomal recessive or X-linked, but without a family history the diagnosis is difficult to make with confidence. To date, nine genes (with 20 HSP loci) have been discovered. Approximately 50% cases are due to mutations in SPG4 or SPG3A[28] but genetic testing is not easily available in routine clinical practice in the UK (a diagnostic service is available from Sheffield: Molecular.Genetics@sch.nhs.uk).

Adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is an X-linked disorder with various phenotypes: cerebral adrenoleukodystrophy, Addison's disease, and adrenomyeloneuropathy (AMN).[29]

Adrenomyeloneuropathy is a slowly progressive spastic paraparesis that can manifest in affected males or in heterozygous female carriers (case 2). The pathogenesis is of a dying-back axonopathy, symmetrically involving the fasciculus gracilis and lateral corticospinal tracts.[30] In affected males, the symptoms emerge predominantly in the third and fourth decades.[29, 31] 20% of heterozygous females present with symptoms, at a mean age of 38.[29] Initial symptoms are frequently of gait disturbance, followed by sensory symptoms and urinary and bowel hesitancy or incontinence.[31]

Testing for plasma very long chain fatty acids (VLCFA) is reliable for screening males[29] but in heterozygous females false negatives occur in up to 20%.[29, 32] The combination of negative plasma VLCFA assay, immunocytochemical studies of the gene product (ALD protein) and known mutation analysis provide reassurance regarding carrier status in females with a positive family history.[32]

Because AMN can present with a "pure" spastic paraparesis,[33] it is important to test for VLCFAs in any "HSP family" where there is no male-to-male transmission. It may be worth looking for features of Addison's disease such as cortisol insufficiency, hyponatraemia, postural hypotension and skin pigmentation.

Friedreich's ataxia

Friedreich's ataxia is caused by an expanded GAA trinucleotide repeat in the gene encoding the "frataxin" protein. Classically it presents before age 25 years with progressive ataxia, absent lower extremity reflexes and

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extensor plantar responses.[27] However, the clinical spectrum has expanded with the use of molecular diagnosis and some patients may present with atypical or variant features, such as spastic paraparesis.[34]

Other inherited causes to consider as outside possibilities

Other inherited conditions can present as a chronic progressive spastic paraparesis, but usually associated with additional features such as cognitive impairment when brain MRI is frequently abnormal and so can be helpful in diagnosis (such as showing characteristic white matter high signal in leukodystrophies or eye-of-the-tiger sign in neurodegeneration with brain iron accumulation):

- Neurodegeneration with brain iron accumulation (NBIA) (previously called Hallervorden-Spatz disease) can present with spastic paraparesis,[35] with onset in childhood.
- Metachromatic and orthochromatic leukodystrophies can also present with spastic paraparesis (fig 4). Diagnosis is aided by clinical history, MR brain and, in metachromatic leukodystrophy, deficiency of the lysosomal enzyme arylsulfatase A in white blood cells or skin fibroblasts.
- X-linked hereditary spastic paraparesis due to mutations in L1 cell adhesion molecule (L1CAM) or proteolipid protein (PLP) can cause a complex phenotype including spastic paraparesis and cognitive impairment.
- Machado-Joseph disease (spinocerebellar ataxia type 3) is an autosomal dominant inherited disease which can present as a spastic paraplegia.[36]
- Spastic paraparesis may be a manifestation of Leber's hereditary optic neuropathy.[37] Therefore the presence of family history of blindness may be relevant.

Dopa-responsive dystonia

This is an important differential diagnosis to consider; the patients can present with limb stiffness which can all too easily be misinterpreted as spasticity, and apparently extensor plantars[38, 39] (case 3). This condition responds dramatically to levodopa and so a trial (100 mg three times daily for 6 weeks) should always be considered in patients

Differential diagnoses of myelopathy with normal spinal MRI

Demyelinating
- Multiple sclerosis
- Neuromyelitis optica (if scanned after recovery from acute attack of tranverse myelitis—that is, after resolution of spinal cord changes)

Metabolic and nutritional
- B_{12} deficiency
- Copper deficiency
- Chronic liver disease
- Chronic renal disease
- Vitamin E deficiency
- Lathyrism, Konzo

Vascular
- Spinal arteriovenous malformation /fistula
- Spinal cord infarct
- CNS vasculitis

Spirochetal diseases
- Syphilis
- Lyme

Viral myelitis, including
- Zoster, Ebstein-Barr, herpes simplex, cytomegalovirus, adenovirus, enterovirus, coxsackie B virus, herpes virus 6
- AIDS-related myelopathy
- HIV seroconversion
- HTLV-I or II

Fungal infections, including
- Cryptococcus, aspergillus

Post infectious autoimmune
- Acute transverse myelitis

Toxic myelopathies
- Radiation induced (acute and chronic myelopathy)
- Decompression sickness
- Electrical injury
- Nitrous oxide
- Intrathecal methotrexate

Arachnoiditis
- Chemical
- Radiation

Autoimmune
- Systemic lupus erythematosus
- Sjögren's syndrome
- Sarcoidosis
- Stiff person syndrome

Paraneoplastic

Neoplastic
- Intravascular B cell lymphoma

Motor neuron diseases
- Amyotrophic lateral sclerosis
- Primary lateral sclerosis

Genetic
- Male adrenomyeloneuropathy
- Manifesting carrier X-linked adrenoleukodystrophy
- Metachromatic/orthochromatic leukodystrophy
- Hereditary spastic paraplegia
- Friedriech's ataxia
- Neurodegeneration with brain iron accumulation
- Hexosaminidase deficiency

Structural lesions outwith the spinal cord
- Parasagittal meningioma (fig 3)
- Arnold-Chiari malformation
- Tethered cord

Dopa responsive dystonia

presenting with an unexplained spastic paraparesis and normal MRI. Clues to the diagnosis, although not present in all patients, include diurnal fluctuation of symptoms, young age of onset, and toe walking.

Infections

HIV

HIV infection can cause an ALS-like disorder,[40] acute transverse myelitis at seroconversion, or a slowly progressive myelopathy. This last, AIDS associated vacuolar myelopathy, occurs in up to 30% of AIDS patients, and may become more common as survival increases with antiretroviral medications.[41] It typically occurs late in the course of HIV infection with slowly progressive asymmetrical spastic paraparesis, dorsal column sensory loss and sphincter involvement. The pathophysiology is unknown, but it is thought not to be due to direct HIV invasion. MRI is usually normal, although atrophy or T2 hyperintensity may be seen.[42] CSF may show mild lymphocytic pleocytosis (<20) and a slightly raised protein.[41]

Human T-cell lymphotropic viruses type I and II

Human T-cell lymphotrophic viruses (HTLV) are endemic in Africa, Japan, South America and American Indian groups and can cause a myelopathy. The mode of transmission is similar to HIV—that is, blood transfusion, sexual contact and vertical transmission. The myelopathy tends to be slowly progressive, but rapid progression (within two years) occurs in 20% of patients[43] especially if the virus was contracted via blood transfusion or organ transplantation.[44] From the time of infection to the development of myelopathy can be over 30 years,[44] with an estimated mean incubation period for blood transfusion related cases of 3–17 years.[43, 45]

Typically there are painful ascending paraesthesiae and early involvement of the sphincters[43] (case 4). Spasticity tends to be out of proportion to the weakness. The spinal MRI is usually normal, but may show atrophy of the thoracic cord.[44] CSF is non-specific. Diagnosis is confirmed by HTLV-I or HTLV-II antibodies or antigens in the blood and/or CSF.[44]

With the increasing accessibility of worldwide travel, we are increasingly inclined to test patients with unexplained progressive spastic paraparesis for HTLV-1 infection.

Other infections

Other infections to consider, because they may be treatable, include varicella zoster (CSF PCR), Epstein-Barr virus (CSF PCR and serology), cytomegalovirus, West Nile virus, enteroviruses, herpes virus 6, coxsackie B virus, syphilis (either by direct infection or by causing an endarteritis resulting in thrombosis of the anterior spinal artery), Lyme disease (CSF serology), and hepatitis C (serum serology).

Metabolic and nutritional problems

Vitamin B_{12}

Vitamin B_{12} (hydroxycobalamin) deficiency causing subacute combined degeneration of the cord typically presents with sensory followed by motor symptoms and tends to be symmetrical. Posterior column signs (loss of proprioception and vibration) are typical. Other features of B_{12} deficiency include optic neuropathy and mental state changes. B_{12} deficiency causing neurological problems may occur without any haematological abnormalities, even sometimes it seems with normal serum B_{12} levels.[46] With a typical clinical presentation in the presence of a normal or borderline B_{12} level, helpful confirmatory investigations include raised urine methylmalonic acid and fasting serum homocysteine.[46]

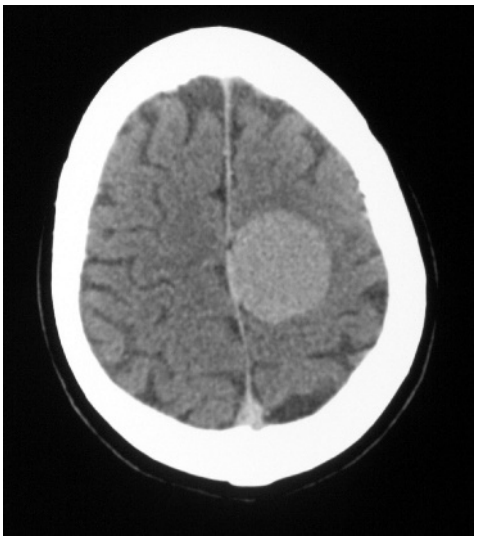

Figure 3
Parasagittal mengioma can present with spastic paraparesis. This post-contrast brain CT shows homogenous enhancement of a mass with a broad base to the falx and surrounding oedema, as evidenced by the effacement of sulci compared to the other side.

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Copper deficiency

Copper deficiency can cause a subacute combined degeneration syndrome (case 5). Copper is absorbed in the stomach and proximal duodenum. Deficiency may be caused by malabsoption after partial gastrectomy, excessive zinc intake (inhibiting copper absorption in the proximal duodenum), or excessive iron intake.[47] Plasma copper and caeruloplasmin levels are reduced. There may be associated haematological abnormalities (sideroblastic anaemia, neutropenia or pancytopenia).[48] Polyneuropathy (on examination or on nerve conduction) may also be present. Spinal MRI can often be normal.[47, 49] When abnormal, there are similar changes to B12 deficiency—that is, increased T2 signal, most commonly in the dorsal midline cervical and thoracic cord.[49] Replacement with copper results in variable degrees of improvement.[50]

Chronic liver disease

Hepatic myelopathy is a slowly progressive spastic paraparesis with minimal sphincter involvement or sensory deficit, usually beginning asymmetrically.[51] It can occur in patients with chronic liver disease even without the insertion of a porto-systemic shunt, and it can sometimes be a de novo presentation.[52] It is usually, but not always, preceded by hepatic encephalopathy.[51] It tends to be a diagnosis of exclusion in patients with chronic liver disease in the presence of a normal CSF and MRI. Hepatitis C can present with a myelopathy with normal imaging[53] and should be excluded. The pathophysiology is thought to be accumulation of systemic toxins.[51] Liver transplantation may halt the progress of the myelopathy,[51] although this may have to be done early because reports of any improvement appear to be in cases with transplantation within 10 months of onset of symptoms.[51, 54, 55]

Chronic renal disease

In some haemodialysis units, it is routine for zinc supplementation to be given either orally or parenterally. This can result in a copper deficiency myelopathy induced by zinc supplementation (see above).[56] In addition, repeated blood transfusions in relation to haemodialysis may increase the risk of HTLV-1 myelopathy.[57]

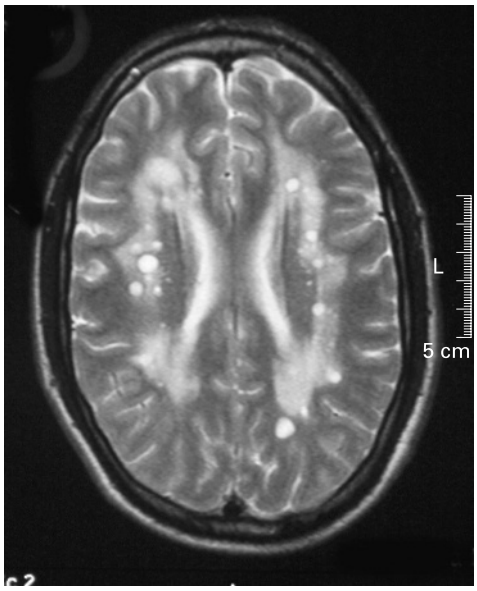

Figure 4
This patient with orthochromatic leukodystrophy presented with a spastic paraparesis. His cranial MRI axial T2 (fast spin echo) image demonstrates multiple rounded areas of hyperintensity in the white matter, consistent with a leukodystrophy.

Vascular disorders

Spinal cord infarct

Most patients have back or neck pain at the onset of an acute myelopathy, usually at the level of the lesion, many also have root pain which resolves within days.[58] Most infarcts are in the anterior spinal artery distribution (motor and spinothalamic deficit), especially in the thoracolumbar cord. Other infarct patterns include posterior spinal artery infarct (motor and posterior column deficit), central infarct (bilateral spinothalamic sensory deficit without motor deficit) or a complete transverse infarct. The latter two are associated with prolonged hypotensive events, or aortic surgery.[58] Sphincter involvement is common. Posterior and anterior spinal artery infarcts may be associated with mechanical triggering movements and acute or chronic spinal disease such as lateral disc herniation and root compression.[58]

MRI is normal in up to one third of patients[58] especially if done within hours of the event. Diffusion weighted imaging (DWI) or line scan diffusion may be more sensitive in detecting early cord ischaemia.[59, 60] The diagnosis is usually reasonably obvious with a more or less sudden onset of myelopathy in the context of a patient with a dissecting aortic aneurysm, abdominal aneurysm surgery, infective endocarditis, vasculitic syndromes or spinal trauma.

Spinal dural arteriovenous fistula/ arteriovenous malformation

Spinal dural arteriovenous fistula (AVF) is an important differential because it is treatable and a mimic of other conditions such as MS (case 1). There is a male predominance, and the mean age of diagnosis is in the sixth decade.[61, 62]

Common early symptoms are of gait and sensory disturbance and back or root pain, with sphincter involvement within a few years.[61] There may be a combination of upper and lower motor neuron signs,[61, 62] and patients have been mistakenly diagnosed as having motor neuron disease, until sphincter or sensory involvement prompts re-consideration. A spinal bruit is mentioned in textbooks but never found in practice. The course is gradually progressive over months to years, often with stepwise deterioration.[62] The pathophysiology is venous hypertension leading to hypoxic damage and subacute necrotising myelopathy.[63, 64] There may be apparent relapses and remissions, with deterioration precipitated by further increases in venous hypertension with exertion.[62] Since such venous hypertension extends far beyond the region of the AVF, the clinical "level" of the cord syndrome may be much higher (for example, high thoracic) than the AVF level.

Spinal MRI can be normal, and if abnormalities are present, they may be subtle and easily missed.[62] Those to look out for are flow voids on the cord surface and T2 hyperintensity within the conus.[65] MR angiography or supine myelography may be needed in cases with a high index of suspicion, and if normal may have to be repeated in a few months. Ultimately catheter angiography may be required.

Although there is a wide differential diagnosis for a myelopathy with normal spinal MRI, certain clinical features can guide one towards one of the broad category of causes:

- *Speed of onset*: an acute or subacute onset suggests a vascular or inflammatory cause, a more prolonged course over months or years suggests a wider differential diagnosis including neurodegenerative disorders.
- *Pattern of deterioration or improvement*: stepwise deterioration, or apparent relapses and recovery suggest a vascular or inflammatory cause.
- *Pain at onset*: in the back or in a root distribution, suggests a vascular or infective cause.
- *Early sphincter involvement*: suggests early intrinsic cord involvement (on MRI this may be subtle and therefore easily missed). For example, HTLV-1 associated myelopathy is associated with early sphincter involvement causing urinary retention that may be clinically silent.
- *Lhermitte's symptom*: suggests posterior column involvement, and is frequently seen in compressive or inflammatory diseases such as multiple sclerosis, but also in subacute combined degeneration.
- *Age of onset, patient demographics*: a middle-aged man with vascular risk factors raises the possibility of vascular pathology, while young age of onset suggests either inflammatory or inherited causes.
- *Family history*: it is important to take a detailed family history, especially enquiring about any early deaths or other "neurological" diagnoses in family members, pointing towards genetic causes.
- *Travel history, sexually transmitted diseases, blood transfusion*: these may guide investigation for a possible infective cause.
- *Rash, dry eyes or dry mouth, recurrent miscarriages, venous thrombosis, mucosal ulceration*: these symptoms may be subtle in the history but important to enquire about suggesting autoimmune or inflammatory causes—for example, Sjögren's syndrome, lupus or the antiphospholipid syndrome, sarcoidosis.
- *Diurnal fluctuation*: raises the possibility of dopa responsive dystonia.
- *Red flags for possible neoplasia*: significant smoking history, weight loss or cachexia raise the possibility of a paraneoplastic syndrome.

Primary CNS vasculitis

A subacute myelopathy with normal spinal MRI can occur. A case was described showing a persistently inflammatory CSF and histology demonstrating occlusion by fibrinoid material of leptomeningeal vessels of the cord.[66]

Toxic and physical causes

These may be evident from the history:

- Radiation (acute or delayed necrosis) and lightning injury can cause a myelopathy.
- Previous myelography with Myodil may cause an arachnoiditis and resultant myelopathy.
- Nitrous oxide can cause a myelopathy appearing like B_{12} deficiency.[67]
- Dietary toxins ("lathyrism" from beans, or "konzo" from cassava) have also been linked to myelopathy.[68]

Paraneoplastic syndromes

A paraneoplastic myelopathy may occur as an acute necrotising myelopathy, stiff person syndrome, or as a motor neuron disease-like syndrome.[69] Most patients have positive anti-Hu antibody in the serum or CSF, usually due to small cell lung cancer, but also associated with other types of lung cancers, prostate, gastrointestinal, breast, bladder, pancreas,

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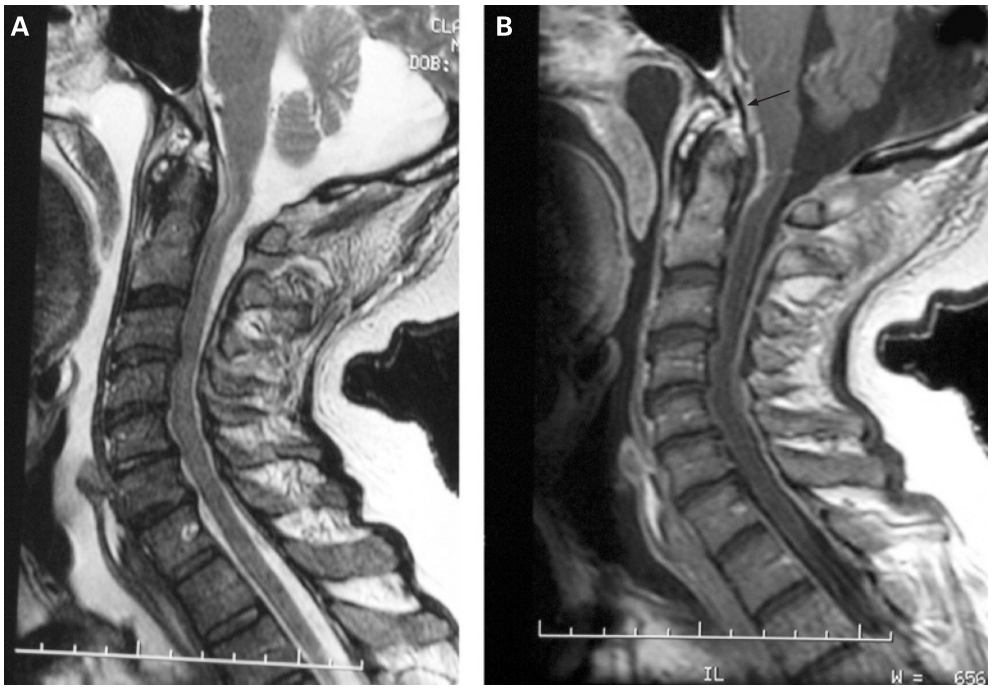

Figure 5
MRI of a patient with a spinal epidural abscess presenting with myelopathy. These abnormalities were initially missed when imaged without contrast and interpreted by general radiologists. (A) Sagittal T2 (fast spin echo) image demonstrating increased signal anterior to the cervical medullary junction at C1 and C2. (B) Sagittal T1 image with contrast, showing enhancement of the abscess, extending through the foramen magnum up to the clivus (arrow).

ovarian cancers and lymphoma.[70, 71] The paraneoplastic presentation tends to precede the diagnosis of cancer by several months.[70] CSF may be normal or show pleocytosis and oligoclonal bands. Usually spinal MRI is normal although T2 hyperintensities may be seen[72] [^{18}F]Fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging improves detection of cancer in patients with paraneoplastic neurological syndromes with well-defined paraneoplastic antibodies, when conventional imaging fails to identify a tumour or when lesions are difficult to biopsy; the sensitivity may be over 80%.[73]

Intravascular lymphoma

Intravascular lymphoma is a rare systemic illness characterised by the proliferation of neoplastic lymphotcytes within the lumens of arteries, veins and capillaries.[74] The initial manifestations are often neurological and rarely occur in the presence of haematological or bone marrow involvement by lymphoma, or with a systemic or intracranial mass.[74] Frequent laboratory abnormalities include anaemia, raised ESR and lactate dehydrogenase, and a raised CSF protein.[74, 75] CSF lymphocytosis is mild (<10) and cytology is usually negative.[74]

Skin involvement may precede the neurological symptoms, and biopsy of a skin lesion may reveal the diagnosis.[74] The characteristic lesions are raised, hyperpigmented or haemorrhagic, often tender and are most prominent on the abdomen and thighs. The adrenal glands may also be involved and can be bilaterally enlarged on CT abdomen, leading to a diagnosis on biopsy.[74]

Spinal cord involvement is common[74] and although MRI of the cord may show T2 hyperintensity, imaging is normal in more than half the cases.[76] The cord pathology is thought to be caused by multiple vascular occlusions by lymphomatous cells.[74, 76]

Patients with intravascular lymphoma commonly have a dramatic but transient response to corticosteroids.[74, 75] The prognosis is poor and frequently the diagnosis is only made at postmortem.[74]

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Diagnostic pathway: myelopathy but normal spinal MRI

- History: any additional clues? Detailed family and travel history/onset/ sensory involvement or not/ age of onset.
- Is the spinal MRI definitely normal?
  - has the whole cord been imaged and looked at by a neuroradiologist (fig 5)?
  - was MRI just of the cord or also the brain? Is the brain normal?
  - any flow voids on the surface of the thoracic and lumbar cord, or high signal within the conus suggesting an AVM or fistula?
- Helpful or important first line investigations:
  - exclude the treatable with appropriate tests
    - serum B_{12}
    - infections: syphilis, Lyme, HIV
    - paraneoplastic autoantibodies
    - ANA, dsDNA, anti-Ro/La, ACE, ESR
    - liver function
  - MRI brain –? multiple sclerosis? leukodystrophy
  - visual evoked responses
  - CSF for cells, protein, oligoclonal bands,
  - chest *x* ray –? neoplasm? sarcoid
- To consider
  - serum copper (especially if previous gastric surgery or sideroblastic anaemia)
  - serology: HIV, HTLV-I or II, Lyme
  - spinal MR angiography if clinically possible vascular malformation/ fistula
  - very long chain fatty acids
  - EMG and nerve conduction studies
  - trial of levodopa (at least 100 mg three times daily for 6 weeks)
  - hereditary spastic paraplegia genetics

PRACTICE POINTS

- Myelopathy with normal spinal MRI is not uncommon.
- A number of causes are treatable and should therefore be carefully considered.
- Review the history: look out for helpful clinical features.
- Review the radiology: was the correct imaging done—when the patient was symptomatic—and were subtle abnormalities missed?
- MRI brain may be helpful in widening the differential diagnosis.

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