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CASE REPORT

Teaching case: A man with a progressive gait impairment and visual compromise

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Abstract
Primary progressive multiple sclerosis can present with a wide variety of symptoms. We report a case of a 52-year-old man presenting with visual symptoms and gait impairment in whom a diagnosis of a primary progressive multiple sclerosis was established. Symptomatic treatment with dalfampridine was started but did not result in a considerable improvement. Gait disorders in multiple sclerosis are common and can have a considerable effect over the patient's quality of life. Dalfampridine is the first drug approved for the symptomatic treatment of gait in MS, although only a 40% of patients show an objective response to this medication. Primary progressive multiple sclerosis represents a therapeutic challenge. Currently, there are no disease modifying treatments approved but there are several medications undergoing assessment for this indication. Further research in the underlying pathophysiology of PPMS will help us develope more successful disease-modifying treatments. Meanwhile, a symptomatic approach should be offered in order to improve the patient's quality of life.

1. Case presentation

A 52 year-old right-handed man presented to our Neurology clinic for evaluation of a 15-year history of a progressive paraparesis associated with left sided hypoesthesia, fatigue and erectile dysfunction. The patient also reported blurred vision while exercising and episodes of constipation and urinary retention without incontinence. Past medical history

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was significant for diabetes mellitus and left cataract surgery.

On examination, his blood pressure was 120/80 mmHg, his pulse rate was 70 beats per minute and his respiratory rate was 18 breaths per minute. The neurological examination revealed a left hyporeactive dyscoria consistent with past history of cataract surgery. Ishihara test detected a loss in color vision, scoring 9/16 and 15/16 in the right and left eye, respectively. His visual acuity was 20/30 on the right eye and 20/30 on the left.

Motor examination revealed bilateral lower limb weakness with a strength of 3/5 in the left lower limb and 4/5 in the right. Hyperreflexia was present in his lower limbs. The plantar response was extensor on the left and flexor on the right. Vibration sense was diminished in the lower limbs and joint position sense was reduced at the toes. The gait was spastic and unstable (Video 1).

A complete blood cell count, chemistry panel, and levels of serum electrolytes were within normal limits.

How should this patient be further evaluated?

1. Lumbar puncture (CSF analysis including oligoclonal bands).
2. Contrasted brain and spine magnetic resonance imaging.
3. Serum vitamin B12, metilmalonic acid and copper levels.
4. Anti-Aquaporin 4 antibodies.
5. All of the above*.

What is the most likely diagnosis?

1. Neuromyelitis Optica.
2. Vitamin B12 deficiency.
3. Copper deficiency.
4. Multiple sclerosis*.
5. Sarcoidosis.

2. Case diagnosis

This 52-year-old man presenting with a progressive spastic paraparesis, left sided hypoesthesia, visual and genitourinary symptoms had a contrasted brain and spinal cord magnetic resonance imaging (MRI), which revealed areas of increased T2 signal corresponding to multifocal subcortical white matter lesions. Small lesions compromised the frontal lobes, pons, medulla and right superior cerebellar peduncle (Figure 1). The spinal cord MRI revealed the presence of multiple small hyperintense lesions compromising the cervical and thoracic cord on the T2 weighted images (Figure 2). None of the observed lesions enhanced after the application of contrast.

Erythrocyte sedimentation rate, C reactive protein, thyroid function tests, liver enzymes, blood glucose, vitamin B12 and folic acid levels were all normal. CSF-VDRL and ELISA for HIV were both negative. Serum antibodies, including Anti-aquaporin-4 antibody (anti-NMO), antinuclear antibody (ANA), and Rheumatoid factor (RF) were also negative. Visual evoked potentials revealed a diffuse bilateral and symmetric compromise of the retino-cortical pathway, associated with axonal loss and demyelination.

A lumbar puncture was performed with an opening pressure of 12 cm of water. Cerebrospinal fluid (CSF) analysis showed a protein concentration of 38.13 mg/dL [15–45 mg/dL], glucose of 77 mg/dL, 0 white blood cells per mm^3 and 2 erythrocytes per mm^3. Gram stain, India ink and CSF cultures were all negative while oligoclonal bands were positive.

A diagnosis of primary progressive multiple sclerosis (PPMS) was done.

Which of the following medications could be used for the treatment of walking impairment in this patient?

1. Glatiramer acetate.
2. Baclofen.
3. Dalfampridine*.
4. Tizanidine.
5. Amantadine.

Symptomatic treatment with oral Dalfampridine and Baclofen were given without major improvement of spasticity or gait (Video 2). A program of physical therapy was also started.

3. Case discussion

Primary progressive multiple sclerosis (PPMS) accounts for 10-15% of patients with multiple sclerosis (MS). This clinical pattern is characterized by an insidious onset, where disability gradually progresses with no clear history of relapse or remission (Katz Sand and Lublin, 2013). The course of MS has been recently revised (Lublin et al., 2014) and now the disease activity and progression are incorporated as modifiers of basic MS phenotypes. Thus, a patient with PPMS who presents an acute attack would be considered to have active PPMS instead of a progressive relapsing phenotype of the disease. On the contrary a patient without acute attacks or MRI evidence of activity (i.e. gadolinium-enhancing lesions or new or unequivocally enlarging T2 lesions) would be considered to have a non-active course of the disease.

PPMS typically presents as a progressive myelopathy (Katz Sand and Lublin, 2013). Difficulties with gait, balance, spasticity, weakness, and bladder or bowel compromise are common, while sensory symptoms occur less frequently than in relapsing-remitting MS (RRMS). There is no clear gender predominance and patients with PPMS also tend to be older than those with RRMS, with a mean age of 40 years (Stys et al., 2012).

The most common clinical phenotype of PPMS is spastic paraparesis, which is seen in 83% of cases (Antel et al., 2012); other symptoms include cerebellar dysfunction (8%), hemiplegia (6%), brainstem syndromes (1%), visual loss (1%), and cognitive decline (1%) (Antel et al., 2012). These phenotypes are not mutually exclusive (Antel et al., 2012), as seen in our patient where a spinal cord syndrome is present in association with visual compromise. Visual loss is more frequently seen in association to RRMS. There is a reported prevalence of visual symptoms in PPMS varying from 1% (Antel et al., 2012) to 4% (Rice et al., 2013). Progressive visual failure is thought to be the result of optic neuropathy (Miller and Leary, 2007) and therefore the prevalence of visual symptoms could be higher. A recent

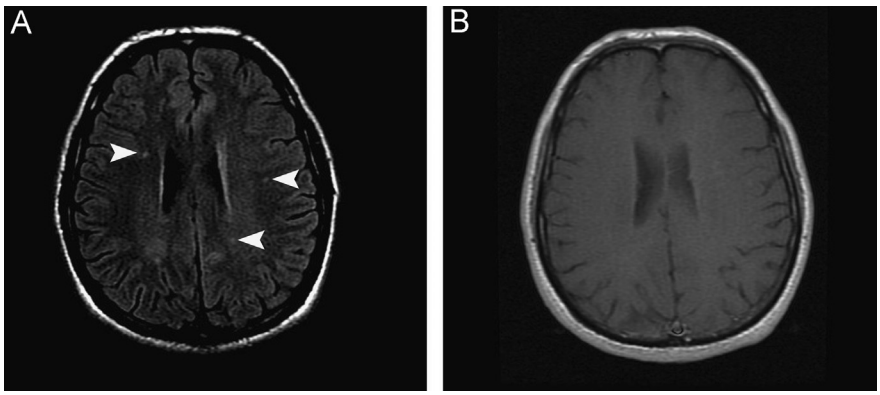

Figure 1 Brain MRI. (A) Axial fluid attenuation inversion recovery (FLAIR) sequence shows multiple demyelinating white matter lesions (arrowheads). None of the observed lesions enhance on the contrasted axial T1 – weighted magnetic resonance image (B).

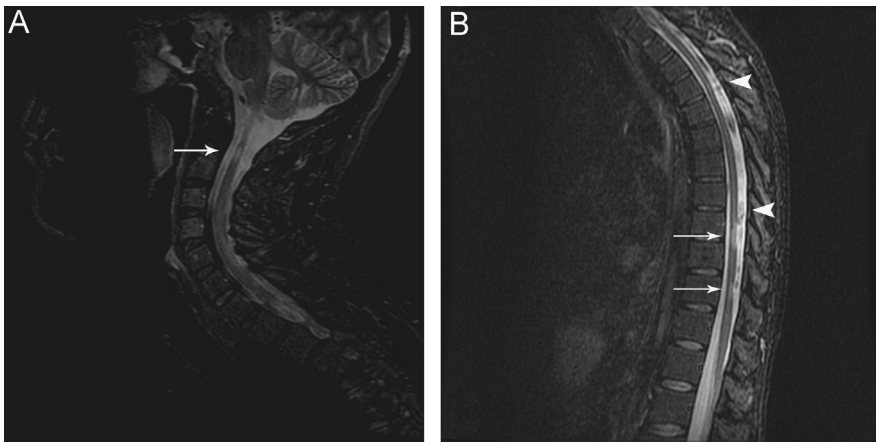

Figure 2 Spinal Cord MRI. (A) Sagittal Short T1 inversion recovery (STIR) of the cervical spinal cord shows a small hyperintense lesion at the C2 level (arrow). (B) Sagittal STIR of the thoracic spine shows two hyperintense lesions, the first at the T9–T10 level and the second at the T11 level (arrows). Spinal cord atrophy is also present (arrowheads).

study found a prevalence of 34.6% of persistent visual complaints in a cohort of MS patients. Of these, 30.5% had PPMS (Jasse et al., 2013).

MRI lesions in PPMS tend to be fewer in number and less likely to enhance with gadolinium compared to RRMS, although they are similar in appearance (Katz Sand and Lublin, 2013). Spinal cord abnormalities are frequently described and lesions are more commonly seen in the cervical spine. The lesions tend to span less than one vertebral segment and their location is eccentric, dorsal, or lateral (Klawiter, 2013). Brain and spinal cord atrophy have been observed in PPMS with spinal cord atrophy being more pronounced in PPMS compared to RRMS (Antel et al., 2012). In addition, gray matter atrophy has been observed as an early feature of PPMS, and may be predictive of progression of the disease (Antel et al., 2012).

The diagnosis of PPMS can be challenging, ruling out other spinal cord diseases that may have similar clinical presentations is important. (Sheremata and Tornes, 2013; Antel et al., 2012; Rice et al., 2013) MRI of the spinal cord can give more information because lesions at this location are more specific and frequent (Rice et al., 2013). CSF, as in RRMS, is positive for oligoclonal bands in 80–90% of patients with PPMS (Rice et al., 2013).

The treatment of the PPMS and other progressive forms of MS is still an unmet medical need. Currently, medications such as fingolimod, natalizumab, ocrelizumab, rituximab, siponimod and masitinib are undergoing assessment in Phase III trials for the progressive forms of MS (Curtin and Hartung, 2014). Neuroprotective drugs that prevent demyelination or improve remyelination would be promising for PPMS, but these drugs are in the early development stage and their efficacy has not been demonstrated yet (Curtin and Hartung, 2014). For the moment, a symptomatic approach is available and recommended to improve the patient's quality of life (Rice et al., 2013).

Gait disturbance is a common concern in patients with MS, particularly in PPMS (Bethoux, 2013). Larocca et al. reported a prevalence of gait disorders in MS of 41%. Walking performance can be used to monitor the progression of MS and the disability of the patient (Bethoux, 2013; Sheremata and Tornes, 2013). In addition, the majority of MS patients with gait disturbances reported that this functional limitation had a negative impact on their daily activities, social life, emotional health, and socioeconomic status (Bethoux, 2013).

Treatment modalities for gait disorders in MS include exercise and rehabilitation, symptomatic medications, assistive devices, and surgical interventions. A combination of treatment modalities is usually recommended, tailored to the patient's individual needs and goals (Bethoux, 2013; Sheremata and Tornes, 2013).

Dalfampridine, an extended-release formulation of 4-aminopyridine, is the first approved medication for the improvement of walking speed in adult patients with MS (Bethoux, 2013; Preiningerova et al., 2013). 4-Aminopyridine is a potassium channel blocker, which has shown to enhance conduction along demyelinated axons (in vitro). An improvement in gait can be seen in approximately 40% of MS patients (Bethoux, 2013; Preiningerova et al., 2013), with an average increase in walking speed of 25.2% (Bethoux, 2013; Preiningerova et al., 2013;). The recommended dose is 10 mg twice daily (Bethoux, 2013).

The medication is primarily excreted in unchanged form via the kidneys (Bethoux, 2013). The most frequent adverse events reported include urinary tract infections, insomnia, dizziness, headache, nausea, and paresthesia. Contraindications to the use of dalfampridine include a personal history of seizure, as well as moderate to severe renal impairment (creatinine clearance of 50 mL/min or lower) (Bethoux, 2013).

PPMS represents a diagnostic and therapeutic challenge. Unfortunately, the available immunomodulatory and immunosuppressive approaches have failed to produce a meaningful impact on the disability progression of the disease (Kantarci, 2013). Treatment should always be individualized and a symptomatic approach should not be underestimated in these patients for improvement on quality of life. A better understanding of the underlying pathophysiology of PPMS will help us delevope more successful disease-modifying treatments.

Author's contribution

All the listed authors have contributed equally to the development of the manuscript.

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Disclosure

Dr. Toro serves as an associate editor for NEJM Journal Watch Neurology and is member of the editorial board of Multiple Sclerosis and Related Disorders. Dr. Burbano, Dr. Zamora and Dr. Jones report no disclosures.

Ethical considerations

This is a teaching case. Patient's informed consent for video publication was given.

Conflict of interest

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