

Syringomyelia and Complex Regional Pain Syndrome as Complications of Multiple Sclerosis

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Objective: To describe a patient from Southeast Asia with the optic-spinal phenotype of multiple sclerosis who developed syringomyelia and resultant complex regional pain syndrome (formerly named reflex sympathetic dystrophy).

Design: Case report.

Setting: Department of neurology at a tertiary care hospital in the Republic of Singapore.

Patient: A 53-year-old Chinese woman with a history of optic neuritis developed an episode of left hemiparesis leading to a diagnosis of multiple sclerosis. Serial neuroimaging studies revealed an active demyelinating plaque

in the cervical area that later progressed into a syrinx. Over a period of 1 year she also developed signs of sympathetic dysfunction including Horner syndrome of the left eye and complex regional pain syndrome in the left hand.

Conclusions: A case of the optic-spinal phenotype of multiple sclerosis that is commonly observed in Southeast Asia is described. This characteristically tissue-destructive form of multiple sclerosis resulted in syringomyelia complicated by a complex regional pain syndrome. Possible pathogenic mechanisms for these associations are discussed.

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MULTIPLE SCLEROSIS (MS) is a chronic demyelinating disorder with a wide range of clinical manifestations that reflects multifocal areas of central nervous system myelin destruction. Multiple sclerosis is an uncommon disease in Southeast Asia; its typical presentation is as a disorder of optic-spinal dysfunction. Invariably, the spinal form of this illness is manifest as transverse myelitis.¹ We present an unusual case of a patient with MS who developed syringomyelia and resultant complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy.

REPORT OF A CASE

A 56-year-old Chinese woman with an unremarkable medical history presented at age 43 years with right optic neuritis. Later, at age 53 years, she had a second bout of optic neuritis affecting her left eye. Both episodes were treated with pulsed high-dose intravenous methylprednisolone. During her second bout of optic neuritis, she also complained of vague pain in her left hand and forearm that was characterized by

cramps and spasms. At that time, results of her neurological examination were remarkable only for left optic neuritis and left arm strength of 4/5. Notably, her reflexes were symmetric. In June 1995, a magnetic resonance imaging (MRI) scan of the brain performed as part of her evaluation showed no evidence of demyelination. Because of persistent complaints of pain and spasms in her left arm, MRI scans of the brain and cervical spine were repeated 2 months later. Biparietal lesions that were hyperintense on T₂-weighted images and that did not enhance with gadolinium were present; these hyperintensities were suggestive of non-acute demyelinating lesions. The cervical spine showed no evidence of demyelination. A lumbar puncture was unremarkable (white blood cell count, 0.002 × 10⁹/L; glucose, 3.5 mmol/L [63 mg/dL], total protein, 0.3 g/L) and cerebrospinal fluid oligoclonal bands were not detected. In the setting of 2 bouts of optic neuritis, an episode of left hemiparesis, and her neuroimaging findings, the patient was diagnosed as having MS.

Fourteen months later (October 1996), the patient had a recurrent episode of pain in her left hand and forearm

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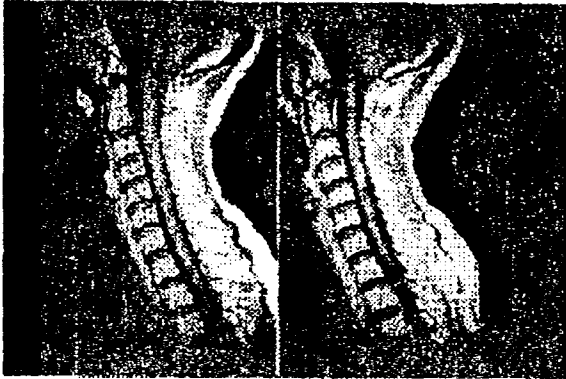


Figure 1. Magnetic resonance imaging scan of the cervical spine before (left) and after (right) gadolinium enhancement done in October 1996, remarkable for an active demyelinating plaque spanning from C2 to C4.

and weakness in her left arm and leg. The left hand and forearm pain was again characterized by vague dysesthesias. She also complained of a constant burning pain in the same region, which did not conform to a pattern of dermatomal or peripheral nerve injury. A neurological examination at this time was notable for left optic atrophy, left afferent pupillary defect, and left hemiparesis with diminished left arm (2/5) and left leg (4/5) strength. In addition, left thenar wasting was observed. Her reflexes were present symmetrically with bilateral flexor plantar responses. Although she complained of sensory disturbances in the left arm, no sensory loss or suspended sensory level was apparent on extensive testing. Treatment with high-dose intravenous methylprednisolone resulted in mild improvement in her symptoms. Repeated MRI scans of the brain and cervical spine (October 1996) showed several areas of hyperintensity on T₂-weighted images in the deep cerebral white matter that did not enhance with contrast on T₁-weighted images. A long segment of increased signal on T₂-weighted images was present in the cervical cord extending from the level of C2 to C5 with slight expansion. This cervical cord lesion enhanced after gadolinium administration at its middle and inferior portions. These neuroimaging findings suggested the presence of an active, demyelinating plaque spanning from C2 to C4 (**Figure 1**). Nerve conduction and electromyographic studies to further assess the left thenar eminence atrophy showed no evidence of neuropathy. Evoked studies were remarkable for prolonged bilateral visual evoked potentials, affecting the left side more than the right. Somatosensory evoked potentials were notable for a conduction abnormality between the left lumbar and left thoracic cord. Brainstem auditory evoked potentials were abnormal on the right side, suggestive of an auditory conduction abnormality in the brainstem.

Over the next year, the patient complained of pain in her left hand and forearm, which she described as a constant burning. She also observed that the nails and skin of her left hand appeared shinier and less wrinkled than the right hand. At the time of her neurological examination in October 1997, she had developed Horner syndrome in the left eye with ptosis, miosis, and enoph-

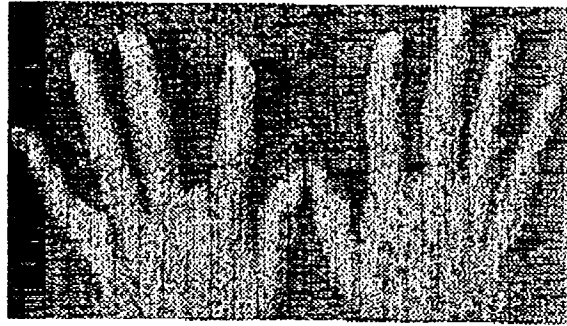


Figure 2. Patient's hands with the left hand appearing edematous.

thalmos. Her left afferent pupillary defect persisted. Her left hemiparesis had improved and her strength remained at 4/5. The thenar eminence and interossei muscles of her left hand were atrophied. Her reflexes continued to remain brisk and symmetric. The skin of her left hand appeared red, shiny, and unwrinkled. Compared with the right hand, her left hand was intermittently edematous, indurated, hyperhidrotic, mottled, and cool to touch (**Figure 2**). These findings suggested a CRPS involving the left hand. Laboratory data including complete blood cell count; electrolytes; glucose, calcium, and magnesium levels; liver function tests; and collagen vascular markers were all unremarkable. A repeated MRI scan of the cervical spine showed that on T₁-weighted images, after gadolinium administration, no enhancement was noted in or around the hypodense area from C3 to C7 to suggest the presence of an active demyelinating plaque. On T₂-weighted images, hyperintensity was present from C2 to C7. No cord swelling was observed. These neuro-radiologic findings were consistent with a syrinx formation (**Figure 3**). The signs and symptoms of sympathetic dysfunction, particularly her CRPS, have been recalcitrant to conventional treatment options of tricyclic antidepressants, anticonvulsants, and physiotherapy. Further treatment considerations include a trial of gabapentin.

COMMENT

Our patient's clinical course is characterized solely by optic nerve and cervical cord involvement. She does not fulfill strict criteria for Devic neuromyelitis optica, which include a severe transverse myelitis and an acute unilateral or bilateral optic neuropathy developing within days or weeks of each other.² However, she clearly manifests an optic-spinal phenotype of MS. During the course of her illness, the patient initially developed a demyelinating plaque in the cervical area that over a year progressed to a syrinx. The clinical manifestations of our patient's cervical syrinx included segmental weakness and atrophy of the left hand and an ipsilateral Horner syndrome. Although the pathogenesis of this syrinx is unclear, we can postulate on its cause. We do know that the gross pathological manifestation of MS is characterized by areas of focal demyelination commonly referred to as MS plaques.² These plaques are frequently found in areas adjacent to cerebrospinal fluid pathways.³ The spectrum of pathology observed in MS in-

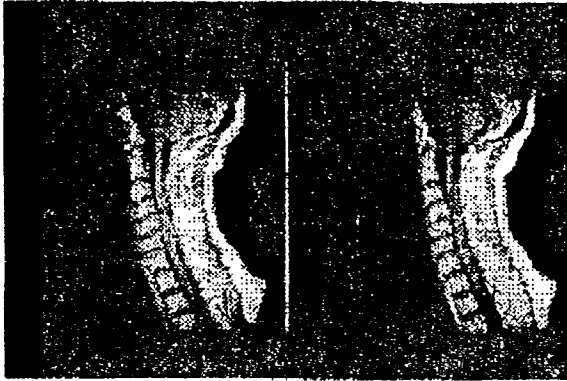


Figure 3. Magnetic resonance imaging scan of the cervical spine before (left) and after (right) gadolinium enhancement done in October 1997, showing a syrinx from C2 to C7.

cludes primary demyelination with little oligodendrocyte damage, extensive oligodendrocyte loss in the course of demyelination, and primary oligodendrocyte damage involving not only myelin and oligodendrocytes but also axons and astrocytes.¹ In our patient's case, she is likely to have had an active MS plaque in the cervical region demonstrated on MRI scan by gadolinium enhancement. Later, the plaque may have undergone degenerative change with resultant cervical syrinx formation involving areas of the plaque site and spinal cord rostral to this plaque. The necrotic process may have begun centrally, extending rostrally and caudally from the poles of the lesion.⁵ Alternatively, a syrinxlike lesion may have developed following atrophy of the swollen spinal cord that had undergone demyelination changes.^{6,7} The spinal cord lesions typically associated with Devic neuromyelitis optica are characterized by demyelination, inflammation, and necrosis.^{8,9} Our patient with the optic-spinal phenotype of MS is likely to have undergone tissue destruction and necrosis resulting in a cervical cord syrinx that has persisted for 3 years.

Since the coexistence of syrinx formation in MS is uncommon, the neurological prognosis of such coexistence remains to be elucidated. A spectrum of spinal cord lesions has been reported in association with MS. In a series by Kato et al⁷ of 37 patients with clinically diagnosed MS with spinal cord lesions, cervical cord lesions occurred more frequently than other spinal cord lesions. At the thoracic level, higher thoracic lesions occurred more often than lower level lesions. Characteristically, these lesions were swollen and enhanced after gadolinium administration in patients with a disease duration of less than 3 years, and atrophic change was observed in patients with a disease duration of greater than 7 years. Syrinxlike lesions were found in 4 patients.⁷ To begin to determine the prognosis of the coexistence of syringes in MS we reviewed previous case reports.^{5,10-12} Remarkably, a majority of the cases reported appeared in the Japanese literature. Since the optic-spinal form of MS is more common in Asian countries and the acute demyelinating spinal cord lesions may have subsequent development of myelomalacia or frank cavitary degeneration, syringes that are the result of spinal disease may occur more frequently in this population. Of the 7 case reports, all but 1 were women.

The age range of the patients was from 26 to 40 years. Four cases involved syringes in the cervical cord and 3 were in the thoracic cord. Unlike the presentation in our case, not all these cases of spinal cord lesions and subsequent syrinx formation were accompanied or preceded by visual symptoms. These cases suggest that the prognosis of MS with syrinx formation is variable, even following repeated episodes of myelopathy.

Recently, Vernant et al¹⁵ described a syndrome of recurrent optic neuromyelitis with endocrinopathies in 8 Antillean women. All 8 women had a demyelinating disease involving only the spinal cord and optic nerves. In 7 cases, the neurologic examination revealed a band-like, dissociated sensory loss and in 2 of these cases there was anterior horn cell involvement or amyotrophy. Cavitation of the cervical cord was noted in 3 and in 1 of the 3, Horner syndrome was observed. All 8 patients had evidence of endocrinopathies resulting in amenorrhea, galactorrhea, hypothyroidism, hyperphagia, or diabetes insipidus.¹⁵ Our patient is similar to these described patients in that throughout the course of her illness, clinical manifestations have been limited to the optic nerves and spinal cord and neuroimaging studies showed a cavitation of the spinal cord. However, our patient is postmenopausal and did not demonstrate any evidence of hypothalamic or hypophysial dysfunction.

Coincident to the development of a syrinx, our patient also developed signs of sympathetic dysfunction including Horner syndrome in the left eye and left-hand CRPS type 1. In our patient, frequent and periodic neuroimaging studies exclude any other cause for the Horner syndrome apart from the development of a syrinx. Although the descending sympathetic fibers are largely or totally uncrossed, their exact course is not clear. Presumably, fibers from the lateral hypothalamic area run dorsal to the red nucleus, then descend to the lateral tegmentum of the midbrain, pons, and medulla to the intermediolateral cell column of the spinal cord.¹⁶ Our hypothesis is that the syrinx involved the fibers to the left intermediolateral cells disrupting sympathetic flow and resulting in Horner syndrome of the left eye and left-hand CRPS. Complex regional pain syndrome is a pain syndrome that usually develops after an initiating noxious event. Typically, evidence of edema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, and allodynia or hyperalgesia are observed. The site is usually the distal aspect of an affected extremity.¹⁷ Of the wide variety of precipitating factors that can cause injury to peripheral or central neural tissue, syringomyelia is a central nervous system cause of CRPS.¹⁸⁻²⁰

Autonomic dysfunction likely contributes to the pathophysiology of CRPS. When a peripheral nerve is injured, vasodilatory neuropeptides, including substance P, are released from stimulated cutaneous nerves with cell bodies in the dorsal root ganglia. Excessive vasodilation and increased vascular permeability result in the affected limb becoming edematous and causing the cutaneous nerves to be further activated. Stimulated cutaneous neurons normally have an inhibitory influence on sympathetic activity at the level of entry of the dorsal root ganglia in the cord. In CRPS, this inhibition is lost, resulting in a hyperactive somatosympathetic reflex.^{21,22} The cause of our patient's

CRPS is also likely due to the cervical syrinx formation. She had no preceding peripheral nerve injury and the distribution of the pain is not in a dermatomal or peripheral nerve pattern. We postulate that due to the syrinx formation, the intermediolateral cell column is stimulated rather than inhibited by branches of second-order sensory neurons. The hyperresponsive sympathetic vasoconstrictor motor fibers severely restrict blood flow to the affected area, resulting in cyanosis, mottling, and hypothermia. This somatosympathetic reflex is likely responsible for our patient's intermittently edematous, mottled, and cold hand.

This case report highlights the peculiar optic-spinal phenotype of MS that is observed in Southeast Asia. The association of syrinx in the setting of MS is rare. However, since degeneration and necrosis of demyelinating lesions characterize the optic-spinal phenotype of MS, an increased risk of syrinx formation is likely to exist. Newer techniques including magnetic resonance cysternography may be useful in confirming the diagnosis of syringes.

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