

Effective management of intractable neuropathic pain using an intrathecal morphine pump in a patient with acute transverse myelitis

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Abstract: Transverse myelitis is a rare inflammatory myelopathy characterized by loss of motor and sensory function below the affected level of the spinal cord, and causes neurogenic bowel and bladder. Occasionally, it also causes neuropathic pain with spasticity. Traditional therapies for neuropathic pain are multiple, including multimodal analgesic regimens, antiepileptic or antidepressant medications, opioids, sympathetic blocks, and spinal cord stimulation. Persistent neuropathic pain can cause emotional distress by affecting sleep, work, recreation, and emotional well-being. Here we report the case of a patient suffering from intractable neuropathic pain following acute transverse myelitis that was not relieved by combinations of nonsteroidal anti-inflammatory, antiepileptic, antidepressant, and opioid medications, or by acupuncture. Implantation of an intrathecal morphine pump controlled the pain successfully without side effects, and enabled the patient to embark on intensive rehabilitation. The patient's muscle strength has improved significantly and the patient may soon be able to use a walker with minimal assistance.

Keywords: intrathecal morphine pump, neuropathic pain, rehabilitation, transverse myelitis

Introduction

Acute transverse myelitis is a rare inflammatory myelopathy, manifesting as inflammatory markers in cerebrospinal fluid, with either pleocytosis or an increased immunoglobulin G index. The etiology of inflammatory transverse myelitis is unknown, but it has been observed in association with multiple sclerosis, neuromyelitis optica, acute disseminated encephalomyelitis, and connective tissue disease.^{1,2} Spinal lesions caused by multiple sclerosis are usually less than two vertebral segments in length, with asymmetric symptoms and signs and previous episodes of neurologic dysfunction. Relapsing demyelination affecting predominantly the optic nerves and spinal cord with more than three vertebral segments affected is suspicious for neuromyelitis optica. Other presentations may raise suspicion for acute transverse myelitis, and viral infection is known to be a potential etiology, with acute transverse myelitis being a differential diagnosis in patients with infections such as herpes zoster virus or herpes simplex virus, and in those with autoimmune diseases such as systemic lupus erythematosus or Sjögren's syndrome. Acute transverse myelitis involves the entire cross section of the cord and extends longitudinally and rostrocaudally along three vertebral bodies, causing complete loss of motor and sensory function below the affected level of the spinal cord, along with a neurogenic bowel, a neurogenic bladder, and sexual dysfunction. Laffey et al have suggested that neuropathic pain is relatively rare in transverse myelitis,³ but chronic neuropathic pain below the level of the lesion can be a late complication.³

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Neuropathic pain arises from damage or pathologic changes in the peripheral or central nervous system. Neuropathic pain may have effects above or below the level of the spinal lesion as a result of loss of innervation. Neuropathic pain is accompanied by spasticity and/or rigidity and is mediated by activation of nociceptive afferents from muscles or by excessive vasoconstriction resulting in tissue hypoxia and activation of chemosensitive nociceptors.⁴ This pain may manifest as a burning, pricking, or an aching sensation. If the pain is not well managed, the patient may become bedridden or immobilized because of joint contractures, muscle atrophy, pressure sores, pneumonia, cardiovascular problems, and decreased functional status. The treatment options for neuropathic pain include antiepileptic or antidepressant medications, sympathetic block, spinal cord stimulation, and intrathecal baclofen or opioids.⁵

Here we report the case of a patient who suffered from intractable neuropathic pain after acute transverse myelitis that was not relieved by nonsteroidal anti-inflammatory drugs, antiepileptics, antidepressants, and opioids, or use of acupuncture. Implantation of an intrathecal morphine pump controlled her pain without side effects, and paved the way for aggressive rehabilitation.

Case report

A 68-year-old woman was admitted with gradual onset of bilateral weakness of the upper and lower limbs. She had been experiencing involuntary trunk movement, dizziness, and ataxia for six weeks, but was still able to perform her daily activities independently. Her symptoms progressed to include frequent headaches, bradykinesia, and postural tremor over her right hand and right arm, and tingling pain localizing to her right posterior auricular area. No skin rash, papulae, bullae, or ulcers were noted on her face, trunk, or limbs. The tremor in her hands progressed, such that she could no longer grasp objects, put on clothes, comb her hair, or stand on one leg. A visit to the neurologic outpatient clinic confirmed that muscle power in all four limbs was normal. However, her trunk and limbs were numb, and she reported pruritus over her entire trunk.

One week before admission, she underwent magnetic resonance imaging of the brain, which revealed multiple small hyperintense spots in her basal ganglia, indicating lacuna infarcts, demyelinating lesions, and arteriosclerosis with tortuosity of the arteries. However, her symptoms and signs were not compatible with these findings, so continued observation was suggested. Four days later, she was noted to have urinary frequency, difficulty voiding, and a residual

urine volume of 856 mL, all of which were indicative of a neurogenic bladder, so a Foley tube was inserted. No diplopia, slurred speech, loss of consciousness, dyspnea, or obvious weight loss was observed throughout the course of her admission. Her limb weakness became severe, and physical and neurologic examination revealed that the muscle power in her right upper and lower limbs had decreased from 5 to 4 and 5 to 3, respectively, and in the left lower limb had decreased from 5 to 4. Further, diminished sensation of pinprick and light touch was noted to be below T4.

On admission, laboratory data showed mildly increased white cells and neutrophils. Electrolytes, renal and hepatic function, vitamin B12, and folate were normal. A lumbar puncture was performed, and showed lymphocyte-predominant pleocytosis and elevation of microproteins and glucose, but her white cell count was normal. No specific laboratory findings indicating tuberculosis, or bacterial or fungal infection were noted, and polymerase chain reaction results were negative for cytomegalovirus, herpes simplex virus, and Epstein-Barr virus. No malignant cells were apparent, and no positive findings of antibodies such as SS-A, SS-B, RA, C3, C4, or antinuclear antibody were noted. T2 weighted axial images on spinal magnetic resonance imaging revealed a patchy diffuse area of hyperintensity extending from C3 to T5, so the patient was diagnosed with transverse myelitis (Figure 1). Given that neuromyelitis optica and optic neuritis should also be suspected even if the visual field is normal, we arranged for visual evoked potentials, which were negative. Her right upper limb and bilateral lower limb weakness and incontinence of urine and stool was unresponsive to treatment.

One month after admission, the patient complained of a cold sensation extending from her bilateral legs to her chest,

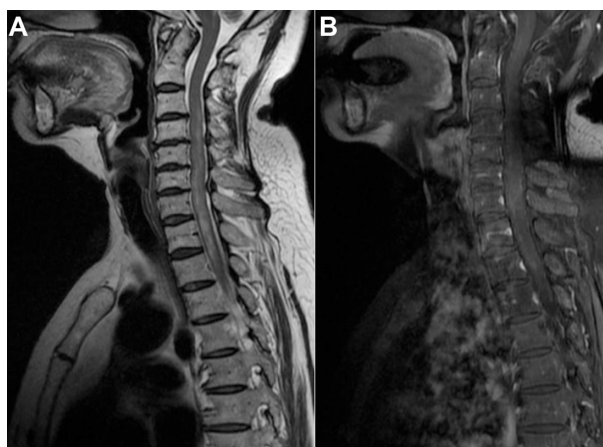


Figure 1 (A) Sagittal T2-weighted axial images showing a patchy diffuse area of hyperintensity from C3 to T5. (B) Sagittal T1-weighted image obtained after intravenous administration of gadolinium showing minimal enhancement.

with abnormal tremor and night sweats. She was treated with clonazepam 0.5 mg twice daily and imipramine 10 mg at bedtime to relieve her discomfort. However, two days later, she suffered from intermittent coldness, numbness, tightness, and a cramping sensation ascending from her leg to her chest, severe tingling pain with duration of 10–15 minutes, and a period of 5–10 minutes. These symptoms lasted throughout the day, with a visual analog pain score >9. Physical examination showed no limitation in range of motion, joint tenderness, hotness, or swelling, so the clinical impression was that of neuropathic pain. Rest did not relieve her pain, and she experienced difficulty sleeping. She was then treated with gabapentin 300 mg at bedtime, clonazepam 0.5 mg twice daily, and tramadol 100 mg three times daily. The patient reported that her pain was intractable, so the tramadol was gradually increased. Half an ampoule of pethidine was also given as needed. On the advice of an anesthesiologist skilled in pain management, 2 mL of patient-controlled analgesia (dihydroxyacetone phosphate and morphine 160 mg infused at a rate 0.2 mL per hour, with a loading dose of 2 mL, a dose ceiling of 10 mL over four hours, and a lockout interval of eight minutes) was arranged for two weeks. Given the potential problem of lethargy as a side effect of morphine, her pain medication was augmented by increasing the dose of her fentanyl patch to 24 µg per hour, along with administration of clonazepam 0.5 mg three times daily, gabapentin 300 mg three times daily, and a combination of acetaminophen 325 mg + tramadol 37.5 mg four times daily. We also added nonsteroidal anti-inflammatories, an antidepressant (sertraline), anticonvulsants (tizanidine, baclofen), and acupuncture, to no avail. Her visual analog pain score remained at 7–8. The dose of gabapentin was gradually escalated from 100 mg to 300 mg three times daily, and titrated by 100–300 mg every 3–7 days to the usually effective daily dose range of 1800–3600 mg.⁶ Her pain became unbearably severe during rehabilitation, to the extent that she cried throughout the day. Morphine 10 mg was given via injection as needed, but caused general weakness, dizziness, dry mouth, and hallucinations, which prevented any further rehabilitation.

Six weeks after starting the patient on medical treatment for her neuropathic pain, we resorted to an intrathecal morphine pump to maintain the lowest dose of morphine able to keep the therapeutic effects and side effects in balance. A catheter was inserted into the dural sac via the L4/5 space, with the morphine dosage maintained at 0.2 mL (0.5 mg) per hour. Her pain was relieved immediately during a preimplantation trial, so an intrathecal pump (Figure 2) was implanted and set to deliver a morphine dosage of 1.3 mL (3.25 mg) per



Figure 2 Intrathecal morphine pump implanted subcutaneously with tube insertion into the dural sac through the L3–4 space.

hour during the day and 1.0 mL (2.5 mg) per hour at night. Her visual analog score decreased to 2–3, and the muscle cramps ascending from the leg to the chest became mild, lasting for about 10–15 seconds and appearing at intervals of about 30–60 minutes. Previous medication was stopped, with only tizanidine 4 mg three times daily being administered after implantation of the pump. Her pain, numbness and tingling, and cold, burning, and cramping sensations were relieved significantly and she was able to return to her rehabilitation program.

After rehabilitation, muscle power in her lower limb improved markedly from 2 to 4. Her neurologic deficit also improved at this point, such that her training program of intermittent catheterization four times daily was discontinued in favor of spontaneous voiding. Functional status, such as ability to sit, improved from poor to fair. Her functional status improved from complete dependence to being able to perform activities of daily living with moderate assistance. Her functional independence score increased from 48 prior to implantation to 74 at the time of discharge, and further to 87 seven months after admission. Her Barthel index increased from 10 to 25 after four months of an aggressive rehabilitation program.

Discussion

This patient had suffered from the common cold one week before the onset of her presenting symptoms. Although findings in cerebrospinal fluid were negative, viral

infection was suspected. The patient had no personal or family history of autoimmune disease, and we ruled out the differential diagnoses of neuromyelitis optica and optic neuritis using visual evoked potentials and other tests. Idiopathic transverse myelitis was the final diagnosis after all test findings were found to be negative.

The prognosis of acute transverse myelitis is poor. Fewer than half of cases gain significant recovery, and many patients remain completely paralyzed below the level of the lesion after the attack.⁷ The initial strategy is to combat the inflammatory process using high-dose intravenous corticosteroids, which generally leads to rapid clinical improvement.⁸ However, long-term follow-up data on patients with acute transverse myelitis show that about one third of cases have severe disability and the remainder recover with little or no sequelae or a moderate degree of permanent disability.^{9,10} Aggressive rehabilitation can improve functional status in terms of ability to perform activities of daily living, and decrease complications such as cardiovascular and respiratory problems, muscle atrophy, and pressure ulcers, given that the nervous system is dynamic and continually changing. Moreover, maintaining optimal activity is essential for neural regeneration and restoration.¹¹

If severe pain and spasticity are noted during the course of treatment and not treated appropriately, the prognosis in these patients is poor. Persistent neuropathic pain can cause emotional distress by impacting sleep, work, recreation, and emotional well-being.¹² Treatment of neuropathic pain is difficult, and involves multiple treatments and/or multimodal analgesic regimens. Effective treatments available for managing neuropathic pain include antiepileptic agents, tricyclic antidepressants, opioids, topical lidocaine, serotonin-norepinephrine reuptake inhibitors (eg, duloxetine), and analgesic agents.^{13,14} Other treatments have also been investigated. Vagela et al¹⁵ reported the case of a patient with transverse myelitis who complained of a constant deep dull pain despite multiple medications, which was relieved after acupuncture.

The Canadian Pain Society recommends tricyclic antidepressants, such as imipramine, as first-line treatment for neuropathic pain.¹⁶ However, anticholinergic side effects, including dry mouth, dry eye, urinary retention, excess sedation, orthostatic hypotension, constipation, and blurring of vision, may be problematic. Tricyclic antidepressants are contraindicated in patients with a history of cardiovascular disease because of reports of tachycardia, myocardial infarction, and sudden cardiac death.¹⁷ Further, the risk of falling increases in the elderly because of cognitive problems.¹⁷

Recently, serotonin-norepinephrine reuptake inhibitors (eg, duloxetine) have been suggested as second-line treatment options, but often cause nausea and may be hepatotoxic.¹⁸ Antiepileptic drugs, such as gabapentin, are a first-line treatment option for painful polyneuropathy, postherpetic neuralgia, partial onset seizures, and central neuropathic pain.¹⁸ However, sedation, somnolence, dizziness, increased risk of falls, and cognitive impairment are common side effects in the elderly,¹⁷ and may affect the patient's ability to participate successfully in a rehabilitation program. Our patient showed no signs of improvement when treated with any combination of the above therapies.

In our patient, the opioids prescribed relieved the symptoms, but did not control the pain well during the course. Not only did the other forms of opioids not maintain the concentration in the blood, but also we did not know the exact extent to which the opioid medication was absorbed systemically. When we gave this patient additional oral and transdermal analgesic medication, the side effects of nausea, transient confusion, hallucinations, and constipation became severe enough to impede rehabilitation and basic activities of daily living. In contrast, the morphine pump is implanted intrathecally, with less risk of dependence, tolerance, and side effects than systemic administration of morphine.¹⁹

Studies of continuous intrathecal morphine infusion for pain control are currently under way. Duse et al²⁰ have reported the impact of intrathecal morphine infusion on perception and psychosocial functioning in patients with chronic nonmalignant pain not responsive to multimodal analgesic medicines. These investigators found a statistically significant improvement in pain control at each assessment point compared with baseline ($P < 0.005$).²⁰ The programmable intrathecal pump delivers medication continuously and directly into the cerebrospinal fluid around the spinal cord.^{21,22} The drug dose can be adjusted and the pump can be refilled using minimally invasive techniques. Morphine administered via this type of delivery system is more effective at lower doses, and has fewer systemic side effects.

The morphine dose administered via an intrathecal pump should be selected according to the patient's clinical status and response. Although a preimplant trial of morphine 0.2 mL (0.5 mg) per hour as recommended by Shaladi et al²³ relieved our patient's pain immediately, she experienced rebound pain in the following days before intrathecal implantation of the pain pump, at which point we were able to adjust the dose until it was optimal. Further, after implantation of the intrathecal pump, the patient's other analgesic medication could be stopped, with the exception of tizanidine, allowing the dose

of morphine administered via the pump to be increased as necessary to relieve her neuropathic pain. Her morphine dosage were set as 1.3 mL (3.25 mg) per hour during the day and 1.0 mL (2.5 mg) per hour at night because symptoms were more severe in the daytime when attending rehabilitation and alleviated at night after resting.

Four months after implantation of the intrathecal pump, we were able to reduce the rate of morphine infusion in this patient. With her pain managed safely and effectively, the patient was able to return to her rehabilitation program. Her muscle strength improved four months after implantation, and it is hoped that she will be able to mobilize using a walker device with minimal assistance.

Side effects arising from intrathecal morphine pump implantation have been reported to include nausea, vomiting, constipation, urinary retention, pruritus, altered mental status, and respiratory depression.²⁴ Tip inflammatory mass, and infection were also reported. Fortunately, no side effects were noted in our patient.

Conclusion

The patient reported here had neuropathic pain caused by transverse myelitis that was managed successfully using an intrathecal morphine pump. A formal therapeutic strategy for neuropathic pain has not as yet been developed, and poor response to combinations of analgesic medication carries a risk of severe complications, including immobilization, and adverse effects involving the musculoskeletal, respiratory, and cardiovascular systems. In view of the fact that combination analgesic therapy has side effects no matter how carefully it is administered, the intrathecal morphine pump has appeal as a safer and more effective option for management of severe neuropathic pain.

Disclosure

The authors report no conflicts of interest in this work.

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