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A Case of Myelopathy Where Combined Administration of Pregabalin and Tramadol Hydrochloride/Acetaminophen Combination Tablets was Effective

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Combined administration of low-dose pregabalin and tramadol hydrochloride/acetaminophen combination tablets significantly reduced refractory myelopathic pain（bilateral leg pain）caused by spinal cord tumor/syringomyelia in a woman in her 80s. Through mutual interaction, combined administration of pregabalin and tramadol hydrochloride/acetaminophen combination tablets, which have different mechanisms of action, might have had an early, beneficial analgesic effect on her myelopathic pain caused by the spinal cord tumor and syringomyelia.

Key words: myelopathy, pain, pregabalin, tramadol/acetaminophen combination tablets

INTRODUCTION

Myelopathic pain due to spinal cord tumor/syringomyelia is often challenging to treat. In the present case, we report an experience where combined use of low-dose pregabalin and tramadol hydrochloride/acetaminophen combination tablets（TRAM/APAP）yielded early, significant mitigation of myelopathic pain（bilateral leg pain）. Informed consent regarding the presentation of this paper was obtained from the family of the patient.

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CASE

A woman in her 80s with a height of 146 cm and weight of 50 kg.

Comorbidities: Hypertension

She underwent a laminoplasty（C3-Th1）for astrocytoma of the cervical cord 10 years prior. Six years prior, she developed a spinal cord tumor in C3-Th1 and syringomyelia in C3-Th1 and Th2-Th6, and experienced right arm paresis, paraplegia, and bilateral leg pain. The bilateral leg pain was reduced with loxoprofen sodium（120 mg/day; one dose in the morning and one dose in the evening）and diclofenac sodium suppositories（25 mg/dose; as needed, 1 dose/day）. However, 3 days earlier, her pain worsened, and the diclofenac sodium suppositories（25 mg/dose）used in the morning and evening failed to relieve her pain. Thus, she visited our hospital's department of neurosurgery.

She was admitted on the same day. Even with added administration of celecoxib（200 mg/day; one dose in the morning and one dose in the evening）, TRAM/APAP（3 tablets/day, in the morning, at noon, and in the evening; tramadol equivalent: 112.5 mg/day and acetaminophen equivalent: 975 mg/day）, her pain symptoms increased, so she was referred to our department the day after admission. On examination, she had pain at rest and on movement in both hip joints and both knee joint areas（pain score of Numerical Rating Scale: NRS 10/10）. Sense of touch was missing at the T4 level and below. She had no allodynia. The patellar and ankle jerk reflexes were enhanced in the left leg but could not

be evaluated in the right leg because of contracture. She had bladder dysfunction, and urinary catheterization was performed. Blood test results showed no renal or hepatic dysfunction. Spine magnetic resonance images and findings are shown in Figure. On hospital day 2, routine prescription of celecoxib (200 mg/day; one dose in the morning and one dose in the evening) was discontinued. We decided on a strategy to address the intensification of pain with as-needed use of diclofenac sodium suppositories (25 mg/dose). On the same day, administration of pregabalin (25 mg/day; once before bed) was started, in addition to TRAM/APAP (once in the morning, noon, and evening, respectively). The following day, her pain at rest and on movement decreased to NRS 5/10, but this was not satisfactory. The pregabalin dosage was increased to 50 mg/day (once before bed) on the same day. On hospital day 9, her pain at rest and on movement decreased to NRS 3/10, and from hospital day 14 onward, her pain at rest and on movement were NRS 0/10. In the meantime, she had no lightheadedness, drowsiness, constipation, or other such symptoms. The as-needed use of the diclofenac sodium suppositories was given only once, on hospital day 3. Over the course of about 3 months thereafter, she has been living at home with favorable analgesia, her pain at rest and on movement both being NRS 0/10.

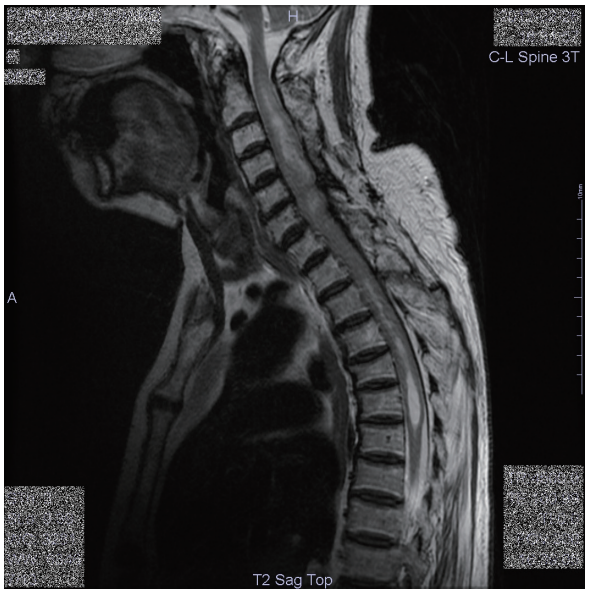

Fig. T2-weighted magnetic resonance image
・Spinal cord tumor and syringomyelia findings from C2 to Th1
・Syringomyelia findings from Th2 to Th6

DISCUSSION

Pain caused by a spinal cord tumor is one form of myelopathic pain. Other causes of myelopathic pain include trauma or spinal cord ischemia. Pain may develop immediately after spinal cord involvement or may take several months to appear [1]. Both forms of pain are frequently refractory, often posing problems for rehabilitation, significantly negatively affecting patients' activities of daily living, and producing mental disorders such as depression [2]. Myelopathy pain is broadly classified into three types, relative to the site of spinal cord involvement, as follows: upper, involvement site, and lower levels [3]. Pain at a higher level than the site of spinal cord involvement is compressive mononeuropathy, and complex regional pain syndrome (CRPS) often develops. Pain at the level of the spinal cord involvement site is caused by damage to the nerve root or spinal cord itself, and results in severe numbness and sustained or inducible electric shock-like (lancinating) pain. Pain at a lower level than the spinal cord involvement site is deafferentation pain and produces spontaneous lancinating pain, burning sensation, and the like [3]. The present case is believed to have presented with neuropathic pain below the damaged site, based on physical symptoms and imaging findings. To treat neuropathic pain with medication, the Guidelines on Pharmacological Treatment of Neuropathic Pain of the Japan Society of Pain Clinicians propose pregabalin, gabapentin, or the like as drugs of first choice, amitriptyline or the like as drugs of second choice, and serotonin-norepinephrine reuptake inhibitors (SNRIs), tramadol, opioids, or the like as drugs of third choice [4]. However, myelopathic pain is difficult to control with any drug, whether as a monotherapy or combination therapy [1]. In the present case, combined use of low-dose pregabalin and TRAM/APAP was effective in treating pain, the mechanism of which will be discussed herein. Pregabalin is a calcium channel α2δ1 receptor agonist that has been reported to increase the expression level of the receptor agonist subunits in the dorsal horn of

the spinal cord in myelopathic rats [5]. It has the potential to be effective for treating pain. If pregabalin alone is administered for myelopathic pain, the dosage will need to range from 25 to 600 mg/day. However, one report indicated that pain alleviation was still inadequate, with many side effects such as malaise [6]. Thus, the effects of pregabalin monotherapy are limited. Acetaminophen has an analgesic effect on myelopathic pain, but the cannabinoid receptor is expressed without decrease in expression level at the spinal cord level in myelopathic rats[7]. Thus, the analgesic effect is thought to be from *N*-acylphenolamine, which is a degradation product of acetaminophen. Tramadol has both a μ-receptor agonist and SNRI action, but the expression level of the μ-opioid receptor in the dorsal horn of the spinal cord is reduced when myelopathy is involved [8]. In such cases, the analgesic effect of tramadol as a μ-opioid receptor agonist may be weak. SNRIs, however, exhibit an analgesic effect by activating a descending pain inhibition system. Oral administration of milnacipran to myelopathic rats reportedly prolonged the latency of the escape response to thermal and tactile stimulations [9]. A clinical report stated that administering 250 mg/day tramadol alleviated myelopathic pain more than placebo [10].

The combination of APAP and gabapentin which has the same mechanism of analgesic effect of pregabalin, was synergistic ameliorating neuropathic spinal cord injury pain in rats study [7].

These are thought to be the possible reason why the combined use of pregabalin and TRAM/APAP was effective in the present case. At the extent of our literature search, we were unable to find any past basic studies or case reports where a combination of pregabalin and TRAM/APAP was administered for myelopathic pain. However, we found a report that suggested that combining these would be effective for relieving pain [11]. In comparison with previous reports where pregabalin and tramadol were each separately administered, the present case yielded better analgesic effects with lower-dosage combined administration, without side effects such as lightheadedness, drowsiness, or constipation. One possible reason is that administration of pregabalin and TRAM/APAP, which have different mechanisms of action, yielded an earlier and more beneficial analgesic effect against pain caused by the spinal cord tumor/syringomyelia in the present case. However, although the present case yielded a favorable analgesic effect with combined use of low-dose pregabalin and tramadol, myelopathic pain is refractory, and different cases are expected to require different analgesic doses. Therefore, they will need to be investigated on an individual case basis.

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