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Case Report

Careful Consideration Should Be Preceded Before Intrathecal Baclofen Pump Implantation in a Patient with Amyotrophic Lateral Sclerosis: A Case Report

Su Ji Lee, M.D.[1], Tae Yong Kim, M.D.[1], Won Seok Chang, M.D., Ph.D.[2] and Sung-Rae Cho, M.D., Ph.D.[1,3]

[1]Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Neurosurgery and Brain Research Institute, Yonsei University College of Medicine, Seoul, Korea
[3]Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea

근위축성 측삭 경화증 환자에서 경막내 바클로펜 펌프 삽입술 전 고려 사항: 증례보고

이수지[1] · 김태용[1] · 장원석[2] · 조성래[1,3]

[1]연세대학교 의과대학 재활의학과 및 재활의학연구소, [2]연세대학교 의과대학 신경외과 및 뇌 연구소,
[3]연세대학교 의과대학 BK21 PLUS 사업 의과학과

Abstract

Amyotrophic Lateral Sclerosis (ALS) is characterized by progressive degeneration of both upper and lower motor neurons. Predominant upper motor neuron involvement causes clinical manifestations of spasticity. We report a case of ALS presenting progressive spastic paraplegia treated with intrathecal baclofen (ITB) test trials before ITB pump implantation. Electrodiagnostic studies confirmed the diagnosis of ALS. After administration of 50 mcg and 25 mcg of ITB separately, severe spasticity of both legs was relieved effectively within 2 hours after a ITB test trial. However, weakness of both lower extremities appeared which eventually led to functional decline in the item "turning in bed and adjusting bed clothes" of the ALS Functional Rating Scale-Revised. Desaturation event also occurred four hours after 50 mcg ITB bolus injection. Therefore, careful consideration is necessary for in a patient with ALS presenting spastic paraplegia before ITB pump implantation. In particular, ITB test trial should be preceded when considering ITB pump implantation.

Key Words

Amyotrophic lateral sclerosis, Intrathecal injection, Baclofen

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Corresponding author : Sung-Rae Cho, M.D., Ph.D.
Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel : 82 2 2228 3715
Fax : 82 2 363 2795
e-mail : srcho918@yuhs.ac

Introduction

Amyotrophic lateral sclerosis (ALS), first described by Jean-Martin Charcot in 1874, is one of the most well-known adult-onset neurodegenerative diseases.[1] The disease is characterized by progressive degeneration of both upper motor neurons (UMN) and lower motor neurons (LMN). The clinical manifestations often start with focal muscle

weakness, but spread systemically including respiratory muscles in a rapid progress. According to population-based studies, the median survival of patients with ALS is 2 to 3 years from symptom onset, with death typically resulting from respiratory failure.[2]

As ALS is a disease in which both UMN and LMN are involved, the UMN and LMN signs may appear in a mixed form. UMN signs including spasticity, hyperreflexia and pathologic reflexes can be seen in patients with ALS. They might also present LMN signs such as muscle weakness, flaccidity, atrophy, fasciculation and hyporeflexia.

Spasticity, common clinical manifestation of predominant UMN degeneration is found in 40% of all ALS patients.[3] Treatment of spasticity is necessary in order to preserve muscle function and to prevent associated complications such as joint contractures, muscle cramps and pain. Spasticity is often treated with classical oral anti-spastic drugs including baclofen, tizanidine and benzodiazepines. However, those medications can not only cause systemic complications such as oversedation, elevation of liver enzymes, and aggravation of muscle weakness but also can be insufficient to treat intractable spasticity in many cases.

Intrathecal baclofen (ITB) treatment is a rising option for spasticity. By implantation of ITB pump, baclofen can be directly delivered into cerebrospinal fluid with small amount and high efficacy. Recent literatures have shown that ITB is a superb treatment option to patients with spastic paraplegia, cerebral palsy and spinal cord injury.[4,5] However, there are few literatures about ITB applied to ALS patients.[6]

Here, we report a case of ALS presenting progressive spastic paraplegia who was treated with ITB test trials before ITB pump implantation. A 71-year-old female, previously misdiagnosed as spastic paraplegia, lately diagnosed as ALS in our rehabilitation center. We conducted ITB bolus injection for symptomatic relief of severe spasticity of both lower limbs. The effect appeared within 2 hours after ITB test trial and the patient presented improvement in spasticity. However, weakness of both lower limbs appeared which eventually led to functional decline.

Case Report

A 71-year old female visited our rehabilitation center to find a cause of progressive weakness and spasticity of both lower limbs on October 2020. She did not have any familial history of neurological disease. In 2017, she experienced lower back pain and had received manual therapy in local clinics. In January 2018, she presented radiating pain of right leg and received several therapies such as traction and epidural block. Then pain declined; however, from April 2018, her lower extremities, especially ankle gradually weakened.

In May 2018, she visited department of neurosurgery. The magnetic resonance imaging of C-spine and L-spine showed mild cervical and lumbar disc degeneration without significant disc herniation and central canal stenosis or neural foraminal stenosis. In October 2018, she was referred to department of neurology. Somatosensory evoked potential studies were conducted, and tibial sensory evoked potential study showed prolonged latencies of cortical evoked potentials on right side. In December 2018, F18 FP-CIT PET CT revealed no remarkable findings. On the impression of spastic paraplegia, several gene studies including direct sequencing of ABCD1, AQP4 Ab, SMN and SPAST gene were conducted but the results showed negative for both genes. To treat spastic paraplegia, oral baclofen and tizanidine were prescribed to her. She was subsequently admitted to several other hospitals for comprehensive rehabilitation therapy. From July 2020, pain as well as spasticity of legs got worse which made her visit our rehabilitation hospital in October 2020.

On the day of admission, neurologic examination was conducted. On the manual muscle test (MMT), muscle groups of upper extremities showed fair grades on both sides. All muscles checked by MMT in lower extremities showed poor grades for both hip flexors, extensors, adductors, left knee flexors and extensors, and trace grades

Table 1. MAS Grade of Lower Extremities on the Day of First Admission (Pre-ITB Test Trial), Post-50 mcg ITB Injection and Post-25 mcg ITB Injection

	Pre-ITB test trial	50 mcg injection	25 mcg injection
Hip flexor	1/1	0/0	0/0
Hip extensor	1+/2	1/1	1/0
Hip adductor	0/0	0/0	0/0
Hip abductor	3/3	1/1	2/1
Knee flexor	1+/1+	0/0	1/1
Knee extensor	1/1	0/0	1/1
Ankle dorsiflexor	0/0	0/0	0/0
Ankle plantar-flexor	1+/1+	1+/1	1+/1

MAS: Modified Ashworth Scale, ITB: Intrathecal Baclofen

for both hip abductors, ankle dorsiflexors, plantar-flexors, left knee flexors and extensors. Muscle tone was increased in both lower limbs causing difficulty in proper positioning and hygiene despite full range of motion. Besides, both upper limbs were normotonic. Hyperactive patellar tendon reflex and ankle jerk reflex were noted on both sides. Ankle clonus and positive Babinski signs were presented at both sides. She was able to turn on both right and left sides and sit alone in chair sitting position without physical assistance for several minutes. However, she could not sit in long sitting position and also could not stand alone.

For the diagnostic confirmation associated with spastic paraplegia, next-generation sequencing (NGS) was performed. The NGS confirmed no pathological gene mutation. We conducted electrodiagnostic studies again. The sensory and motor nerve conduction studies, F-waves and H-reflex studies did not show any abnormal findings. The electromyographic study showed reduced interference patterns on full contraction on all extremities. It also showed abnormal spontaneous activities in several muscles of all extremities and bilateral paraspinal muscles of C5-T1, T10 and L3-S1 levels, which meets the Awaji-Shima consensus diagnostic criteria of ALS.[7] The patient also presented dysarthria and dysphagia. Tongue fasciculation and atrophy were presented. Combining all of the evaluations and findings together, the patient was diagnostically confirmed with ALS.

Because severe spasticity of both lower limbs was intractable after the treatment of oral anti-spastic medication, we conducted ITB test trial despite the diagnostic confirmation of ALS. We checked the modified Ashworth Scale (MAS) before and after 50 mcg and 25 mcg intrathecal baclofen injection. Before the trial, both hip flexors were grade 1, right hip extensors were grade 1+, left hip extensors were grade 2, both hip adductors were grade 3, and both knee flexors and ankle plantar-flexors were grade 1+. Two hours after intrathecal injection of 50 mcg baclofen, both hip flexors were grade 0, both hip extensors were grade 1, both hip adductors were grade 1, both knee flexors were grade 0, right plantar-flexors were grade 1+ and left plantar-flexors were grade 1 (Table 1). Spasticity was reduced effectively; however, MMT showed all muscles of both lower extremities became trace grade (Table 2). Before the ITB test trial, the patient was able to turn on both right and left sides and sit alone for several minutes. However, after the trial, she could not turn on and sit alone. Although the patient did not present dyspnea, oxygen saturation decreased from baseline 96% to 92% four hours after the trial. After 6 hours, the patient complained of nausea and vomiting. Oxygen saturation recovered without any

Table 2. MMT Grade of Lower Extremities on the Day of First Admission (Pre-ITB Test Trial), Post-50 mcg ITB Injection and Post-25 mcg ITB Injection

	Pre-ITB test trial	50 mcg injection	25 mcg injection
Hip flexor	P / P	T / T	T / P
Hip extensor	P / P	T / T	T / P
Hip adductor	P / P	T / T	T / P
Hip abductor	T / T	T / T	T / T
Knee flexor	T / P	T / T	T / P
Knee extensor	T / P	T / T	T / P
Ankle dorsiflexor	T / T	T / T	T / T
Ankle plantar-flexor	T / T	T / T	T / T

MMT: Manual Muscle Test, ITB: Intrathecal Baclofen, P: Poor Grade, T: Trace Grade

supplementary oxygen treatment.

Two days after the initial trial, we decided to conduct an ITB test trial with lower dose of baclofen. 25 mcg baclofen was injected intrathecally with the same technique. Two hours after 25 mcg injection, both hip flexors were grade 0, right hip extensors were grade 1, left hip extensors were grade 0, right hip adductors were grade 2, left hip adductors were grade 1, both knee flexors were grade 1, right plantar-flexors were grade 1+ and left plantar-flexors were grade 1 (Table 1). Although the baclofen dose was reduced by half, weakness of lower limbs appeared for all muscles of right leg showed trace grade (Table 2). At this time, the patient did not complain about nausea and vomiting, but still complained of general weakness and could not sit alone. In the ALS Functional Rating Scale-Revised (ALSFRS-R), the item "turning in bed and adjusting bed clothes" score decreased from 1 to 0 after the trial.

The initial pulmonary function at the diagnosis of ALS was not evaluated, since the patient did not present respiratory symptom. Riluzole was not applied to this patient regarding the recent controversy on the efficacy of riluzole if it is not treated in the early stage.[8,9] Later, in February 2021, dysphagia got worse and aspiration symptom appeared frequently. The patient also presented dyspnea while sleeping. Pulmonary function test showed that vital capacity was 810 ml, which was 25.6 % of predicted value, and peak cough flow was uncheckable. Considering the natural course of ALS, noninvasive ventilator was applied at first.

Consequently, the patient got tracheostomy and continuous mechanical ventilator has been applied. The home ventilator was applied in assist-control ventilation mode and set with tidal volume 380 mL, respiratory rate 12 per minute, inspiration-expiration ratio 1:2, and positive end expiratory pressure 4. Applying mechanical ventilator and tracheostomy, overnight maximal carbon dioxide partial pressure improved from 42.2 mmHg to 36.7 mmHg and overnight mean carbon dioxide partial pressure improved from 40.8 mmHg to 29.1 mmHg. Spasticity was managed with dose escalation of oral baclofen and tizanidine. The baclofen dose was increased from 20 mg to 45 mg and the tizanidine dose was increased from 2 mg to 4 mg until February 2021.

Discussion

Baclofen, first synthesized in the 1960s as a specific agonist of gamma-aminobutyric acid-B receptors, was traditionally used as oral medication. Until the mid-1980s, baclofen was used only orally.[10] In 1984, intrathecal baclofen

pump implantation was first established by noble and pioneering work of Penn and Kroin to alleviate spasticity of spinal cord injury.[10,11]

ITB application to spastic paraplegia was first introduced in 1989 by Oches G et al.[12] Currently, eleven studies assessed ITB treatment for 58 patients with hereditary spastic paraplegia were identified.[13] In practical, quite many patients with spastic paraplegia visit our clinic for ITB treatment. ITB has few side effects compared to systemic anti-spastic medication, and it can be very effective even with a small dose. In addition, ITB is suitable as an alternative method for patients who are intractable with oral anti-spastic medication.

ITB application to ALS is very rare in literature. In 2007, McClelland and his colleagues conducted ITB pump implantation to eight ALS patients. They found ITB as an effective and safe treatment modality for relief of spasticity-related pain.[14] However, changes in muscle power and functional level cannot be informed from the study.

In our case, a patient previously misdiagnosed as spastic paraplegia visited our clinic for ITB pump implantation. Progressive weakness and prominent UMN signs are common features of both ALS and spastic paraplegia, which cause difficulties in differential diagnosis. The El Escorial criteria is important in differential diagnosis suggesting that definite ALS requires evidence of LMN degeneration and progressive spread of symptoms or signs within at least three body regions among bulbar, cervical, thoracic or lumbar region. In this case, the physical examination and electrodiagnostic study met the criteria and we concluded that the patient was ALS.

Above all, decline in muscle power and functional level in the ALSFRS-R were clearly seen. MMT changed from poor to trace grade in several muscle groups two hours after 50 mcg ITB bolus injection (Table 2). The number of muscle groups with change of MMT from poor to trace grade after 25 mcg ITB injection was less compared to 50 mcg ITB injection (Table 2). In fact, hypotonia has been addressed as dose-dependent complications of ITB. A multicenter study of 51 children with ITB therapy found hypotonia in 7.8%.[15] Adjuvant side effects such as nausea, vomiting and general weakness were also problematic. Additionally, our case implies a possible negative effect of ITB to respiratory muscle dysfunction, as oxygen saturation decreased six hours after 50 mcg ITB bolus injection.

Adverse symptoms such as nausea, transient urinary retention and headache have been reported after ITB therapy.[14] Compared to oral baclofen, ITB is expected that respiratory dysfunction would be less since it was designed for fewer systemic side effects. However, previous studies have suggested that ITB therapy can cause respiratory arrest in association with overinfusion.[16,17] Therefore, we should keep in mind that lower dose of ITB could even affect respiratory function considering the characteristics of ALS.

Regarding the case, when planning ITB pump implantation to a patient with spastic paraplegia, the clinician should pay attention to the accuracy of the diagnosis. In addition, test trial and evaluation must precede ITB pump implantation. As a limitation of this case report, we did not check how the pulmonary function changed before and after the ITB test trials considering that the most common and fatal complication of ALS is pulmonary dysfunction. In this case, there was a desaturation event six hours after 50 mcg injection of ITB. Since ITB may have also affected the respiratory muscles, in a future study, we will conduct pulmonary function test before and after the ITB test trials. Additionally, we may start the ITB test trial with a lower initial dose of 12.5 mcg and a gradual dose escalation up to 50 mcg. However, it is meaningful that this report addresses the importance of accurate diagnosis and careful consideration of the ITB test trial before ITB pump implantation in a patient with ALS who presents spastic paraplegia.

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