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Intrathecal baclofen therapy for Lesch-Nyhan disease: illustrative case

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BACKGROUND Lesch-Nyhan disease (LND) is a very rare metabolic disorder involving the purine salvage pathway. LND manifests hyperuricemia, self-mutilation, cognitive impairment, and movement disorders such as spasticity and dystonia, whose control is difficult pharmaceutically.

OBSERVATIONS Intrathecal baclofen (ITB) therapy was received by a 22-year-old male for generalized dystonia. His paroxysmal abnormal dystonic posturing reduced after surgery, making the task of caregivers easier despite the unchanged assignment on the dystonia scale during a follow-up period of 4 years.

LESSONS ITB may be a safe and feasible option for dystonic symptoms and difficulty with nursing care in patients with LND.

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KEYWORDS intrathecal baclofen therapy; Lesch-Nyhan disease; dystonia; nursing care

Lesch and Nyhan first described this syndrome in 1964 when they recognized a recurring pattern of neurological abnormalities in two brothers who had hyperuricemia, an extrapyramidal motor disorder, and compulsive self-injurious behavior—a combination of features suggesting a metabolic disorder.[1] Lesch-Nyhan disease (LND) is an extremely rare inherited disorder of purine salvage metabolism caused by congenital deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase.[2] At the adult stage of this disease, dystonia management is often the focus of clinicians, whereas the effect of pharmacotherapy is limited. These measures are merely mildly and temporarily beneficial.

The motor symptoms of LND include a severe action dystonia superimposed on a baseline hypotonia.[3] Dystonia is generalized to all parts of the body; its severity may lead to an inability to stand up and walk, and patients are wheelchair users. These symptoms are associated with voluntary movements and an increase in excitement and anxiety. Dysarthria, dysphagia, and opisthotonos are also frequently reported. Corticospinal tract signs such as spasticity, hyperreflexia, and extensor plantar reflex are generally reported in later years and may reflect an acquired defect. The multiplicity and combination of the above-mentioned symptoms make nursing care for those patients very difficult.

Continuous infusion of intrathecal baclofen (ITB) has been shown to decrease spasticity and control dystonia in children and adults with central nervous system dysfunction.[4–6] Its effects on patients with LND have scarcely been reported, however.[2,7,8] We report a case of a patient with LND with generalized dystonia who received ITB, and we describe in detail the postoperative course for a follow-up period of 4 years.

Illustrative Case

A 22-year-old man with LND was referred to our clinic for consideration of ITB as a treatment for paroxysmal abnormal dystonic posture. At the time of referral, he had undergone medical treatment with haloperidol, diazepam, folic acid, dantrolene sodium hydrate, and allopurinol. In addition, he regularly received botulinum toxin A injections at his extremities in the neighboring clinic, but the therapeutic effects were unsatisfactory. His parents were in favor of ITB after they confirmed that an intrathecal test injection of baclofen (25 μg) led to a satisfactory decrease of tonus in all extremities. The parents decided to allow the patient to undergo ITB pump implantation after giving written informed consent.

The patient was able to communicate verbally only with his relatives; his speech was severely slurred. Oral intake was dependent on assistance but without any tube feeding. He showed tetraparesis, but voluntary movements were seen more in his upper extremities. His hip joints were almost always flexed. He exhibited paroxysmal opisthotonos, typically with his head turning to the right side and his trunk to the left side (Fig. 1A). His Unified Dystonia Rating Scale (UDRS)[9] score was 40 preoperatively. His surface electromyogram (EMG) revealed

ABBREVIATIONS BADS = Barry-Albright Dystonia Scale; CP = cerebral palsy; CT = computed tomography; DIS = Dystonia Impairment Scale; EMG = electromyogram; GABA = γ-aminobutyric acid; ITB = intrathecal baclofen; LND = Lesch-Nyhan disease; NRS = numeric rating scale; UDRS = Unified Dystonia Rating Scale.

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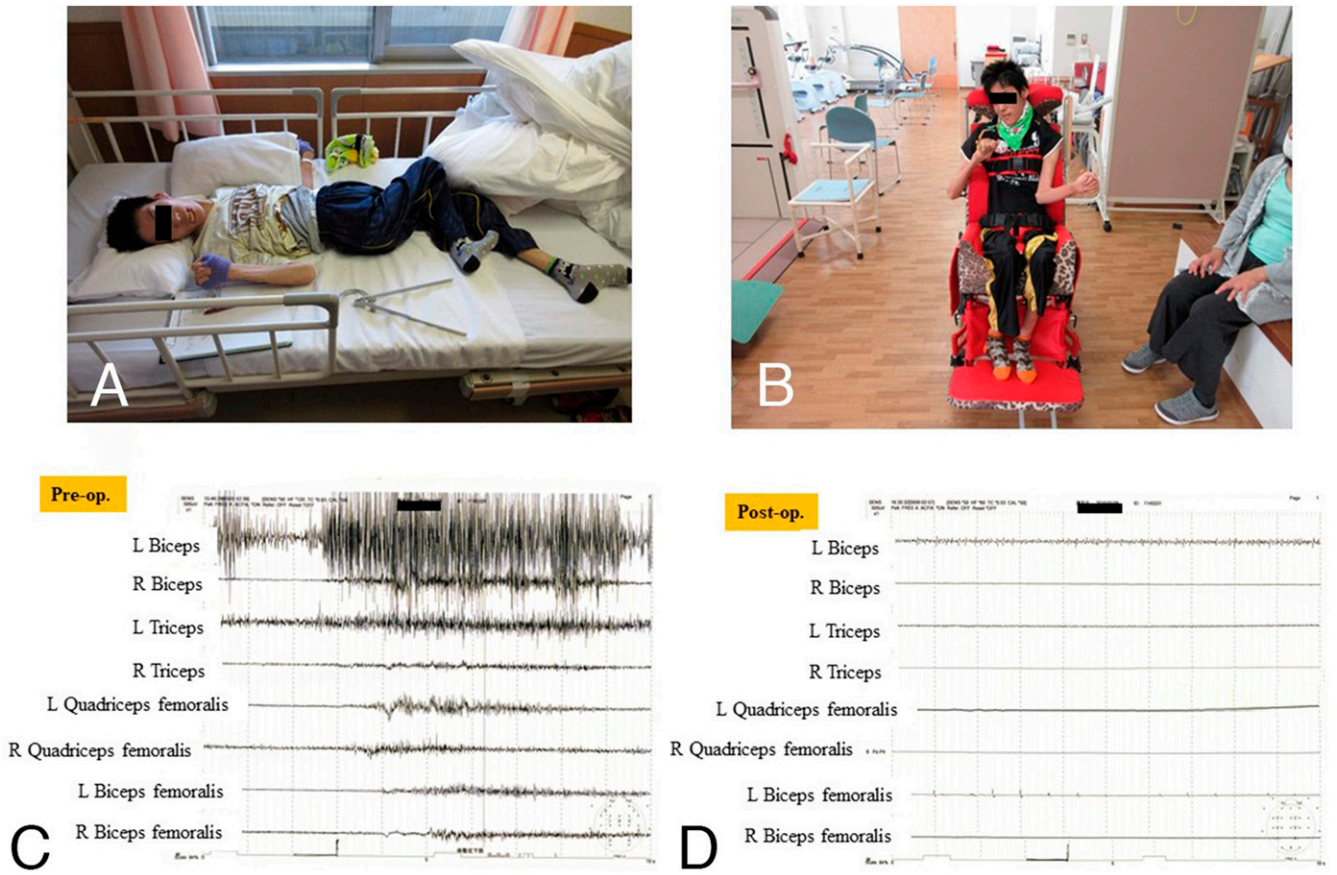

FIG. 1. Posture of the patient (**A**) before and (**B**) 1 year after implantation of the ITB pump. After the operation, the patient could ride stably in a wheelchair, particularly with his hip joints relaxed. Surface EMG at rest (**C**) before and (**D**) after the operation. Abnormal and excessive discharges are significantly diminished in the upper and the lower extremities after ITB, which vanished in the period soon after surgery.

abnormal and sustained EMG activities with excessive cocontraction of antagonist muscle and overflow into leg muscles (Fig. 1C).

The patient's case history revealed that he had been born in a normal full-term delivery. At age 7 months, neck holding was absent and hypertonus in his extremities and developmental delay caused him to be referred to a pediatric medical center. Computed tomography (CT) of the brain did not show any abnormality at age 11 months. Hypertonus of the extremities did not subsequently resolve, and paraplegia was suspected. At age 18 months, magnetic resonance imaging of the brain did not show any abnormality. As an infant, the patient was initially considered to have athetoid cerebral palsy (CP).

Self-mutilation by lip biting, hitting his mouth on the floor, and hitting his mouth with his own right hand were described as starting at 5 years of age. At that point, by reviewing blood records from age 16 months, it was found that his uric acid had increased to 9.2 mg/dL. This prompted his attending doctor to consider LND. The patient's family history did not reveal any similar illness. He was thereafter followed up at the pediatric medical center for medical treatment and at the neighboring clinic for botulinum toxin A injection treatment.

At age 21, genetic testing was conducted after obtaining informed consent from his parents. An *HPRT1* gene mutation (g.3766_17799delinsA, c.294+3472_15320+2380delinsA) was found, and a definitive diagnosis of LND was made.

Surgical Intervention

While under general anesthesia, the patient was placed in the prone position[10] because of severe scoliosis. On the basis of fluoroscopy with a right anterior oblique angle, we judged that we could perform lumbar puncture between L3 and L4. A paramedian puncture on the right side was successfully carried out, and an intrathecal catheter (Ascenda, Medtronic) was advanced to the level of T9 under fluoroscopic guidance.

The patient was then moved to a lateral decubitus position with the left side down because the preoperative abdominal CT scan showed that there was no space to place the pump except in the right anterior abdominal wall. A baclofen pump (SynchroMed II, Medtronic) was implanted subfascially between the rectus abdominus and the external oblique muscles and the respective anterior fascial layers[11] after the catheter and the pump were connected. The catheter and the pump were fixed to the fascia with nylon thread.

The operative field was adequately irrigated with normal saline, and the wound was reapproximated.

Postoperative Course

The pre- and postoperative changes in the baclofen dose and UDRS score are shown in Fig. 2.

ITB was begun at a dose of 24 μg/day with a simple continuous mode. One week after the operation, a surface EMG showed a

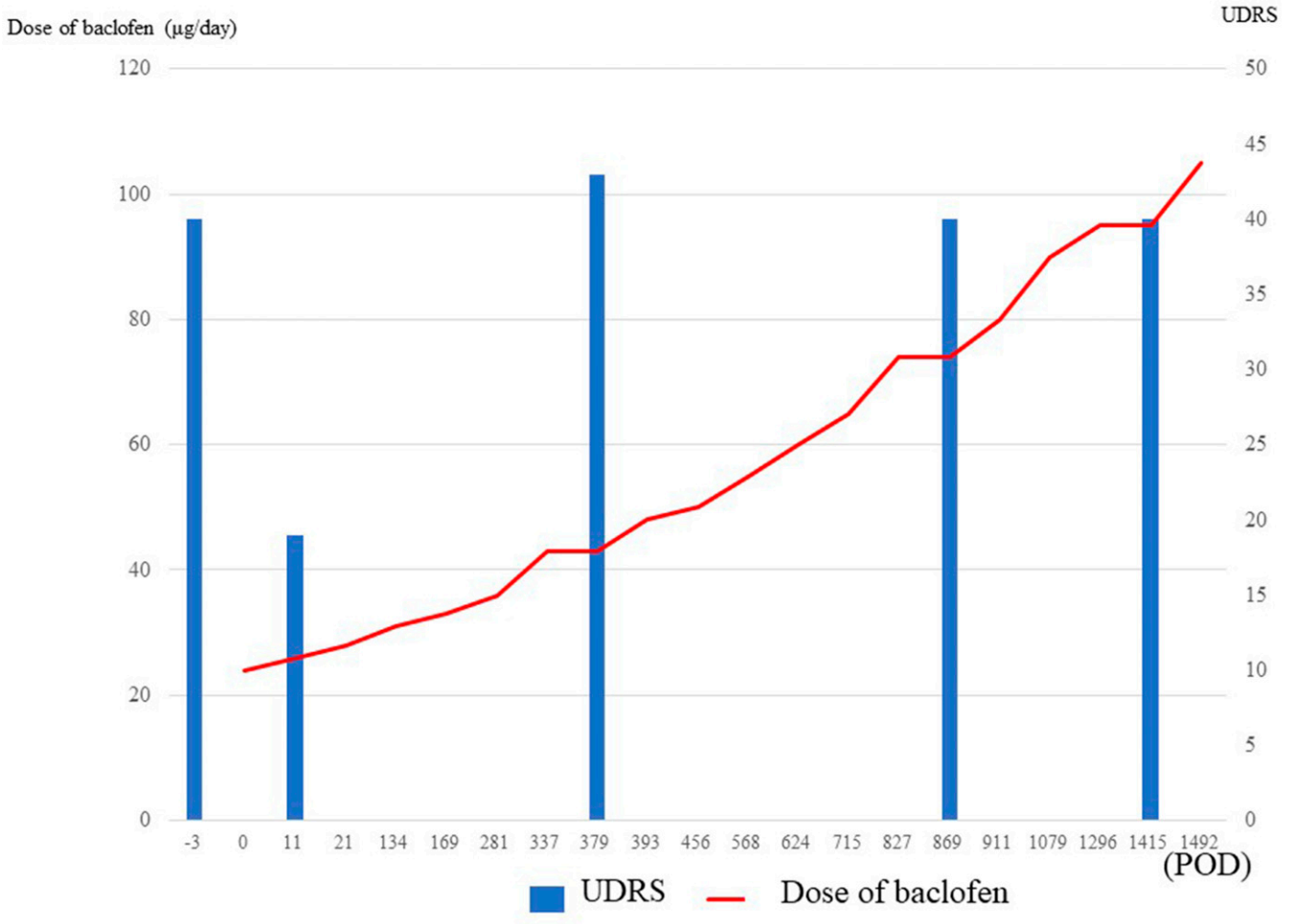

FIG. 2. Course of the dose of baclofen and UDRS score before and after the operation. POD = postoperative day.

significant decrease in muscle tone (Fig. 1D), and the patient's UDRS score had fallen to 19. Paroxysmal opisthotonos also decreased in frequency. The caregiver was satisfied with this treatment (100 of 100 on a numeric rating scale [NRS]) because it brought about an ease in care; for example, the patient could sit quietly in the wheelchair with his legs relaxed (Fig. 1B). Subsequently, adoption of abnormal postures was aggravated occasionally by emotional excitement; the dose of baclofen was increased gradually at such times. The patient's UDRS score returned to the baseline level at 1 year into the follow-up. At 1 year after the operation, the caregiver's satisfaction remained 80 of 100 (NRS). At the last visit 4 years after surgery, the dose of baclofen was 105 μg/day, and the patient's UDRS score was 40, which was identical to that before surgery. The caregiver's satisfaction index rated the treatment as 75 of 100 (NRS). After surgery, the patient never received botulinum toxin A injections.

Discussion

Observations

In this report, ITB was carried out for a patient with LND with severe dystonia after other noninvasive treatment had failed to control his symptoms satisfactorily. His score on the standardized dystonia scale significantly improved immediately after the operation but returned to the baseline level thereafter. His caregiver reported satisfaction with the treatment because nursing care was made easier. No adverse events occurred during the follow-up period of 4 years.

Baclofen is an agonist at γ-aminobutyric acid $(GABA)_B$ receptors located in the spinal cord and brain. $GABA_B$ receptors are metabotropic receptors linked via G proteins to voltage-sensitive potassium channels, and activation of $GABA_B$ receptors results in inhibition. ITB acts as an inhibitory $GABA_B$ agonist, reducing descending excitatory impulses. ITB reduces spasticity by binding to $GABA_B$ receptors in the dorsal spinal cord. For dystonia, it may also work at a central level; the exact mechanism is undetermined.[6,12]

A total of 6 patients with LND treated with ITB have previously been reported in the literature.[2,7,8] Jinnah et al.[2] reported 2 patients with LND who received ITB, but they stated only that both showed good results without giving any objective assessments. McCarthy et al.[8] included 1 child (aged less than 20 years) who received ITB for reduction of muscle tone in their population study in the United Kingdom; detailed clinical information was not specified. Pozzi et al.[7] reported 3 patients with LND treated with ITB and gave detailed descriptions of clinicobehavioral results. They emphasized behavioral improvement, showing cessation of aggression and self-injurious behavior; this could be due to an interaction between baclofen and dopamine. They also

evaluated the dystonic symptoms with the UDRS, as in the present case. The UDRS total score in those 3 patients fell significantly after ITB (case 1 from 27 to 5; case 2 from 23 to 6.5; case 3 from 38 to 11). The UDRS total score of the present patient fell significantly soon after ITB (as shown in Fig. 2) but increased gradually thereafter. This might be due to a tolerance of baclofen as a result of downregulation of $GABA_B$ receptors,[6] although the ITB dosage in the present patient (105 μg/day) might not be enough compared with the dose in those patients (270–550 μg/day). For ITB for generalized dystonia, the higher position of the catheter tip (T4 rather than T6) led to better postoperative dystonia scores for at least 2 years.[6] In the present patient, the catheter tip was positioned at the level of T9, which might be another cause of the return to baseline in the dystonia scale. A further possibility for the remarkable decline in the dystonia score immediately after the operation is the effect of general anesthesia, which has never been mentioned in the literature.

A multicenter, randomized, double-blind, placebo-controlled trial has recently demonstrated the safety and efficacy of ITB for dyskinesia in patients with CP.[13] The primary outcome was evaluated by means of goal attainment scaling obtained by questioning parents and patients and showed significant improvement after ITB. In that study, 2 dystonia scales, the Barry-Albright Dystonia Scale (BADS) and the Dystonia Impairment Scale (DIS), were measured as a secondary outcome. The BADS score of the ITB group did not improve at 3 months relative to that in the control group, but the DIS score was significantly more favorable with ITB. The UDRS score also returned to the baseline level in the longer follow-up period.[13] The impression of caregivers might better reflect the efficacy of ITB for those with dystonia from CP, as in the present patient.

Limitation of the Study

This is a single case of a patient with LND with dystonia for whom care was reduced after ITB implantation. Therefore, it is not possible to generalize our experience. Nevertheless, because of the rarity of LND, this case may contribute to future treatment options for LND with dystonia.

Lessons

ITB is a safe and feasible option for dystonic symptoms and difficulty with care for a patient with LND.

Acknowledgments

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Satow, Ogawa. Acquisition of data: all authors. Analysis and interpretation of data: Satow, Ogawa. Drafting the article: Satow. Critically revising the article: Ogawa. Reviewed submitted version of manuscript: Ogawa. Approved the final version of the manuscript on behalf of all authors: Satow. Administrative/technical/material support: Ogawa.

Supplemental Information

Previous Presentations

A part of this study was presented as an abstract in the poster session of the 17th Quadrennial Meeting of the World Society for Stereotactic and Functional Neurosurgery held in Berlin, Germany, on June 26–29, 2017.

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