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Intrathecal Baclofen Therapy for the Treatment of Spasticity in Sjögren-Larsson Syndrome

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Abstract

Intrathecal baclofen therapy (ITB) is widely accepted as a treatment option for patients with severe spasticity. The current treatment of spasticity in patients with Sjögren-Larsson Syndrome (SLS) is largely symptomatic, given that no effective causal therapy treatments are available. We report the outcome of two patients with SLS who had pump implantation for ITB. We observed a positive response, with a decrease of spasticity, reflecting in the Modified Ashworth Scale, and parents and caregivers observed a functional improvement in both patients. One patient experienced skin irritation 15 months after surgery, necessitating pump repositioning. No infection occurred. Our report shows ITB can have a positive therapeutic effect on spasticity in patients with SLS, and therefore may be a promising addition to current treatments.

Keywords

Sjögren-Larsson Syndrome; intrathecal baclofen therapy; spasticity; baclofen pump; Modified Ashworth Scale

Introduction

Sjögren-Larsson Syndrome (SLS) is a rare autosomal recessive disorder characterized by congenital ichthyosis, intellectual disability, and spastic paresis.¹ SLS arises from deficient activity of fatty aldehyde dehydrogenase, which is necessary for the oxidation of long-chain aliphatic aldehydes to fatty acids.² It is believed that the accumulation of long-chain aliphatic aldehydes in the tissues of patients with SLS is responsible for their symptoms, including spasticity.³ Spasticity arises prior to 3 years of age⁴ and is generally bilaterally present predominantly in hamstrings, hip adductors, and gastrocnemii muscles. Contractures in the lower extremities are more common than in the upper extremities and severely limit the ability of SLS patients to ambulate.⁵ SLS is a non-progressive syndrome, but spasticity

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increases with age, and the independence of patients with SLS can be reduced significantly as mobility, daily care, and hygiene become more difficult. Therapeutic options for the spasticity in SLS include surgical procedures and botulinum toxin (Botox) injections, which may become less effective with repeated use. In treating spasticity, muscle relaxants, benzodiazepines and anticholinergics have been used, but these medications often have significant side effects such as loss of coordination, drowsiness, fatigue and nausea.

Baclofen, a γ -aminobutyric acid (GABA) analogue, is used in treating spasticity. Intrathecal baclofen (ITB) has efficacy in reducing spasticity with acceptable systemic side effects.^{6–9} We report our experience of ITB therapy in two pediatric patients with SLS. Our early results support the use of ITB as a treatment option for the spasticity in this rare disease.

Patients and Methods

Two pediatric patients diagnosed with SLS were followed at the University of Nebraska Medical Center and selected for ITB therapy at the New York University Langone Medical Center. Both patients had ichthyosis at birth and developed spasticity with motor delay in the first two years of life. They exhibited intellectual disability and had pseudobulbar dysarthria. Brain MRI showed periventricular white matter disease and MR spectroscopy revealed characteristic lipid peaks within the white matter. The diagnosis of SLS was confirmed by identification of mutations in *ALDH3A2*. The *ALDH3A2* genotype of Patient 1 was c.764delA/c.682T>A. Patient 2 was homozygous for the c.710G>A mutation.

Baclofen Trial

Each patient first underwent a lumbar injection of ITB as a trial to predict results of long term ITB. Fifty mcg of baclofen was injected slowly over 1 minute. Before and after baclofen administration, change in spasticity was clinically assessed using a Modified Ashworth Scale (MAS).¹⁰ The MAS score is used pragmatically for the assessment of patients at baclofen trials at our institution. The MAS has well known assessment challenges including low interrater reliability, and limitations in quantifying spasticity and in detecting and differentiating spasticity from contractures have been described in pediatric patients.^{11,12} However, the MAS is widely used since it can be performed in a reasonably timely manner and due to its constant clinical availability.¹³

The patients were examined before and after the injection of baclofen by the same team of physiotherapists. Values pre-injection and 2, 4, and 6 hours after injection were compared. At the four-hour mark of the trial, Patient 1 was able to abduct legs, and a 1-point decrease for the hip extensors abductors was seen in Patient 2. A positive clinical response to the baclofen test formed the basis for proceeding with placement of a baclofen pump.

Operative technique and initial postoperative treatment

The patients were given chlorhexidine wipes the night before the surgery for preoperative skin cleaning. After induction of general anesthesia, the patients were placed in left lateral decubitus position, prepped with chlorhexidine, and the skin incision was infiltrated with lidocaine / epinephrine. Antibiotics were given prior to the incision. The pump (Medtronic SynchroMed® II), was prepared according to the manufacturer's protocol and soaked in a

bath of bacitracin. The spinal catheter was first inserted in a typical fashion, and the pump was then placed into a subcutaneous pocket under Scarpa's fascia. The wounds were irrigated copiously with bacitracin and closed in several layers using a subcuticular suture for the abdominal wound and a running suture for the lumbar wound. Sterile dressings were applied to the wound. Antibiotics were subsequently administered intravenously for 24 hours. Baclofen therapy was initiated immediately after implantation.

Patients were re-evaluated one day following surgery to analyze functional mobility, transfers, tone, and ambulation and rehabilitation was planned. The initial baclofen dosage varied between 25 mcg/day to 40 mcg/day dependent upon age, weight, prior medications, and relative effect of baclofen on the trial injection.

Follow up

After surgery, the patients were transferred to an inpatient rehabilitation facility for four weeks of intensive therapy, focused on improved range of motion, prevention of deformities, and improve gait and activities of daily life. Dosing of baclofen was adjusted accordingly.

After rehabilitation, the patients were seen at the ITB Clinic for dosage adjustments, evaluations, and pump refills approximately every 3 months. The postoperative MAS was measured regularly by the same professional at those appointments.

Results

The results of the MAS, after 12 months (Patient 1) and 27 months (Patient 2) of ITB therapy, reflected a reduction in spasticity in some muscle groups. (Table 1).

Case report 1

Patient 1 was a 5-years male at the time of initial implantation. He had clinical features consistent with SLS including ichthyosis, mild truncal and upper extremity hypotonia, and spastic paraparesis with tight hip adductors, hamstrings, and heel cords. At age 4 years, he was given Botox injections to both hip adductors and gastrocnemii followed by serial castings. Transient benefit was noted.

Prior to surgery, he was able to ambulate with a posterior walker in a crouch pattern and with assistance while wearing braces. His walking was also characterized by excess plantar flexion; crawling was his main mode of locomotion. He had a scissoring gait with increased spasticity primarily in the lower extremities with a MAS III in the knee flexors and MAS I in the hip extensors.

Implantation of an ITB pump was uneventful, as was the perioperative period. Improvements in his spasticity and range of motion were noted during inpatient rehabilitation. The patient received a minimum of three hours daily of individualized, comprehensive inpatient rehabilitation, including physiotherapy, occupational therapy, neuropsychology, and recreation therapy. Baclofen dosage was adjusted from 25 to 215 mcg/day over the course of a year.

With dosage increases, the patient was observed to have less scissoring, “smoother” steps during gait training, improved hip movement and trunk extension during physiotherapy, better tolerance of range of motion exercises at home, and relaxation of both legs. Significant contractures persisted but seem to be likely more structural rather than related to dynamic tone.

The patient re-presented 15 months after surgery with erythema, mild swelling, and discrete pain at pump site. Signs of infection were absent and the skin over the pump was intact. To avoid skin breakdown at the pump site, the pump was electively repositioned. The pump was placed subfascially and connected to the existing intrathecal catheter. This technique was described by Kopell et al., and is indicated for the pediatric population with a dearth of soft tissue mass to cover a subcutaneously implanted baclofen pump.¹⁴ The skin irritation resolved and no signs of pump dysfunction were noted.

Case report 2

This SLS patient was a 19-year old female with generalized ichthyosis, intellectual disability, underlying hypotonia, and spastic paraparesis. She had bilateral radial head dislocation of the elbows and had undergone hamstring release 16 years previously. An ITB trial 6 years earlier made her floppy and unable to walk, so a pump was deferred. At baseline, the patient had daily physical and occupational therapy and was on oral baclofen 10 mg TID. She was capable of walking 2–3 blocks with her posterior walker and ankle-foot braces, but ambulated with great difficulty and employed a manual wheelchair often. Her increasing tone impeded daily care and hygiene. She was considered for ITB therapy to ease care while weighing the potential for interference with her potential for ambulation.

After a positive ITB trial, she underwent ITB pump implantation. The initial baclofen dose was 39.9 mcg/day. After surgery and rehabilitation, an observable improvement was noted with muscle tone relaxation in both legs, but without lethargy, excessive hypotonia or loss of axial control. She continued to have daily physical and occupational therapy.

Over the ensuing of six months, her ITB dose was increased to 135 mcg/day to progress with gait training, strengthening, and to address residual spasticity. This ITB dose was intermittently too high, resulting in difficulty with gait and hypotonia, causing her knees to buckle, so the ITB dosage was titrated to allow active standing and lower extremity strengthening. A daily flexible dose delivery was eventually programmed. Three years after surgery, her standing dose is 86 mcg/day due to potential drug interaction with an antidepressant (citalopram). At this dose, the patient has a substantial improvement compared to baseline spasticity (see Table 1) and shows no signs or symptoms of ITB over- or underdosage.

Discussion

We report the first successful use of ITB therapy for spasticity in SLS. ITB was employed as a long-term treatment option for spasticity and to assist in patient care. Management of patients with SLS is largely symptomatic, given that no effective curative therapy exists,¹⁵ and spasticity in SLS is generally treated by intensive physiotherapy to maintain ambulation.

As symptoms progress, and physiotherapy may become less effective, skeletal deformities and increased tone can be palliated by orthopedic tendon release procedures.¹⁶ However, these surgeries are usually performed once physiotherapy and/or Botulinum injections have failed to halt progression. Most SLS patients have deficits in gross motor functions and limitations in their participation in society.⁵

The response to ITB therapy and the long-term benefits for SLS patients will require longer follow-up and additional patients. Although our two patients both responded favorably to ITB, the optimal time to initiate this therapy is undetermined. Moreover, the need for a higher baclofen dose in our younger patient (Patient 1) suggests that the dosage should be tailored to each individual rather than their age or body weight. Significantly, Patient 2 had already been treated with oral baclofen and hamstring release surgery, but still gained additional benefit from ITB therapy. As seen in Patient 1, treatment with ITB may potentially delay the need for orthopedic surgery, increase the benefit of physiotherapy and have a possible positive effect on the quality of movement.

In pediatric patients with cerebral palsy (CP), baclofen pumps have long been used for severe spasticity and have shown to decrease pain and improve ease of care.⁷⁻⁹ In CP patients, ITB therapy reduces MAS from a median 3 to 2 within a year.¹⁷ Since ITB is a safe treatment for patients affected by various diseases associated with spasticity, we believe it should also be considered as an option for those with SLS.

In Patient 1, irritation of the skin overlying the pump was noted 15 months after surgery. This is possibly due to the dearth of soft tissue mass covering the subcutaneously implanted pump in this young patient. The causal contribution of the ichthyosis in SLS to this complication is unclear. The pump was initially placed subcutaneously, as this placement has a faster recovery after surgery due to lower pain levels. At the revision, the pump was placed subfascially; no infection occurred. This complication is not uncommon, and wound dehiscence and infections occur in 10–32% of pump implantations.^{7,18} In a study recently published by Motta et al. analyzing the complications of 403 consecutive pediatric patients with ITB pumps, it was found that at least one complication was present in 25% of the patients.¹⁸ Furthermore, the risk of infections in subcutaneously vs. subfascially placed pumps differed substantially, with 20% vs. 4% risk respectively. Due to our experience and this new data, primary subfascially placed pumps in select cases with low weight and congenital skin diseases, as SLS, should be considered.

Conclusion

ITB therapy is a potential addition to current surgical and medical treatments for the spasticity in patients with SLS. In addition to its benefit with respect to spasticity, it may also have a positive effect on the quality of movement of the patient. ITB should be considered for SLS patients with severe spasticity after a positive response to a trial dose of ITB.

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Table 1

Spasticity measured using the Modified Ashworth Scale in both patients prior to and after starting ITB therapy. The MAS scores shown represent the scores bilaterally. MW: manual wheelchair; NT: not tested.

	Patient 1		Patient 2	
	Pre-operative	12 Months Post-operative	Pre-operative	27 Months Post-operative
Elbow flexors	0	0	1–2	0
Elbow extensors	0	0	1+	0
Hip flexors	0	0	1	1
Hip extensors	1	1–2	3	2–3
Hip adductors	0	NT	3	1
Knee flexors	3	0	1	1
Knee extensors	0	1–2	3	2–3
Ankle clonus	Clonus response	None	Clonus response	Clonus response
Aids for ambulation	Uses MW, braces and posterior walker for ambulating	unchanged	Uses MW, braces and posterior walker for ambulating	unchanged