Movement Disorders
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CASE SERIES

Intraventricular Baclofen for Treatment of Severe Dystonia Associated with Glutaryl-CoA Dehydrogenase Deficiency (GA1): Report of Two Cases

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Abstract: Two individuals with intractable generalized dystonia secondary to glutaric aciduria type 1 (GA1) were treated with continuous intraventricular baclofen (IVB) infusion. On IVB of 220 μg/day, one 10-year-old girl had an 85% reduction in dystonia, from Barry-Albright Dystonia Scale (BADS) score 30.7 to 4.5 (maximum score: 32) at 30 postoperative months. Her enteral dystonia medications were reduced >60%, and she discontinued medications for pain, anxiety, and depression. A second GA1 patient, age 23, experienced a more modest 18% reduction in dystonia (BADS decrease from 29.7 to 24.3) on IVB of 1,665 μg/day at 14 postoperative months. He substantially reduced his enteral dystonia medications and reported meaningful pain relief. These cases demonstrate that IVB may be a palliative option in the intractable dystonia of GA1. Our provisional observations suggest that IVB may be more beneficial in younger GA1 patients.

Glutaryl-CoA dehydrogenase deficiency (glutaric aciduria type 1; GA1, MIM 231670) is a rare hereditary metabolic disorder that can result in striatal degeneration during early brain development, either precipitated by an infectious illness or presenting as insidious motor delay subsequent to perinatal brain injury. In recent years, advances in dietary therapy have allowed effective prevention of brain injury in more than 90% of asymptomatic children diagnosed by newborn screening. Nevertheless, a large number of adolescent and adult GA1 patients worldwide have irreversible striatal lesions and consequently suffer from chronic, medically intractable dystonia.

Pallidotomy and internal pallidal DBS have been attempted in GA1 patients, but compared to their utility in treating primary dystonias have proven minimally effective for relieving the secondary dystonia of GA1 (Table 1).[1–4]

We successfully treated 2 GA1 patients with severe dystonia using intraventricular baclofen (IVB). We based this approach on the work of Albright and Ferson, who pioneered the use of IVB and demonstrated that it is more effective for treating secondary dystonias in children than the intrathecal route of baclofen delivery.[5] Importantly, 2 of their study subjects with neurogenetic disorders that share pathophysiological similarities to GA1 (pantothenate kinase deficiency and methylmalonic acidemia) responded well to IVB, with Barry-Albright Dystonia Scale (BADS) scores decreasing by 83% and 100%, respectively.[5] Based on these observations, we implanted IVB catheters in 2 GA1 patients and here report favorable postoperative outcomes.

Patient 1

A 10-year-old girl presented with generalized dystonia of 8 years' duration. After an uneventful gestation and term delivery, she made good developmental progress until 17 months of age, when she suffered acute striatal lesions during a febrile illness, prompting the diagnosis of GA1. She subsequently

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TABLE 1 Published outcomes after pallidotomy or DBS for treatment of GA1-associated dystonia

Article	Procedure	Age	Pre-op Dystonia Score	Post-op Dystonia Score	Improvement in Dystonia Symptoms
Air et al.[1]	Bilateral DBS	17 yrs	28 (BADS)	23 (BADS)	18%
Eltahawy et al.[2]	Bilateral pallidotomy	12 yrs	113 (BFM)	99 (BFM)	13%
Hwang and De Salles[3]	Bilateral pallidotomy	6 yrs	115 (BFM)	NA	15%
Rakocevic et al.[4]	Bilateral pallidotomy	18 mo	NA	NA	Temporary improvement

NA, not available; mo, months; yrs, years.

TABLE 2 Barry-Albright Dystonia Scales for two GA1 patients pre- and post-IVB therapy*

	Patient 1 (Age 10 yrs)			Patient 2 (Age 23 yrs)	
	Pre	Post (18 mo)	Post (30 mo)	Pre	Post (14 mo)
Intraventricular baclofen (μg/day)	—	200	220	—	1,665
Medication doses (mg/kg/day)					
Diazepam	1.6	1	0.6		
Oxycodone	0.5	—	—		
Chloral hydrate	27	—	—		
Fluoxetine	1	—	—		
Baclofen (enteral)				1.2	—
Clonazepam				0.15	0.04
Carbamazepine				15	15
Barry-Albright Subscores					
Eyes	2.7	1.0	1.0	2.0	2.3
Mouth	4.0	1.0	1.0	4.0	3.0
Neck	4.0	0.7	1.0	4.0	3.7
Trunk	4.0	0.3	0.0	4.0	3.3
Left arm	4.0	1.0	1.5	3.7	2.7
Right arm	4.0	1.0	0.0	4.0	3.3
Left leg	4.0	0.0	0.0	4.0	3.0
Right leg	4.0	0.0	0.0	4.0	3.0
Total	30.7	5.0	4.5	29.7	24.3

*Scores calculated as the average of scoring sheets completed independently by each parent, a study investigator (K.A.S.), and, in case 2, the patient himself. Inter-rater concordance was high in all cases.
mo, months; yrs, years.

developed severe generalized dystonia exacerbated by emotional distress.

She endured volatile, painful muscle contractions throughout each day, necessitating extreme, but still inadequate, enteral doses of sedative, analgesic, and anxiolytic medications, including diazepam, oxycodone, chloral hydrate, and fluoxetine (Table 2). Methadone, trazodone, gabapentin, enteral baclofen, and botulinum toxin injections had been used to no avail. At presentation, the patient's BADS score averaged over three observers (both parents and primary clinical provider) was 30.7 (of a possible 32.0; Table 2), reflecting chronic muscle contortions and rigidity that caused unremitting pain, insomnia, anxiety, and depression (see Video 1). She also suffered from frequent life-threatening "dystonic storms"—nocturnal episodes of intense pain, hyperthermia, tachycardia, and pupillary dilation —that often required hospitalization.

An intraventricular catheter and abdominal infusion pump (Medtronic Synchromed II; Medtronic Inc., Dublin, Ireland) were placed under general anesthesia. Following Albright,[6] a catheter tip was placed in the third ventricle for even flow through both foramina of Monro and more uniform distribution of the baclofen. Frameless neuronavigation and endoscopic guidance were used to confirm a safe and effective location of the catheter tip. The baclofen pump was placed in the infraumbilical abdominal wall and the catheter tunneled to an incision in the right retroauricular region, as an intermediate point for passage and connection to the ventricular catheter.

Over the first 18 postoperative months, IVB was titrated to an effective dose of 200 μg/day as dystonia dramatically improved; BADS score decreased from 30.7 to 5.0 (83% improvement), and the patient was weaned completely from oxycodone, chloral hydrate, and fluoxetine (Table 2). "Dystonic storms" ceased. She no longer experienced chronic pain, emotional distress, insomnia, or autonomic dysfunction. On examination at follow-up, she sat comfortably in her wheelchair and had regained the ability to point, grab objects, and communicate effectively using directed eye gaze and blinking (see Video 1). These outcomes were sustained at 36 months on IVB of 220 μg/day.

Patient 2

A 23-year-old male presented with severe generalized dystonia secondary to GA1-related bilateral striatal necrosis suffered at 1 year of age. At presentation, his average BADS score among

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four observers (each parent, primary clinician, and the patient himself) was 29.7 (Table 2). He had dystonia-related nocturnal back pain that disrupted sleep and severe posturing of arms and hands that precluded their use. Painful hamstring contractions necessitated a series of palliative botulinum toxin injections, but the localized therapeutic effects were modest and transient. He suffered from several chronic morbidities entrained by dystonia, including joint dislocations, scoliosis, mutism, dysphagia, constipation, and recurrent aspiration. High enteral combinations of baclofen, clonazepam, and carbamazepine (Table 2) were of minimal benefit. Symmetric pallidotomy performed at age 9 was completely ineffective.

An IVB pump system was surgically placed as described above. Based on the effective daily dose of IVB for patient 1, we chose a 20-mL pump reservoir for delivery of concentrated (2,000 μg/mL) baclofen.

At 14 postoperative months, BADS score averaged across four raters was 24.3, representing an 18% improvement. A much larger IVB dose of 1,665 μg/day was required to achieve this modest benefit, but did allow for substantial reductions of enteral medications (Table 2). To minimize pump refills, the original 20-mL pump reservoir was replaced with a 40-mL reservoir. The relatively high IVB dose was well tolerated by the patient, who could communicate his subjective experience through use of a gaze-directed DynaVox system (DynaVox Mayer-Johnson, Pittsburgh, PA). He reported sustained pain relief as a result of IVB and claimed it was the most effective dystonia therapy he had received to date. Tragically, however, he continued to be plagued by chronic pulmonary disease, which culminated in his death at 18 postoperative months.

Discussion

Burdened with progressively more painful, debilitating, medically intractable dystonia, both patients presented here had a clinical condition that warranted compassionate use of an emerging surgical treatment. For patient 1, maximal medical therapy provided only marginal benefit and caused sedation and cognitive slowing. Her autonomic dysfunction could not be controlled, and her anxiety and emotional lability were worsening as she matured. Before IVB surgery, patient 2 had some response to enteral benzodiazepines, baclofen, and tegretol, but his motor disability, chronic pain, and pulmonary compromise had nevertheless progressed with age. The refractory nature of these patients' dystonia reflects the experience of others with GA1.

Generalized dystonia associated with GA1 is notoriously difficult to treat. Trihexyphenidyl, other anticholinergics, levodopa, and dopamine receptor agonists that can be effective for primary torsion dystonias have limited efficacy in GA1 and other secondary dystonias. A case of improvement in hemidystonia with enteral baclofen (30 mg/day) in 1 GA1 patient has been reported,[7] and a small series of 3 patients had moderate benefit on enteral baclofen at 2 mg/kg/day.[8] However, when the latter received doses of 3 mg/kg/day, all 3 developed headaches, generalized hypotonia, and lethargy.

At the Clinic for Special Children, we treat more than 100 GA1 patients, many of whom suffer from dystonia. We find that enteral baclofen doses typically required to adequately suppress GA1-associated dystonia also reduce seizure threshold and cause intolerable sedation. In our experience, the benzodiazepine, diazepam, strikes an acceptable balance between efficacy and side effects in dystonic GA1 patients. However, patients treated long term develop tolerance and often require very high doses (≥1.5 mg/kg/day).

Botulinum toxin therapy, which involves repeated injections into individual muscle groups, has had mixed outcomes in GA1. Botulinum toxin can relieve extreme muscle pains that emerge from focal sites, but in our experience, the diffuse anatomical distribution of dystonia in GA1 severely limits the application of this strategy in GA1 patients.

DBS was considered in patient 1, but published results are equivocal (Table 1). Whereas pallidotomy is seldom used since the application of DBS, patient 2 had undergone the procedure with no benefit, and reports of other older cases of modest improvement can be found (Table 1). This is consistent with our unpublished experience in 2 adults with GA1, who reported modest subjective improvement and decreased pain after DBS surgery, but had no change in objective signs of dystonia. The timing and extent of neuronal loss and the motor circuit remodeling that occurs in the wake of early injury appear to limit the therapeutic potential of DBS for this indication.[9]

Based on the experience of Albright, an intraventricular route for baclofen administration was chosen as a palliative approach in patients 1 and 2, as opposed to an intrathecal, spinal route, given that IVB is as safe as intrathecal baclofen[10] and the postulated site of action for the dystonia is thought to be supraspinal.[5] In our patients, intraventricular catheter was also favored because of concerns regarding dystonia-related neuromuscular scoliosis of tremendous severity, which can be associated with an increased risk to spinal catheters over time.

In response to IVB, patient 1, age 10, had pronounced dystonia relief sustained at 36 months without serious side effects. Her comorbid pain, dysautonomia, depression, and anxiety resolved. She made gains in social development, communication, and nutritional status. Moreover, her current IVB dose (220 μg/day) provides a viable long-term therapeutic window, allowing for substantial dose increases as indicated in the future. In contrast, patient 2 required a much higher IVB dose (1,665 μg/day) to maintain a modest therapeutic benefit, comparable to responses observed in some GA1 patients after pallidal ablation or stimulation. In older patients, a 40-mL pump reservoir may be more indicated, because there is no additional risk to a larger size and the therapeutic dose of baclofen can vary widely.

Although biological variation certainly contributes to these variations of patient response, the developmental timing might be a critical determinant of IVB efficacy for secondary dystonias in general and GA1 in particular. Through the mechanism of long-term potentiation, neuronal networks that support dystonia

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may undergo pathological synaptic reinforcement, making them less responsive to all interventions over time. Such maladaptive plasticity can readily explain a common observation: The force and intractability of dystonia tends to worsen in GA1 patients as they grow older, even as their brain lesions remain static. This suggests that for patients with GA1 who suffer from severe dystonia, IVB can be considered early in life as a relatively safe and effective palliative therapy.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

S.G.: 1B, 1C, 2A, 2B

M.A.K.: 1C, 2A, 2B

A.M.R.: 1C, 2B

K.A.S.: 1A, 1B, 1C, 2A, 2B

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Supporting Information

A video accompanying this article is available in the supporting information here.

Video 1. Video illustrating key aspects of pre- and postoperative clinical condition of patient 1. Video was captured by the patient's parents who provided it for publication with their written consent. Segments, as labeled in the video: **Pre-surgery.** Patient 1, in pain from severe dystonic posturing of the neck, arms, and trunk; experiernces some pain relief with additional doses of medications, as indicatied (see Table 2 for full list of preoperative medications). **Post-Surgery.** Three months after surgery. Visible reduction in dystonia symptoms and associated pain and anxiety. Patient is communicating her subjective experience by blinking.

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