Original Clinical Article

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Orthopaedic manifestations of glutaric acidemia Type 1

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Abstract

Purpose: Glutaric acidemia type 1 (GA1), a rare hereditary metabolic disease caused by biallelic mutations of *GCDH*, can result in acute or insidious striatal degeneration within the first few years of life. We reviewed the orthopaedic sequelae and management of 114 neurologically injured patients with a confirmed molecular diagnosis of GA1.

Methods: We performed a retrospective chart review spanning 28 years identifying 114 GA1 patients, most from the Old Order Amish population of Lancaster County, Pennsylvania, who were homozygous for a pathogenic founder variant of *GCDH* (c.1262C>T). We collected demographics, medical comorbidities, muscle tone patterns, Gross Motor Function Classification System level, gastrostomy tube status, seizure history, inpatient events, orthopaedic diagnoses and operative characteristics.

Results: Over an average follow-up of 4.7 ± 3.4 years, 24 (21%) of 114 patients had musculoskeletal problems requiring orthopaedic consultation. Scoliosis (n = 14), hip dislocation (n = 8/15 hips), hip subluxation (n = 2/three hips), and windswept hip deformity (n = 2) in the spine and hip joint were most common. In total, 35 orthopaedic surgeries were performed in 17 (71%) patients. The most common primary operations were one-stage procedures with proximal femoral varus derotation osteotomy and/or pelvic osteotomy (n = 8/14 hips) for subluxation or dislocation. In all, 11 patients had posterior spinal fusion for severe scoliosis. With the recommended metabolic management, there were no disease-specific complications in this cohort.

Conclusions: Children with GA1 who have static striatal lesions are at risk for musculoskeletal complications, especially scoliosis and hip dislocation, and appropriate operative management requires consultation with a metabolic specialist with specific considerations for fluid management and nutrition.

Level of Evidence: IV

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Keywords: glutaric acidemia; scoliosis; hip surgery; operative management

Introduction

Glutaric acidemia type 1 (GA1; OMIM #231670) is a disorder of systemic and cerebral organic acid metabolism caused by biallelic variants of glutaryl-CoA dehydrogenase (*GCDH*), which encode the mitochondrial flavin-dependent *GCDH* that mediates degradation of lysine, hydroxylysine and tryptophan.[1] The birth incidence of GA1 is approximately one per 90 000 worldwide,[2] but is much higher among certain endogamous groups such as the Old Order Amish of North America,[3] a modern religious sect descended from a few hundred Swiss Anabaptists who immigrated to Pennsylvania during the eighteenth century.[4] Within certain Amish demes, a pathogenic *GCDH* c.1262C>T founder mutation has reached carrier frequencies of approximately 10%,[5] resulting in disease incidence rates as high as one per 400 births. High-risk *GCDH* founder alleles are also found in other endogamous populations such as the Oji-Cree natives of Ontario[6] and 'Travelers' of Ireland.[7]

Neuronal *GCDH* deficiency results in proximal accumulation of glutaryl-CoA and its neurotoxic derivatives glutaric (GA) and 3-hydroxyglutaric (3HGA) acids,[8] which become concentrated in brain tissue.[9-13] Without presymptomatic detection and appropriate treatment, cerebral *GCDH* deficiency predisposes to sudden, histologically selective, and developmentally restricted degeneration of medium spiny neurons within the lentiform nuclei.[14] More than 80% of untreated children develop striatal lesions,[15] which typically strike within the first two years of life.[15-17] These encephalopathic crises most often manifest as sudden motor regression during an acute infectious illness but can occur in the absence of an apparent trigger and may even happen *in utero*.[16,18]

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Outcomes for GA1 have improved considerably over the last two decades; with the combination of newborn screening for glutarylcarnitine (C5DC), adherence to a lysine-restricted/arginine-enriched prescription diet,[19,20] and inpatient therapy during intercurrent illnesses,[18,21] fewer than 10% of GA1 patients develop brain injury.[19] Those who remain neurologically healthy until their second birthday face an excellent long-term prognosis.[22,23] Nevertheless, the risk for striatal degeneration remains high for patients born in resource-limited settings who do not have access to tandem mass spectrometry-based newborn screening or prescription medical foods.[8,24]

Regardless of their timing or mechanism, static striatal lesions result in a complex extrapyramidal movement disorder that is the principal determinant of clinical outcome.[8,16-19,22] Severe, generalized dystonia is the most common motor pattern observed among neurologically injured GA1 patients, and entrains serious gastrointestinal, pulmonary and musculoskeletal complications that exact a heavy disease burden.[22,25] The orthopaedic surgeon can play a critical role in alleviating this burden. Here, we review orthopaedic complications and their surgical management in a large cohort of GA1 patients treated at a single tertiary care centre.

Methods

Following institutional review board approval, we retrospectively collected data on 114 patients found within our institutional database who had a confirmed diagnosed of GA1. For subjects born between 1988 and 1994, the diagnosis was based on a characteristic clinical phenotype paired with detection of GA and 3HGA in urine by gas chromatography-mass spectroscopy. Detection of a pathognomonic metabolite (C5DC) using tandem mass spectrometry was incorporated into Pennsylvania newborn screening in 1994, and detection of the *GCDH* c.1262C>T founder allele was introduced as a reflex second-tier screening test in 1999. Sanger sequencing of *GCDH* was performed to confirm neonatal screening results or corroborate a clinical diagnosis of GA1 in older symptomatic patients.

Using our institution's inpatient and outpatient electronic medical records system, we extracted data about the method and age of diagnosis, current age, Gross Motor Function Classification System (GMFCS) score, medical comorbidities, gastrostomy tube status, seizure history, orthopaedic diagnoses, surgical interventions and postoperative follow-up. The large majority of physical examinations and operative decisions were conducted by a single senior pediatric orthopaedic surgeon (FM).

Indications for reconstructive surgery of a subluxed or dislocated hip included severe movement restriction, difficulty in perineal care, or pain with ambulation, transfers or sitting. The primary surgical technique was proximal femoral varus derotation osteotomy (VDRO) performed in a single stage. The reconstructive procedure combined routine varus shortening osteotomy with soft-tissue lengthening[26] and acetabular reconstruction with peri-ilial pelvic osteotomy[27] commonly used in children with cerebral palsy. No hip spicas were used. Physical therapy commenced on the first postoperative day and hip movement was allowed as much as the patient could tolerate. A smooth perioperative transition typically required aggressive management of both pain and the movement disorder using epidural blocks, oral and intravenous analgesics, and high doses of diazepam.

When structural scoliosis was evident on physical examination, patients were evaluated with sitting whole spine radiographs; spinal curvature ≥ 60 degrees was typically considered an indication for fusion. The strategy for posterior spinal fusion (PSF) followed rules of scoliosis secondary to cerebral palsy, meaning all curves were fused from T1 or T2 to the pelvis. These patients similarly needed careful postoperative monitoring to control pain and exacerbation of extrapyramidal movements while also mitigating any risk for metabolic instability.

Statistical analysis

Parametric and nonparametric analyses were performed. Descriptive and frequencies statistics were used to describe the population by mean and standard deviation. Statistical analysis was performed using SPSS v25 (IBM, Armonk, New York).

Results

Our retrospective review included a total of 114 children (50% female) diagnosed with GA1 during a 28-year period from 1988 to 2018 (Table 1). Mean age at follow-up was 11.9 ± 9.0 years (range six months to 40 years). In all, 24 (21%) GA1 patients had significant orthopaedic pathology on physical examination. The most common problems were severe scoliosis (n = 14) and abnormalities of the hip joint, including dislocation (n = eight patients/15 hips), subluxation (n = two patients/three hips), windswept deformity (n = 2), and dysplasia (n = 1) (Table 2). Although 48% of the patients in this cohort were GMFCS I (normal motor function) and 22% had milder motor problems (GMFCS II or III), primarily patients with severe impairments (GMFCS IV-V) developed significant orthopaedic deformities requiring surgical treatment (Table 1).

A total of 35 surgeries were performed in 17 (71%) of 24 patients with musculoskeletal pathology. The mean age at first operation was 13.8 ± 4.8 (range six months to 25 years) and mean postoperative follow-up was 4.7

JOURNAL OF CHILDREN'S ORTHOPAEDICS

Table 1 Demographic characteristics of overall cohort of patients with glutaric aciduria type 1 (GA1)

Medical comorbidities		Total number of patients with orthopaedic aspects (n = 24)	Total number of patients with GA1 (n = 114)
Normal muscle tone, n (%)		0 (*0*)	51 (*45*)
Hypotonic type, n (%)		1 (*4*)	15 (*13*)
Dystonic type, n (%)		15 (*63*)	27 (*21*)
Mixed type, n (%)		8 (*33*)	31 (*27*)
Pattern type (%)			
	Diplegic, n	0 (*0*)	6 (*5*)
	Hemiplegic, n	2 (*8*)	3 (*3*)
	Quadriplegic, n	22 (*92*)	37 (*32*)
Type of GMFCS, n (%)			
I		0 (*0*)	55 (*48*)
II		1 (*4*)	19 (*17*)
III		5 (*21*)	6 (*5*)
IV		3 (*13*)	11 (*10*)
V		15 (*63*)	23 (*20*)
Seizure history, n (%)		9 (*38*)	19 (*17*)
Feeding tube, n (%)		16 (*67*)	27 (*24*)

GMFCS, Gross Motor Function Classification System

Table 2 Case list of patients with significant musculoskeletal pathology

Study ID	Sex	Type of CP	Seizure	GMFCS	Feeding tube	Orthopaedic diagnosis	Operation	First operation age (years)	Last follow-up age (years)	Follow-up (years)
1	M	Mix, quadriplegic	Yes	3	Yes	Windswept hips	Yes	13	15	2.1
2	M	Spastic, quadriplegic	No	5	Yes	Bilateral hip subluxation and severe scoliosis	Yes	11	20	8.4
3	F	Mix, quadriplegic	Yes	5	Yes	Severe spasticity	Yes	8	14	5.7
4	F	Spastic, quadriplegic	No	4	Yes	Severe scoliosis	Yes	13	18	5.5
5	F	Mix, quadriplegic	No	5	Yes	Right hip dislocation, severe neuromuscular kyphoscoliosis and pelvic obliquity	Yes	10	20	9.2
6	F	Mix, quadriplegic	Yes	4	Yes	Severe scoliosis	Yes	17	19	1.8
7	F	Mix, quadriplegic	No	3	Yes	Windswept hips	Yes	14	16	1.9
8	F	Hypotonic	Yes	3	Yes	Pes plano valgus	No	-	7	-
9	M	Mix, quadriplegic	No	3	No	Crouched gait and bilateral genu varum	No	-	10	-
10	M	Spastic, diplegic	No	4	No	Right hip dysplasia and bilateral pes plano valgus	Yes	11	21	10.2
11	F	Dystonic	No	2	No	Right patella dislocation	No	-	9	-
12	M	Mix	No	5	Yes	Bilateral hip dislocation and severe scoliosis	Yes	16	17	1
13	F	Dystonic, quadriplegic	No	5	Yes	Bilateral hip dislocation and severe scoliosis	No	-	24	-
14	F	Spastic, quadriplegic	No	5	No	Severe scoliosis	Yes	11	20	8.3
15	M	Dystonic, quadriplegic	Yes	5	Yes	Severe scoliosis	Yes	22	30	7.8
16	M	Spastic, quadriplegic	Yes	5	Yes	Severe scoliosis	Yes	10	12	2.3
17	F	Spastic, quadriplegic	No	5	Yes	Bilateral hip dislocation	No	-	11	-
18	F	Dystonic, quadriplegic	No	5	No	Severe scoliosis	Yes	17	34	7.6
19	F	Dystonic, quadriplegic	Yes	5	Yes	Bilateral hip dislocation and severe scoliosis	Yes	11	12	1.1
20	M	Dystonic, quadriplegic	Yes	5	Yes	Bilateral hip dislocation and severe scoliosis	Yes	12	14	1.6
21	M	Spastic, quadriplegic	No	5	Yes	Severe scoliosis	No	-	14	-
22	F	Dystonic, quadriplegic	No	5	No	Bilateral hip dislocation and severe scoliosis	Yes	17	17	1.7
23	M	Mix, diplegic	No	3	No	Left hip subluxation	No	-	23	-
24	F	Spastic, quadriplegic	Yes	5	No	Bilateral hip dislocation and scoliosis	No	-	26	-

CP, cerebral palsy; GMFCS, Gross Motor Function Classification System

± 3.4 years (range six months to 10 years). Nine (38%) individuals required multiple procedures (two surgeries (n = 3) three surgeries (n = 4), five surgeries (n = 2)) and the mean interval between the first and second operation was 3.4 ± 1.4 years (range nine months to five years). The most common primary surgical procedures were PSF for severe scoliosis (n = 11) and one-stage VDRO and/or pelvic osteotomy for subluxation or dislocation of the hip (n = eight patients/14 hips) (Table 3). Three patients experienced significant postoperative complications: blade plate prominence caused skin irritation requiring removal in three hips of two patients and one individual (patient 5, Table 3) underwent revision VDRO due to recurrent hip dislocation.

Table 3 List of orthopaedic procedures performed

Study ID	Operation 1	Operation 2	Operation 3	Operation 4	Operation 5
1	Bilateral VDRO and left AL and left PIPO				
2	1-bilateral AD and gracilis lengthening with anterior branch obturator nerve neurectomies 2-bilateral VDRO and medial inferior capsular release 3-bilateral PIPO	Botox injections into the paraspinal muscles	1-removal of bilateral hip plate 2-bilateral DH lengthening 3-bilateral Botox injection to the paraspinal muscles		
3	ITB pump	1-ITB pump replacement 2-bilateral AL and gracilis lengthening	ITB pump revision		
4	Anterior spinal release from T9 to L3 and a posterior PSF	1-bilateral AL and gracilis lengthening 2-release of the proximal triceps and teres minor from right shoulder 3-Botox injection to the cervical spine			
5	1-bilateral AL and gracilis lengthening with obturator neurectomy 2-right adductor brevis and pectineus lengthening 3-right IP lengthening with medial capsular release 4-right VDRO and PIPO 5-left DH lengthening	1-anterior spinal release 2-T10 thoracotomy and rib resection 3-thoracotomy tube 4-PSF 5-posterior spinal osteotomies, T6-T10 and T12-L5 6-application and removal of cranial tongs for intraoperative positioning and traction	1-Botox injections into the left IP muscle and hamstring muscles 2-ITB pump	1-left hip tensor fascia lata and sartorius lengthening 2-open hip flexor lengthening including IP, iliacus, and rectus femoris muscles 3-AL lengthening 4-hip capsulotomy with anterior capsule lengthening 5-gluteus medius and hip abductor lengthening 6-Botox injections into various hip flexor muscles and gluteus muscles	1-ITP pump replacement 2-removal of the right hip plate 3-right secondary VDRO
6	1-PSF 2-left FCU tenotomy				
7	Bilateral VDRO, open right hip AL and gracilis lengthening, right PIPO	ITB pump	1-PSF 2-removal of bilateral hip plates		
9	1-right AL and gracilis lengthening with obturator neurectomy 2-right adductor brevis and pectineus lengthening 3-right IP lengthening with medial capsular release 4-right VDRO and open reduction 5-right PIPO 6-left AL and gracilis lengthening 7-left DH lengthening				
10	1-right AL and gracilis lengthening 2-right IP recession	1-left VDRO 2-bilateral tibial derotational osteotomies with varus correction 3-bilateral lateral calcaneal column lengthening 4-bilateral DH lengthening and Botox injections 5-right gastrocnemius recession 6-bilateral navicular osteotomies with medial plication of the talonavicular joints and advancement of the PTT	Right tibialis anterior Botox injections	1-right AL and gracilis lengthening 2-right DH lengthening 3-Botox injections into the right anterior tibialis and rectus femoris	1-right knee arthroscopy with lateral release, patellar chondroplasty, and MPFL reconstruction 2-right knee fractional lengthening of the iliotibial band 3-Botox injections into the rectus and vastus lateralis muscles
12	1-proximal femoral head resection 2-PSF				
14	AL release				
15	PSF				
16	PSF				
18	PSF				
19	1-bilateral VDRO and PIPO 2-right AL and gracilis lengthening	ITB pump	PSF		
20	Bilateral VDRO and AL lengthening	PSF			
22	Bilateral VDRO and AL lengthening	PSF			

AD, adductor; AL, adductor longus; DH, distal hamstring; FCU, flexor carpi ulnaris; IP, iliopsoas; ITB, intrathecal baclofen; MPFL, medial patellofemoral ligament; PIPO, peri-iliac pelvic osteotomy; PSF, posterior spinal fusion; PTT, posterior tibial tendon; VDRO, varus derotation osteotomy
Note. Case numbers in Table 3 correlate to the same case in Table 2, case numbers missing in Table 3 are those who had no surgery.

An intrathecal baclofen (ITB) pump was implanted in four patients to palliate severe, medically intractable dystonia. The catheter tip was positioned at the low cervical-high thoracic spinal cord level and average ITB usage time was 4.1 years (range seven months to ten years). The ITB pump was replaced three times in two patients, twice due to expired battery life and once due to dysfunction. (Table 3). Four patients had one or more botulinum toxin injections in paraspinal (n = 2) or lower extremity (n = 2) muscles for transient relief of focal dystonia.

Discussion

When the diagnosis of GA1 is made after an acute encephalopathic crisis, irreversible degeneration of striatal neurons leaves patients with a dystonic movement disorder irrespective of *GCDH* genotype.[9,22,28-32] This pattern of motor disability is consistent across GA1 cohorts, as reported in two large natural history studies from 2003 (n = 77)[22] and 2006 (n = 279),[33] which document incident brain injury rates of 77% and 66%, respectively, among a genetically diverse group of GA1 patients. In the modern era, fewer than 10% of GA1 patients suffer neurological lesions,[8,16,33,34] attributable to the combined benefits of newborn screening,[16,18] timely inpatient neuroprotective therapies[14,35,36] and more widespread use of lysine-free, arginine-enriched medical formulas.[19,20] However, disability rates remain high among GA1 patients born in nations that do not screen newborns for elevated C5DC.[9,24,37]

We found a relatively high incidence of neurological injury among individuals in our cohort (Table 1), most of whom were *GCDH* c.1262C>T homozygotes born prior to the advent of statewide newborn screening (ca.1994).[38,39] Only 36% of our patients had normal motor function (GMFCS I) whereas 40% had severe functional motor disability (GMFCS III–V). Among this latter group, 62% with GMFCS V developed major musculoskeletal complications[40,41] (Table 1). The outcome of the scoliosis management with spinal fusion allowed patients to improve seating alignment with no recorded reoperations or postoperative infections. This is consistent with our outcomes of a much larger cohort of children with cerebral palsy.[42,43] The outcomes of treating dysplastic and dislocated hips in which one revision for recurrent dislocation and three hardware removals were required are also similar to our outcomes in children with cerebral palsy.[44,27] All treated hips were located and pain free at last follow-up. Based on this experience, the outcome of hip and spine treatment in children with GA1 should produce similar results to the treatment methods used for children with cerebral palsy. However, since the predominant motor pattern is dystonia, there were fewer significant contractures or spastic deformities requiring surgical management typically seen in patients with spastic cerebral palsy.

Because GA1 manifests clinically as a static rather than progressive encephalopathy, the orthopaedic approach is similar to that for cerebral palsy, but with a critical distinction: surgical planning in patients with GA1 should include a detailed anticipatory strategy to support intermediary metabolism during fasting and surgical stress.[45] We recommend that elective procedures be planned in consultation with a metabolic specialist, who can cooperate with an anesthesiologist to develop a perioperative treatment protocol that safeguards against metabolic complications[45-48] (Table 4).

For any patient with severe dystonia, medical providers should also recognize risks for pulmonary aspiration, post-extubation laryngeal dystonia and adverse reactions to paralytic agents.[48] During the postoperative period, effective analgesia is especially important to prevent a self-reinforcing cycle of pain, anxiety and worsening dystonia that can escalate to life-threatening status dystonicus.[25,39] High intravenous doses of analgesic and anxiolytic medications are typically required to control such 'dystonic storms'. Recognizing the risk for this and other serious complications, we prefer to correct all musculoskeletal deformities in a single surgical session.

The literature includes reports of botulinum toxin injection and ITB for treatment of the dystonia associated with GA1.[31,49] In four patients with focal or generalized dystonia, Burlina and colleagues found that botulinum toxin was particularly beneficial for the upper extremities but had minimal impact on craniocervical dystonia.[49] Kyllerman et al[31] used ITB to successfully treat two patients with

Table 4 Management guidelines for elective surgery with glutaric acidemia type 1

Preoperative precautions	2 to 3 hours intravenous infusion of dextrose 10% normal saline (D10/NS) prior to general anesthesia at a rate 1 to 1.5 times maintenance fluid requirement
During surgery	Continue to hydrate with D10/NS – DO NOT USE RINGER'S LACTATE
Postoperative management	1. Maintain D10/NS infusion until enteral or gastrostomy tube feeding is well established. Once feeding is well established, decrease D10/NS rate to half rate for several hours before discontinuing. Expect that the patient will be in the hospital longer than a normal individual with the same procedure. 2. Administer intravenous L-carnitine starting with the first dose prior to anesthesia and continue every eight hours until hospital discharge. Dosage: children < 20 kg – 100 mg/kg/dose, children over 20 kg – 2000 mg/dose. 3. If total parenteral nutrition is necessary, total daily 'intact' protein intake should be 0.5 to 1.0 g/kg/day. (Intralipids and lipid-based general anesthetics can be used safely in children with glutaric acidemia type 1.) 4. We do NOT recommend the use of benzodiazepine reversal agents for patients who are chronically exposed to high doses of benzodiazepines. Rather, if patients require postoperative doses of anxiolytics and analgesics that suppress respiratory drive, we recommend assisted forms of ventilation and oxygenation until recovery of spontaneous respiration to avoid dystonic crisis.

severe dystonia, and found that botulinum toxin injection of the cervical paraspinal and lower extremity muscles controlled focal dystonia following PSF. In four patients from our cohort, ITB provided relatively effective palliation for intractable dystonia but required close follow-up for pump refills and management of mechanical problems.

In conclusion, severe dystonia and its attendant musculoskeletal complications are common among GA1 patients who develop static stiatal lesions during the first few years of life. Encephalopathic crisis strikes fewer than 10% of affected children in the modern era of newborn screening and appropriate prospective care,[8,9] but this outcome still remains tragically high in resource-limited settings.[24,37] Among neurologically injured patients with GA1, scoliosis and hip dislocation are the predominant indications for orthopaedic intervention, and all elective surgeries should be executed with a perioperative strategy to minimize metabolic stress (Table 4) and a postoperative plan to control the cycle of pain and anxiety that can culminate in life-threatening status dystonicus.[25,39]

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None declared.

AUTHOR CONTRIBUTIONS
AI: Substantial contributions to the conception or design of the work; Acquisition, analysis or interpretation of data for the work; Drafting of the work; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
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