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Five-parameter evaluation of dysphagia: A novel prognostic scale for assessing neurological decline in Gaucher disease type 2

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ABSTRACT

Background: Gaucher disease type 2 (GD2) is defined by acute neurological decline, failure to thrive, and early demise. Currently, there is no clear standard for evaluating, staging, and counseling regarding neurological decline in GD2. Due to the high prevalence of progressive dysphagia secondary to acute neurological involvement, we aimed to identify key components of swallow function which could serve as markers of disease progression in GD2.

Methods: A post-hoc analysis of modified barium swallow studies was performed. Six parameters of swallowing were scored in a retrospective chart review of eleven infants with GD2. Mixed effects regression, principal component analysis (PCA), and a transition analysis were used to evaluate swallow function and model disease progression.

Results: All patients exhibited impaired swallow function. There was no association between any of the swallow parameters and age, indicating non-linear disease progression. PCA and transition analysis identified five parameters capturing multiple dimensions of swallowing which defined two distinct disease states.

Conclusion: A five-parameter swallow evaluation was sufficient to identify distinct states of GD2 and model prospective outcomes. This multi-dimensional evaluation could be a useful efficacy parameter for future therapeutic trials in GD2 and other neurodegenerative disorders of infancy.

1. Introduction

The autosomal recessive lysosomal storage disorder Gaucher disease (GD) is caused by deficiency of the enzyme glucocerebrosidase (EC 3.2.1.45) due to mutations in *GBA1*. While manifestations span a broad continuum, GD has classically been divided into three types based on the presence and severity of neurological involvement: non-neuronopathic type 1 (GD1), acute neuronopathic type 2 (GD2), and chronic neuronopathic type 3 (GD3) [1–3]. Although enzyme replacement therapy is highly effective in treating the visceral symptoms of GD, it does not cross the blood-brain barrier. There is currently no effective treatment for the neurological manifestations of GD2 and GD3, though different strategies are under consideration [1]. GD2 has a severe and progressive disease course, with neurological decline and death within the early years of life [1]. Findings may include hydrops fetalis, congenital ichthyosis, massive organomegaly, thrombocytopenia, anemia, and early failure to thrive [4,5]. Additionally, marked deterioration in swallow function is a common finding in patients with GD2 [4].

Swallowing is a complex neurological function involving a specific sequence of sucking, swallowing, and breathing, that is anatomically divided into three phases: oral phase, pharyngeal phase, and esophageal phase [6]. Oral sensorimotor function, swallowing, and respiration are controlled by brainstem and cerebral pathways, which start to develop during the fetal period and continue after birth. Normal swallow function plays a vital role in all stages of growth and maturation. In utero, fetal swallowing is important for amniotic fluid balance, as well as proper gastrointestinal development [7]. During the neonatal period and infancy, intact swallow function allows for adequate nutritional intake, and avoidance of aspiration [7]. Difficulty swallowing

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Table 1
Six swallow parameters utilized to score the results of the modified barium swallow.

	Aspiration and/or laryngeal penetration (ALP)	ASHA NOMS	Oral phase dysphagia (OP)	Head extension (HE)	Dyssynchronization of suckle, swallow and breathing (DS)	Vocal or speech development
0			1:1 suck to swallow	No head extension	No dyssynchronization of suckle, swallowing, breathing	
1	Profound: Aspiration of > 50% of intake, no cough/cough inconsistent or ineffective to expectorate materials	Swallow not safe by mouth. All nutrition and hydration by non-oral means	> 2:1 suck to swallow	Head extension noted	Dyssynchronization of suckle, swallow and breathing (disorder in timing of the bolus flow through the pharynx) noted	Vocalization
2	Severe: Severe aspiration of 10–15% of intake with use of compensations and/or intermittent penetration, cough intermittently on patient's own volition	Swallow not safe by mouth, may have some oral intake if appropriately cued	No suck or swallow			Babbling
3	Moderate: Contrast enters the airway consistently on one or more textures	Alternative method of feeding required, < 50% nutrition and hydration by mouth, and/or swallow safe with consistent compensatory strategies and/or no solid foods				True words
4	Minimal: Minimal risk with intermittent laryngeal penetration and retrograde excursion on one or more textures	Swallowing safe with moderate cues to use compensatory strategies, and/or moderate diet restrictions, and/or requires tube feeding and/or oral supplements				Phrases
5	Normal: No obvious aspiration risk or penetration	Swallowing safe with minimal diet restriction, occasionally requires compensatory strategies. All nutrition and hydration needs met by mouth				
6		Swallowing safe, individual eats and drinks independently, rarely requires minimal cueing. May need to avoid specific food items				
7		Able to eat independently. Swallowing safe and efficient for all consistencies				

(dysphagia) can therefore represent a significant health risk and may lead to aspiration pneumonia, inadequate feeding, and early failure to thrive, among other issues [1,8]. However, impaired swallow function is not always evident on clinical exam, as silent aspiration can be common [9]. If dysphagia is at all suspected, additional tools should be employed to assess swallow efficacy [6,10]. A modified barium swallow (MBS) is the gold standard as an initial diagnostic tool for patients with suspected neurogenic oropharyngeal dysphagia. The MBS utilizes videofluoroscopy and radiography to inspect the movement of structures involved in swallow, and monitors the progression of a variety of viscosities and volumes of barium-laced foods through the oral cavity and hypopharynx [11]. This provides valuable information about the degree of dysphagia, an indication of neurological dysfunction in patients with neurodegenerative disease, including GD2.

Analyzing the results of the MBS based on quantitative scales provides a means to objectively score and monitor swallow impairment, enhancing our understanding of early neurological involvement in patients with GD2 [12,13]. However, in practice, these scales are often replaced by more informal evaluations of swallow [6]. In order to provide consistent assessment of dysphagia across clinics and clinical trials, a simple and effective quantitative tool is necessary. We explored functional tools to assess swallow impairment that may be used to guide patient management and serve as an efficacy parameter in future therapeutic trials of brain-penetrant therapies. The utility of these tools as a combined paradigm for assessment are demonstrated through analysis of MBS results gathered from a comprehensive retrospective chart review of eleven patients with GD2.

2. Methods

2.1. Study population

Twenty-two patients with GD2 were enrolled by informed parental consent in a natural history protocol (NCT00001215) approved by the National Human Genome Research Institute Institutional Review Board. Patients underwent a comprehensive evaluation, including physical and neurological examination, abdominal and bone imaging, electroencephalography (EEG) and brainstem auditory evoked response (BAER), neuro-ophthalmological evaluations, and swallow studies. Evaluations varied based on the clinical indication, and not all evaluations were performed at each visit. Fourteen swallow studies were performed on eleven patients, two with follow-up visits. These eleven patients are the focus of this study.

2.2. Molecular analyses

Biological samples were collected for both clinical and research analyses. Genotyping was performed by sequencing all exons of *GBA1*, as previously described [14].

2.3. Swallow studies

Clinical assessments of oral pharyngeal swallow function consisted of oral administration of liquid and/or pureed food, as appropriate, via the patients' utensils and bottles. Twelve of the fourteen studies were performed by a single speech-language pathologist (B.S.) who assessed and evaluated the clinical swallow. The two remaining studies were performed at outside institutions, prior to initial presentation to the National Institutes of Health (NIH) Clinical Center; these results were obtained through outside medical records. Decision to perform MBS was based on safety, and the presence and identification of key swallowing attributes, such as coughing while eating or drinking, stridor with breathing, choking episodes, wet/gurgling vocal quality during eating or drinking, poor oral intake, history of recurrent chest illness, and a known history of aspiration.

2.4. Parameters

MBS results from medical records were scored by the speech-language pathologist of this study, using six parameters to assess different components of swallow: aspiration and/or laryngeal penetration, ability to eat, oral phase dysphagia, head extension, dyssynchronization of suck, swallow, and breathing (dyssynchronization), and vocal/speech development (Table 1). Aspiration and/or laryngeal penetration was assessed using a 5-point scale developed by speech-language pathologists (SLPs) at the NIH for internal use. Inspired by the Rosenbek Penetration-Aspiration Scale (PAS), this scale quantifies the degree and frequency of contrast entry into the airway, with 5 representing no obvious risk of aspiration or laryngeal penetration [13]. While the PAS primarily addresses the depth at which intake is aspirated into the airway and the amount of material expelled, the NIH aspiration/penetration scale provides a more comprehensive picture of the entire MBS by also including aspects like risk of aspiration with various textures and viscosities of intake. Ability to eat was assessed using the American Speech-Language-Hearing Association National Outcome Measurement System (ASHA NOMS) swallowing level scale, which measures whether swallowing is safe, if an alternative method of feeding is required, and whether nutritional needs can be met with current swallow function. For this scale, 7 indicates that the ability to eat is not limited by the patient's swallow [15]. Findings of oral phase dysphagia, head extension, dyssynchronization, and vocal/speech development, all commonly reported in MBS assessments, were quantified by the SLP. Oral phase dysphagia assesses the volitional aspect of swallowing, whereas dyssynchronization involves the start of the pharyngeal phase of swallow, which is involuntary. Oral phase dysphagia was documented using a 3-point scale, with 0 being a normal suck to swallow ratio, 1, an abnormal ratio, and 2, no suck/pharyngeal swallow. Dyssynchronization is defined as a disorder in the timing of the bolus flow through the pharynx. It was evaluated by clinical and videofluoroscopic evaluation and was scored as a binary 0/1, for absence/presence of dyssynchronization [16,17]. Head extension is commonly seen in patients with dysphagia as a compensatory measure that aids in the oral phase of swallowing, when the swallow itself is inadequate for passage of a bolus into the esophagus [4,18]. Head extension was also scored as a binary 0/1, for absence/presence of this finding. A 4-point vocal/speech development scale was created to quantify different levels of vocal/speech abilities, with 1 being vocalization and 4, the ability to produce phrases.

2.5. Complete neurological profiles

Pertinent findings related to the patients' neurological status were extracted through thorough review of the electronic medical records. Demographic data, patient presentation, attainment of developmental milestones, and other relevant medical information are reported in Tables 2, 3, and 4.

2.6. Statistical analysis

All statistical analyses were performed using R (Version 3.3.3) in RStudio (Version 1.0.136) [19,20]. To evaluate the relationship between age and swallow deterioration, a mixed effects regression, with subject ID as a random intercept effect, was performed using the *lme4* package [21,22]. 95% Confidence Intervals (CIs), obtained via the *lme4* basic bootstrap method on 1000 iterations, were used to assess significance of associations between age and each swallow parameter [21,24]. Significance was defined as any CI which excluded zero. A *p*-value for significance of the overall model was obtained by a likelihood ratio test compared to a null model (intercept and random effect only) [22]. Principal component analysis (PCA) was performed using the *FactoMineR* package to evaluate whether the six parameters captured unique dimensions of swallow function [25–27]. Scores were

Table 2
Summary of demographics and presentations of each patient.

Subject ID	Ages at evaluations	Sex	Genotype	Race	Age at onset of reported symptoms	Age at diagnosis	Presenting symptoms	Age of death
A	7m 3w	F	W184R/D409H	Caucasian	Birth	4m	Hyperbilirubinemia, thrombocytopenia, splenomegaly	3y
B	14 = m	F	T323I/L444P	Caucasian	4m	6m	Aspiration pneumonia, splenomegaly, thrombocytopenia, anemia	ND
C	9m 1w	M	RecTL/L444P	Caucasian	4m	10m	Choking, upper respiratory infection, organomegaly	ND
D	8m 3w	F	Y313H/L444P	Caucasian	4m	7m	GERD, back arching and eyes rolling back, FTT	10m
E	21m, 4y	F	L444P/L444P	African American	12m	14m	Organomegaly, increased fatigue, developmental delay	ND
F	4w, 4.5m	M	L444P/Rec*Ncil*	African American	4.5m	4w, diagnosed by genetic testing	Stiffness, FTT	8m
G	11m, 11.5m, 22m, 1y	F	c.84insG/D409H	Caucasian	2d	5.5m	Splenomegaly, thrombocytopenia, hyperbilirubinemia	3y 4m
H	13m, 16m	F	D409H/Rec*Ncil*	Caucasian	7m	10m	FTT, developmental delay, splenomegaly	ND
I	6w, 3m 2w	F	L444P/Rec*Ncil*	Caucasian	Birth	At birth, diagnosed by NBS	Choking, feeding difficulty	N/A
J	8m	F	RecTL/L444P	Caucasian	4m	6m	Splenomegaly, FTT, feeding difficulty, GERD, irritability	ND
K	4m	F	L444P/IVS2 + 1	Caucasian	2m	4m	Neonatal alloimmune thrombocytopenia, feeding difficulty, splenomegaly	N/A

Abbreviations: m, months; w, weeks; y, years; PNA, pneumonia; FTT, failure to thrive; GERD, gastroesophageal reflux disease; NBS, newborn screening; ND, not documented; N/A, not applicable.

Table 3
Other pertinent findings contributing to complete neurological profiles.

		Gastrointestinal			Neurological					Ears/Nose/Throat		Pulmonary	
Subject ID	Age at evaluation	HSM	Gastrostomy tube (G tube)	Subjective	Objective	Seizures (age onset)	EEG	BAER	Pertinent developmental findings (age of onset)	Choking episodes	Other pertinent findings	Pertinent findings (age)	Tracheostomy
A	7m	Y	N at this visit, Y at 11m	Formula and supplemental stage 1 food	Central and peripheral hypertonia, OA, hyperreflexia, slow saccades	Y	Normal	Abnormal	Monosyllable sounds, no words, does not sit or pull to stand, transfers objects between hands	ND	Stridor and noisy breathing while sleeping	Hazy parenchymal lung densities on CXR	Y
B	14m	Y	Y	Colic, GERD	B/l strabismus, central hypertonia, peripheral hypotonia, myoclonus, supranuclear gaze palsy, opisthotonus tendency, slow saccades	Y	Normal	Abnormal	Babbled prior to tracheostomy, follows some commands, head control (2.5m), sitting (5m), thumb-finger opposition	ND	Tracheomalacia	Frequent lower respiratory tract infections (4m), aspiration PNA (3m), asthma, diffuse perihilar infiltrates on CXR	Y
C	9m 1w	Y	N	Difficulty latching onto breast or bottle	OA, b/l strabismus, slow saccades	Y (6m)	Abnormal	Abnormal	Babbles, brings bottle to mouth with assistance, regression of milestones- no head control, no longer rolls over or sits assisted	Y	Noisy breathing while sleeping	Increased interstitial marking on CXR	N
D	7m	Y	N at this visit, Y later secondary to FTT	Stopped gaining weight at 4m, GERD	OA, b/l intermittent convergence strabismus, head thrust, peripheral hypotonia, central hypertonia, brisk DTRs, slow saccades	N	Normal	Abnormal	No babble, difficulty transferring objects between hands, regression of milestones- now does not roll over or sit	ND	Stridor	Lung hypoinflation on CXR	N
E	21m	Y	N	Difficulty swallowing solid food	B/l esotropia, broad based gait with some instability, supranuclear gaze palsy, hyperreflexia lower extremities, tight b/l Achilles tendon	N	ND	Normal	Mild speech delay, follows commands, mild motor delay, sits (17m), walks (20m), drinks from bottle by herself	Y	Stridor	Infiltrates in right upper/lower lobe; patchy ground glass appearance to lower lobes on CXR	N
E	4y	Y	N	Difficulty swallowing, oral aversion	Large angle infantile esotropia, supranuclear gaze palsy, unsteady gait, slow saccades	Y (2y)	Abnormal	ND	25-word vocabulary, 6-word sentences, follows 1- step commands, walks (20m), walks up and down stairs (3.5y), drinks from cup (2.5y), scribbles with pen, stacks 5 blocks	Y	ND	ND	N
F	4w	Y	N	ND	ND	ND	ND	ND	ND	ND	ND	ND	N
F	4.5m	Y	N, recommended proactively	ND	Generalized hypertonia, supranuclear palsy, OA	Y (2y)	ND	ND	ND	ND	Stridor	ND	N
G	11m	Y	N, Y at 1y 10m	Formula via Avent variable flow nipple, poor feeding with spoon, gags when food touches tongue	BLE hypotonia	N	ND	ND	Cognitive function of a 10m old, motor delay (at 6m level when 10m)	ND	ND	ND	N at this visit, Y later
G	11.5m	Y	N, Y at 1y 10m	Stage 2 food	Supranuclear gaze palsy, OA, increased startle reflex, absent blink	N	Normal	Normal	Babbles, does not sit independently, transfers objects between hands, 3 finger grasp	ND	Stridor	Hazy infiltrates on CXR	N at this visit, Y later

(*continued on next page*)

Table 3 (*continued*)

		Gastrointestinal			Neurological					Ears/Nose/Throat		Pulmonary	
Subject ID	Age at evaluation	HSM	Gastrostomy tube (G tube)	Subjective	Objective	Seizures (age onset)	EEG	BAER	Pertinent developmental findings (age of onset)	Choking episodes	Other pertinent findings	Pertinent findings (age)	Tracheostomy
					reflex, head thrust, slow saccades								
G	22m	Y	N, Y at 1y 10m	Oral aversion	Central hypertonia, peripheral hypotonia, R foot clonus, right hand tremor, OA, absent blink reflex	N	Normal	Normal	Babbles, sits (16m), does not walk but pulls to stand, drinks from cup	ND	Stridor, breath holding spells with perioral cyanosis	ND	N at this visit, Y later
G	24m	Y	Y	Drooling	Head extension, no tremor, supranuclear gaze palsy	N	ND	ND	Babbles, sits with difficulty getting into sitting position, transfers objects between hands, immature pincer grasp	Y	Stridor due to laryngomalacia diagnosed 3m of age	Interstitial lung disease on CXR, history of recurrent PNA	N at this visit, Y later
H	13m	Y	N	Stage 2 food, gags with stage 3 food	Poor head control, BLE scissoring, horizontal ophthalmoplegia, OA, doll's eye, slow saccades	N	Abnormal	ND	Babbles, briefly sits, pulls herself up, reaches for objects	ND	Anterior carriage of tongue	Diffuse b/l infiltrates on CXR	N
H	16m	Y	N	ND	Does not turn to localization of sound, mild wide esotropia, hypertonia BLE and b/l ankles, ataxia, OA, slow saccades	N	ND	Abnormal	Pulls up with support, toe walking, unstable gait with support	ND	Anterior carriage of tongue	Diffuse b/l parenchymal infiltrates on CXR	N
I	6w	Y	N	Emesis, GERD, requires Haberman feeder to coordinate suckle and swallow	Central and peripheral hypotonia, diminished DTRs, severe sensorineural hearing loss b/l	N	Normal	Abnormal	Normal head support (1m), social smile, visually tracks objects	ND	Tracheomalacia, stridor, wet airway sounds	ND	N
I	3m 2w	Y	Y	GERD, erythromycin for decreased gastric motility, requires Haberman feeder to coordinate suckle and swallow, nightly G tube feeds	Hypertonia in all extremities, some degree of optic atrophy, slow lateral eye movements, some degree of hearing loss, apneic episodes during sleep	N	ND	ND	Rolls from back to sides, holds objects in hands but does not reach for them	Y (rare)	ND	Patchy lung infiltrates	N
J	7m	Y	N	Emesis, fussiness, GERD	Irritability, L eye Horner's syndrome, strabismus, no saccades, opisthotonus, b/l lower extremity scissoring, decreased eye blink rate	N	ND	ND	Social smile, reaches for objects	Y	Frequent coughing	ND	N
K	4m	Y	N	GERD, irritability secondary to umbilical hernia or GERD	Hypertonia in all extremities, b/l esotropia, strabismus, minimal blinking	N	ND	ND	Social smile, makes screaming noises, does not actively reach for objects, does not roll over	Y	Noisy breathing, wet airway sounds, breath holding	ND	N

Abbreviations: Y, yes; N, no; N/A, not applicable; ND, not documented in patient charts; m, months; w, weeks; y, years; BLE, bilateral lower extremities; b/l, bilateral; HSM, hepatosplenomegaly; OA, oculomotor apraxia; CXR, chest x-ray; PNA, pneumonia; GERD, gastroesophageal reflux disease; R, right; L, left; DTRs, deep tendon reflexes.

Table 4
Summary of the scored results of the modified barium swallow and vocal/speech assessment for each participant.

Subject ID	Age at evaluation	Aspirational laryngeal penetration	ASHA NOMS	Oral phase swallowing	Head extension	Dyssynchronization of suck, swallow, breathing	Vocal/speech development
A	7m	5	7	0	Yes	No	1
B	14m	4	3	1	Yes	Yes	2
C	9m 1w	4	6	1	Yes	Yes	ND
D	7m	4	2	2	No	No	1
E	21m	5	3	1	No	No	3
F	4.5m	5	7	1	Yes	No	ND
G	11m	4	6	1	No	No	ND
G	11.5m	4	6	1	Yes	Yes	2
G	22m	4	6	1	Yes	Yes	2
H	16m	4	6	1	No	No	2
I	6w	4	6	0	Yes	Yes	1
I	3m 2w	5	5	1	Yes	Yes	ND
J	7m	3	4	1	Yes	Yes	1
K	4m	4	2	1	Yes	Yes	1

Abbreviations: ASHA NOMS, American Speech-Langugage-Hearing Association National Outcome Measurement System swallowing level scale; ND, not documented in patient charts; m, months; w, weeks.

normalized between 0 and 1 prior to performing PCA, to account for unequal variances. To determine whether the swallow parameters could be used to stage swallow deterioration and disease progression, a transition analysis, using a Hidden Markov Model, was performed with the *depmixS4* package [28].

3. Results

3.1. Sample demographics and initial presentation

Eleven children, two males and nine females, with GD2 were evaluated by MBS (Table 2). The age at time of evaluation ranged from 6 weeks to 4 years. Patients presented with a wide continuum of signs and symptoms. The age of onset of reported symptoms ranged from birth to 12 months, with a majority of patients exhibiting symptoms before 5 months. Two patients were identified by genetic screening or testing, while the nine others had an average of 3.3 months between symptom onset and the diagnosis of GD2. Mutation analysis revealed multiple genotypes among the patients; RecTL/L444P was the only genotype found in more than one patient.

3.2. Systemic manifestations

All patients exhibited hepatosplenomegaly. Six patients had a reported history of choking episodes, and a majority of the patients had symptoms of stridor and/or tracheomalacia. Five patients had gastrostomy tubes (G tubes) placed. Pulmonary findings, such as episodes of pneumonia, recurrent pneumonias, or lung infiltrates on chest x-ray, were reported in eight patients. Three patients ultimately required tracheostomy (Table 3).

3.3. Neurological profiles

There was remarkable variability in neurological involvement. Five patients had a history of seizures, three had abnormal EEG findings, and six had abnormal BAER findings. Five had early regression of developmental milestones. Objective and descriptive findings for each patient and visit are listed in Table 3.

3.4. Longitudinal evaluations

Longitudinal results were available for patients G and I, providing valuable documentation of disease progression in GD2 (Tables 2–4). Patient G was evaluated four times, at 11, 11.5, 12, and 22 months. Swallow studies were performed at three visits. At the initial visit, patient G presented with oral phase dysphagia, as reflected by an abnormal suck to swallow ratio. Over subsequent visits, there was progression to head extension and dyssynchronization, as well as oral aversion and choking episodes with multiple episodes of pneumonia. Neurological function worsened with regression of developmental milestones. Intervention with G tube placement and tracheostomy were performed later.

Patient I was evaluated at 6 weeks and 3 months. Initially, there was minimal aspiration risk, mildly impaired ability to eat, and dyssynchronization. A G tube was placed at age 2 months. By 3 months, ability to eat and neurological status had deteriorated further, and chest x-ray revealed patchy lung infiltrates.

3.5. Swallow study results

Fourteen MBS studies were successfully completed on eleven children. Swallow dysfunction was identified in all patients, with oral phase dysphagia seen in ten patients, pharyngeal dysphagia in seven patients, and aspiration/penetration in eight patients. Oral phase dysphagia manifests as food pooling in the oral cavity, with difficulty progressing to the pharyngeal phase. Pharyngeal dysphagia is comprised of difficulty initiating the pharyngeal response, where food does not adequately move through the pharynx. Recommendations following the MBS included continued oral intake, with specific compensatory and/or adaptive devices, for ten children and no oral intake for one child.

MBS results, scored using the six parameters, are shown in Table 4. No patient scored below 3 on the aspiration/laryngeal penetration scale, with a score of 4 being most frequent. On the ASHA NOMS swallowing scale, all but one patient scored a 3 or above, indicating that at least some oral intake was safe, though accommodations were required. The oral phase dysphagia scale indicated dysfunction (score ≥ 1) in ten patients. Head extension was present in eight patients and six patients exhibited dyssynchronization. Vocal/speech development could not be assessed in all patients but did not surpass babbling for all but one of the scored patients. Due to missing scores, vocal/speech development was excluded from further analyses.

To determine if scores on the remaining five parameters were associated with age, a linear mixed effects regression, with age as the outcome variable, was performed. A random intercept effect for Subject ID was included to control for multiple assessments. Regression model parameters, beta estimates, and 95% CIs are shown in Table 5. No parameter estimate had a CI which excludes zero, indicating no linear association between age and any parameter.

Principal Component Analysis was utilized to determine whether the five parameters assessed unique aspects of swallow function. PCA transforms data into new dimensions, which best represents variation in

Table 5
Mixed effects regression model shows lack of association between age and swallow parameters.

Random effects	SD
Subject ID	9.9
Residual	17.3
Fixed effects	Beta (95% CI)
Aspiration/laryngeal penetration	0.59 (−18.24, 33.76)
ASHA NOMS swallow scale	0.46 (−6.37, 10.68)
Oral phase dysphagia	0.26 (−29.02, 32.92)
Head Extension	−1.61 (−84.57, 9.71)
Dyssynchronization	1.02 (−21.46, 67.92)

Standard deviation (SD) indicates the amount of variance in random intercept estimates that can be explained by inclusion of that random effect. Beta represents change in age (weeks) associated with a 1-point increase in the indicated parameter.

Table 6
Correlation of principal components to parameters shows dimensions of swallow are well-captured.

Principal component	Scale	Correlation (%)	*P* value
1	HE	91%	< 0.0001
1	DS	66%	0.01
1	OP	−69%	0.007
1	Age	−60%	0.02
2	ALP	77%	0.001
2	ASHA NOMS	67%	0.009
2	DS	−66%	0.01
3	Age	70%	0.005

Abbreviations: ASHA NOMS, American Speech-Language-Hearing Association National Outcome Measurement System swallowing level scale; ALP, aspiration and/or laryngeal penetration; OP, oral phase dysphagia; DS, dyssynchronization of suckle, swallow, and breathing; HE, head extension.

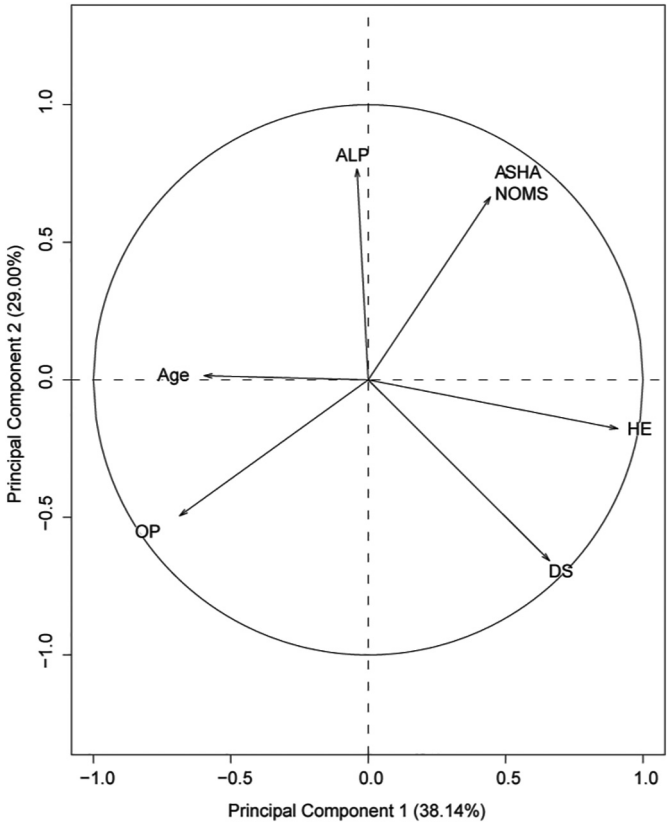

Fig. 1. Parameters measure distinct dimensions of swallow function. Graphical representation of the dimensions which capture the most variance in swallow function. Arrow directions show how each parameter relates to principal components 1 and 2, which account for 67% of data variance. Arrow lengths are proportional to the highest percent correlation of each parameter to principal component 1 or 2.

that data. Principal components 1 and 2 represent the dimensions which capture the most variance. However, because each principal component does not necessarily represent a measure used in the original dataset, a correlation analysis between known measures and the principal components must be performed to interpret the meaning of a principal component. Correlation between the five parameters and the principal components shows how the parameters relate to dimensions which capture the most variance in swallow function. Higher correlation with the first few principal components indicates a large proportion of variance is captured by that parameter, making it a good measure. Table 6 shows percent correlation between each parameter and the first three principal components. A map showing correlation of each parameter with the first two principal components, which account for more than half of the variance, is shown in Fig. 1. Head extension, dyssynchronization, oral phase dysphagia, and age had a 91%, 66%, −69% and − 60% correlation with principal component 1, respectively. The aspiration and/or laryngeal penetration, ASHA NOMS swallow scale, and dyssynchronization had a 77%, 67%, and − 66% correlation with principal component 2, respectively.

Utility of the parameters in staging progression of swallow deterioration, as a proxy for neurological decline, was assessed by transition analysis. To best identify distinct states and the probabilities of moving between states, a Hidden Markov Model (HMM) was used. An optimal fit was achieved with a two-state model. Table 7 shows the probability of being assigned a given parameter score in each state. For oral phase dysphagia, an individual in state 1 would have an 21% probability of scoring 0 (no oral phase dysphagia), 79% probability of scoring 1 (abnormal suck to swallow ratio), and 0% probability of scoring 2 (no suck or pharyngeal swallow). Comparatively, in state 2, there is an 11%, 78%, and 11% probability of scoring 0, 1, and 2, respectively. This defines a crucial transition point between the two states. A score of

Table 7
Response parameters representing the probability of scores within each scale and state.

	State 1	State 2
HE 0	0.59	0.13
HE 1	0.41	0.87
OP 0	0.21	0.11
OP 1	0.79	0.78
OP 2	0	0.11
ALP 3	0	0.11
ALP 4	0.38	0.78
ALP 5	0.62	0.11
ASHA NOMS 2	0	0.22
ASHA NOMS 3	0.21	0.11
ASHA NOMS 4	0	0.11
ASHA NOMS 5	0	0.11
ASHA NOMS 6	0.38	0.45
ASHA NOMS 7	0.41	0
DS 0	1.0	0.13
DS 1	0	0.87

Abbreviations: ASHA NOMS, American Speech-Language-Hearing Association National Outcome Measurement System swallowing level scale; ALP, aspiration and/or laryngeal penetration; OP, oral phase dysphagia; DS, dyssynchronization of suckle, swallow, and breathing; HE, head extension.

2 for oral phase dysphagia is impossible in state 1, meaning an individual with that score must be assigned to state 2. Scores ≤3 on the aspiration/laryngeal penetration scale (consistent entrance of multiple textures into the airway), ≤2 on the ASHA NOMS swallow scale (score at which swallowing begins to be considered unsafe), and presence of

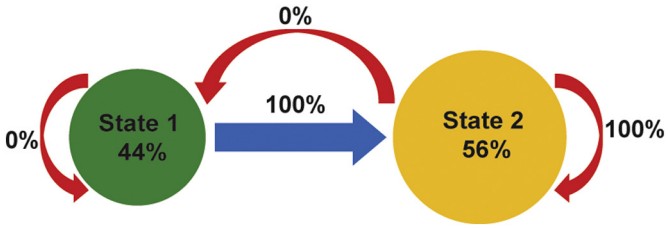

Fig. 2. Probabilities of transition between state 1 and state 2.
Transition analysis by Hidden Markov Model indicates a 44% chance of being assigned to state 1 initially. There is a 100% probability of transitioning from state 1 to state 2. An individual in state 2 has a 100% probability of remaining in state 2.

dyssynchronization, also mark transition points. Although head extension is more likely in state 2 than state 1 (87% vs 41% probability), there is no a clear transition point. Transition probabilities define the likelihood of moving between states. An individual initially assigned to state 1 has a 100% probability of transitioning to state 2, and an individual initially assigned to state 2 has a 100% probability of staying in state 2. Individuals have a 44% probability of being initially assigned to state 1 (Fig. 2).

4. Discussion

This study provides a comprehensive retrospective review of disease presentations and analysis of dysphagia in eleven patients with GD2. Although the small sample size is a clear limitation of this study, it is a valuable reference for different disease presentations and progressions in GD2, a rare presentation of a rare disorder. This is the first known study to provide an in-depth analysis of swallow function as an indicator of neurological decline. Of the six parameters utilized to assess swallow function and deterioration, five of the parameters, aspiration/laryngeal penetration, ASHA NOMS swallow scale, oral phase dysphagia, head extension, and dyssynchronization, had sufficient data to evaluate different aspects of the swallow process. Thorough statistical analysis performed in this study validates the novel joint-use of these five parameters to assess for swallow impairment. This can be applied in the clinical setting for infants and young children with neurodegenerative disorders to assess for risks of common life-threatening complications resulting from neurogenic oropharyngeal dysphagia, like aspiration and recurrent respiratory illness.

A mixed effects regression of these five parameters revealed no linear association between age and any specific parameter, supporting the clinical observation that in patients with GD2, the rate of neurological decline cannot be predicted by age. PCA showed that the head extension, dyssynchronization, oral phase dysphagia, aspiration and/or laryngeal penetration, and ASHA NOMS swallow scales were significantly correlated with principal components 1 and 2. This indicates that a high proportion of variance in swallow function can be explained using these parameters. Moreover, the spread and directionality of parameters, shown on the map in Fig. 1, demonstrates that these parameters are capturing unique dimensions of swallow function. PCA also showed a − 60% correlation of age with principal component 1. While the mixed effects regression analysis revealed no linear relationship between age and any of the parameters, PCA results suggest a nonlinear relationship between age and swallow function. This is reflective of the nonlinear neurodegeneration seen clinically in patients with GD2.

Transition analysis, using a Hidden Markov Model, revealed two distinct states of GD2. Four parameters, the ASHA NOMS swallow scale, aspiration/laryngeal penetration, oral phase dysphagia, and dyssynchronization, showed clear transition points to guide assignment of individuals to a state. Presence of head extension is 46% more likely in state 2 than state 1, indicating that development of this compensatory action implies assignment to state 2, however there was no clear transition point. PCA also identified these five parameters as capturing a large proportion of swallow function variance. These transition points were defined by the probability of achieving any parameter score, given a state assignment. This indicates higher probabilities of swallow dysfunction in state 2 and marks state 2 as a more severe disease state. Transition probabilities revealed a 100% probability of transition to state 1 from state 2, with 0% probability of returning to state 1.

The directionality, of both the severity of scores and the transition probabilities between the two states, implies that all individuals will progress to state 2 and will not return to state 1. State 2 appears to represent end-stage disease, and transition into this state may be measured by parameter scores at or past the identified transition points. Individuals who are in the process of transitioning from state 1 to state 2 may have met/passed transition points on one or more, but not all, of the parameters. This five-parameter scoring system provides a clear delineation of stages of disease progression. Establishing disease progression is important when counseling families and healthcare providers on treatment options. MBS can help identify which compensatory procedures enable patients to swallow safely, such as postural changes, modification of dietary and feeding strategies, use of adaptive equipment and utensils, and/or sensory enhancement techniques, depending on degree of dysphagia [11,29]. When swallow function has declined to the extent of severe dysphagia, compensatory procedures may no longer be effective. Hospice care, or other non-oral therapeutic interventions, may be considered [11,29]. Deciding when, or if, to implement life-sustaining interventions is a major challenge and source of ethical debate in the management of infants and very young children with neurodegenerative disorders. By evaluating the MBS using this five-parameter scoring system, the physician and speech-language pathologist can provide important objective insights that can help to guide clinical care.

This scoring system may be used as an additional prognostic tool to assess neurological function when physical examination alone may not fully reflect the trajectory of the clinical course. We have shown its utility in staging disease progression in GD2, which will be extremely important in establishing meaningful efficacy parameters for future therapeutic interventions, given the lack of brain-penetrant therapies for GD. Since this five-parameter scoring system assesses swallow function as a proxy for neurological decline, it can also be used to inform studies for other infantile neurodegenerative disorders and provide new insights into disease progression.

Disclosure statement

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