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CLINICAL RESEARCH SHORT REPORT

Prospective Dysphagia Assessment in Adult Patients With Nephropathic Cystinosis

Stacey Sullivan[1] | Carina Stafstrom[2] | Natalie Grant[2] | William S. David[2] | Feodor Price[3] | Lee Rubin[3] | Florian Eichler[2] | Reza Sadjadi[2]

[1]Department of Speech, Language and Swallowing Disorders, Massachusetts General Hospital, Boston, Massachusetts, USA | [2]Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA | [3]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, Massachusetts, USA

Correspondence: Reza Sadjadi (rseyedsadjadi@mgh.harvard.edu)

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ABSTRACT

Introduction: Myopathy and dysphagia are common manifestations of nephropathic cystinosis, a rare autosomal recessive lysosomal storage disorder. We previously demonstrated that both the oral and pharyngeal phases of swallowing are affected and impact function and quality of life in patients. To better understand and characterize swallowing impairment, we evaluated patients with nephropathic cystinosis experiencing dysphagia and myopathy.

Methods: We prospectively evaluated patients who had participated in a prior clinical trial readiness study of myopathy and dysphagia, using functional outcomes and video fluoroscopic swallowing studies.

Results: Eight patients underwent functional and swallowing assessments. Oral and pharyngeal stages of swallowing were affected in all subjects. There was an improvement in oral stage dysphagia (Visit 3 8 [3:9]; Visit 4 5 [1:5]) between Visits 3 and 4 median of 1090 days (IQR [921:1288]) while pharyngeal stage dysphagia Modified Barium Swallow Impairment Profile scores stayed unchanged in the same amount of time. There was also improvement in M. D. Anderson Dysphagia Inventory (MDADI) scores (MDADI-C Visit 3 73 [62:87], Visit 4 96 [76:99]; MDADI-F Visit 3 18 [17:21], Visit 4 25 [23:25]), indicating a higher quality of life pertaining to swallowing.

Discussion: Despite the progressive nature of the myopathic changes typically described in patients with nephropathic cystinosis, we demonstrated improvement in some swallowing metrics. This may suggest a possible late-onset effect of respiratory training or cognitive-behavioral impact from repeated swallowing measurements.

1 | Introduction

Nephropathic cystinosis is a rare autosomal recessive lysosomal storage disorder caused by *CTNS* mutations [1–5]. Patients are often diagnosed in childhood with symptoms starting within the first year of life [1]. Adult patients frequently manifest myopathy [6, 7], which presents as distal and proximal muscle weakness [8–10], dysphagia [11], and dyspnea [12]. Dysphagia

Abbreviations: 25-FW, timed 25-foot walk; 9-HPT, the 9-hole peg test; EAT-10, the 10-item eating assessment tool; IQR, interquartile range; MBSImP, modified barium swallow impairment profile; MDADI, the M. D. Anderson dysphagia inventory; MEP, maximum expiratory pressure; OI, overall impairment; OT, oral total; PAS, penetration-aspiration scale; PCF, peak cough flow; PT, pharyngeal total; QOL, quality of life; SLP, speech language pathologist; TUG, timed up and go test; VFSS, videofluoroscopy swallow study.

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compromises quality of life [13] and predisposes patients to complications such as aspiration pneumonia and death [14].

In a preceding clinical trial readiness study, we employed video fluoroscopic swallowing studies (VFSS) at baseline (Visit 1) and at one-year follow-up (Visit 2). We repeated evaluations following a 5-week respiratory therapy program (Visit 3), the Expiratory Muscle Strength Training (EMST) [15, 16]. The EMST program is a series of resistance training exercises to target the neck and submandibular muscles involved with expiration [16]. VFSS using the Penetration Aspiration Scale (PAS) [17] revealed major dysfunction in 3/20 patients (15%), evidenced by airway invasion during swallows at Visits 1 and 2 [16]. Following a five-week EMST program, all three patients had improved PAS scores at Visit 3. To better quantify swallowing dysfunction, we retrospectively analyzed VFSS from Visits 1, 2, and 3 using the Modified Barium Swallow Impairment Profile (MBSImP) [18]. This methodology allowed us to observe more subtle abnormalities in different phases of swallowing and evaluate for changes over time. Most patients displayed abnormal MBSImP oral and pharyngeal scores; however, no significant difference was observed between the scores from Visits 1 and 2. Additionally, there was no significant change following EMST (Visits 2 and 3). There was a significant correlation between oral scores and dysphagia-specific quality of life outcomes. To further elucidate swallowing kinematics and look for changes over time, we prospectively evaluated patients from the initial clinical trial readiness study cohort using VFSS and MBSImP.

2 | Methods

The study received approval from the local Institutional Review Board and the Mass General Brigham Human Research Committee (MGBHRC). Informed consent was obtained from all participants. Of the original participants, 19 of 20 were invited for re-evaluation. Additionally, patients with genetically confirmed nephropathic cystinosis were invited through the Cystinosis Research Foundation newsletter.

A schedule of all assessments completed in Visits 1 through 4 is described in Table S1. All participants underwent a neuromuscular examination, including manual muscle testing of proximal and distal upper and lower extremities and video fluoroscopic swallowing evaluation at each visit. Patients completed patient-reported and clinical outcome measures. MBSImP was used to analyze the VFSS data. The 17 components of MBSImP were rated on an ordinal scale, with ratings based on specific observations of structural movement or bolus flow. The 5 MBSImP oral (items 2–6) and 10 pharyngeal (items 7–16) domain items were aggregated to yield Oral Total (OT) scores (0–22) and Pharyngeal Total (PT) scores (0–29) [19]. Furthermore, patients underwent electrodiagnostic evaluation, including needle electromyography and motor unit potential (MUP) analysis of the right vastus lateralis and right first dorsal interosseous muscles.

2.1 | Statistical Analysis

Wilcoxon signed-rank test was used to compare individual items and total scores between visits [20]. *p*-values of less than 0.05 were considered significant. We used SAS Release3.8 (Basic Edition) statistics (SAS Institute Inc., Cary, NC, USA) and GraphPad software (Graphpad Software, Boston, MA) for statistical analysis.

3 | Results

Of the original participants, seven participated in this study. The remainder of the original cohort was unable to participate due to travel and lifestyle restrictions from the COVID-19 pandemic. Additionally, one patient participated through the Cystinosis Research Foundation newsletter advertisement who did not participate in the original study.

TABLE 1 | Clinical and patient-reported outcome measures (median [IQR]) for Visits 1, 2, 3, and 4.

	Visit 1	Visit 2	Visit 3	Visit 4
EAT10	3.5 [1:24.3]	3.5 [1:20]	3 [0.8:17.8]	4 [0.3:17]
GRIP (KGF)	31.9 [22.7:58.2]	27.1 [22.4:36]	25.4 [21.6:36.5]	21.9 [19.7:28.2]
9HPT (S)	20.5 [19.3:22.4]	20.2 [18.4:24.3]	20 [16.9:23.8]	23.5 [20.5:27.6]
TUG (S)	6.0 [5.2:7.6]	7.1 [6.1:10]	7.3 [6.3:8.1]	7.8 [7.1:9.1]
25FT (S)	4.3 [3.6:5.4]	5.6 [4.9:6.5]	5.3 [4.6:6.3]	5.8 [4.7:6.6]
MDADI-E	25 [23:30]	24 [21:49]	24 [22:26]	28 [21:30]
MDADI-F	21 [19:22]	19 [12:21]	18 [17:21]	25 [23:25]
MDADI-P	33 [26:40]	26 [20:40]	31 [25:37]	37 [26:39]
MDADI-C	82 [70:92]	66 [50:88]	73 [62:87]	96 [76:99]
MUP-FDI (MS)				6.0 [5.2;6.4]
MUP-VL (MS)				12.5 [9.9;13.4]

Abbreviations: 25-FW, 25-foot walk test; 9-HPT, 9-hole peg test; EAT-10, the 10-item eating assessment tool; MDADI, The M. D. Anderson Dysphagia inventory sub scores, emotional (E), functional (F), composite (C), physical (P); MUP-FDI, motor unit potential duration—first dorsal interosseous; MUP-VL, motor unit potential duration—vastus lateralis; PAS, penetration-aspiration scale; TUG, timed up and go test.

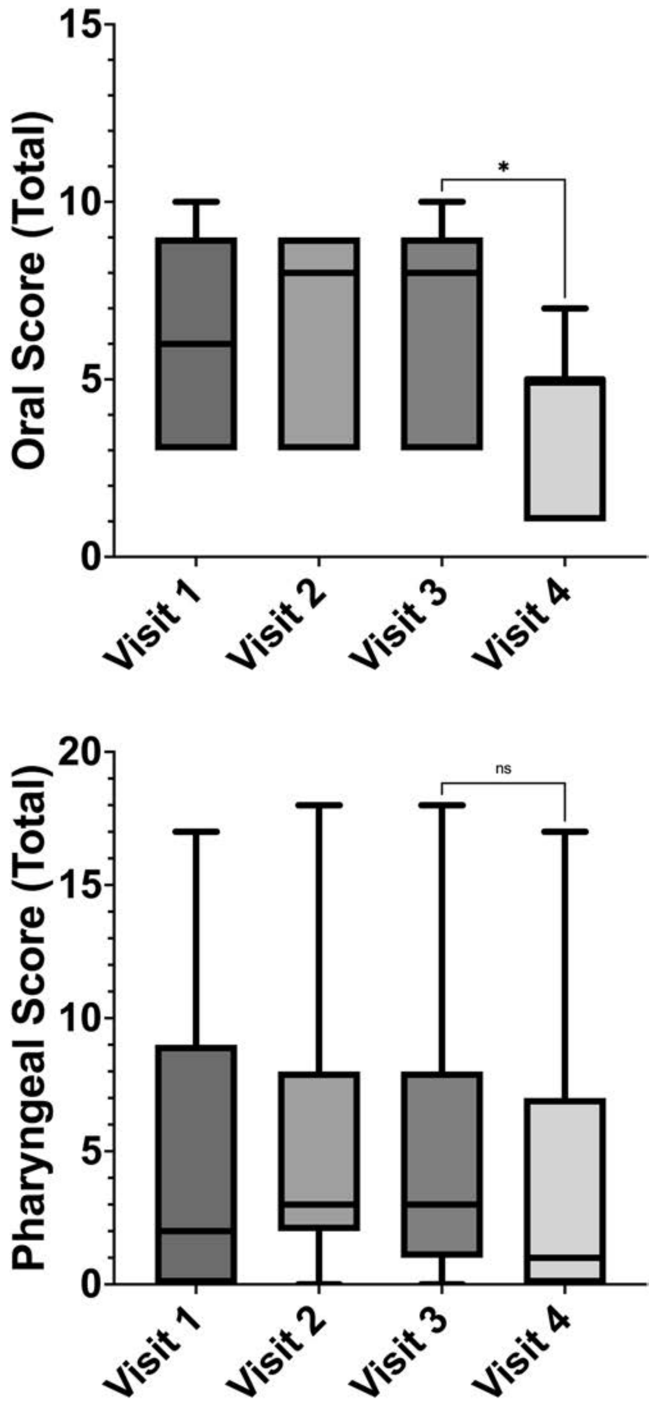

FIGURE 1 | The distribution of MBSImP oral and pharyngeal total scores at Visits 1, 2, 3, and 4. Box and whisker plots show the median, upper, and lower quartiles. (ns = not significant) *p-value <0.05 (Wilcoxon signed-rank test).

Eight patients (four males and 4 females, aged 30 to 60 years [median 34, IQR (31.5:43)]) participated in the prospective study. The median follow-up duration between Visits 3 and 4 was 1090 days (IQR [921:1288]). Table S2 presents details on patients in this cohort.

Clinical and patient-reported outcome measures are detailed in Table 1. Overall, there was no significant worsening in grip dynamometry, 9HPT, TUG, and 25FWT. MDADI-F and MDADI-C scores were significantly higher at Visit 4, indicating improved quality of life. EAT-10 remained unchanged between visits.

Of the seven patients who had prior evaluations, improvements were observed in various aspects of swallowing physiology: tongue control (three patients), bolus transport and lingual motion (five patients), amount of post-swallow residue (three patients), laryngeal elevation (four patients), timing of pharyngeal swallow response (four patients). Three patients had worsening in the amount of post-swallow residue. Oral total score was significantly lower at Visit 4 compared to Visit 3 (Visit 3 8 [3:9]; Visit 4 5 [1:5]). Pharyngeal total score remained unchanged between Visit 3 and Visit 4 (Figure 1). Table 2 summarizes qualitative swallow assessments in individual patients.

4 | Discussion

Despite the progressive nature of the myopathic changes typically described in patients with nephropathic cystinosis, we observed some reduction in disability related to primarily the oral phase of swallowing in most patients. Concurrently, there was significant improvement in quality-of-life measures pertaining to the functional aspects of swallowing. Improvements in the volitional oral phase of swallowing may be related to the use of intention and focused effort on behalf of the patient when eliciting a swallow [21]. Improved intentional lingual force generation may also align with improved epiglottic deflection in this patient population.

A possible explanation for these improvements may be repeated exposure to one's own swallowing physiology over the course of several years via videofluoroscopy, paired with counseling/education following an instrumental exam. This may impact a patient's ability to volitionally improve function. There may also be a cognitive behavioral effect resulting from an understanding of swallowing mechanics in the oral phase that influences a patient's ability to improve swallowing mechanics despite disease progression [22]. This was not specifically tested or measured. These interesting considerations may serve as a framework for investigation in future studies. Laryngeal elevation is generated by the suprahyoid muscles, the mylohyoid, geniohyoid, stylohyoid, and the anterior belly of the digastric muscle [23]. These muscles can be activated by EMST [24]. The presence of improved laryngeal elevation in 5 of 7 patients may suggest a delayed effect of treatment. This also raises the possibility that muscles involved in laryngeal elevation or laryngeal vestibular closure may respond to potential interventions or serve as future treatment targets. Tongue strengthening and cognitive behavioral therapy may serve as potential treatment approaches, as these interventions can influence other phases of the swallow that impact safety and efficiency.

Test re-test reliability is high with the use of the MBS ImP standardized rating system; variables such as bolus size and positioning are controlled for that may impact variation in scoring across studies. Due to the small size of our cohort, we are unable to determine if other variables such as pharmacological treatment of cystinosis, treatment adherence, delayed therapeutic response to targeted exercise (EMST) or participation in additional rehabilitative interventions, such as speech therapy, impacted

TABLE 2 | Changes in MBSImp item scores overtime.

Patient	Improvement	Worsening
1	• Tongue control • Bolus transport • Oral residue • Laryngeal vestibular closure	• Superior pharyngeal constrictor • Pharyngeal residue
2	• Bolus transport • Pharyngeal swallow response • Laryngeal elevation	
3	• Oral phase	• Laryngeal vestibular closure • Tongue base retraction • Pharyngeal residue
4	• Timing of pharyngeal swallow	
5	• Bolus transport • Oral residue • Laryngeal elevation • Laryngeal vestibular closure	
6	• Initiation of pharyngeal swallow response • Tongue base retraction	• Pharyngeal residue
7	• Tongue control during bolus hold • Bolus transport • Initiation of pharyngeal swallow • Laryngeal elevation	

patient results. Evidence highlights that the benefit from EMST may last up to 3 months when measuring respiration metrics, such as sustained vital capacity. After 3 months, patients demonstrated a detraining effect, where there was a slight decrease in SVC, but still higher than the initial baseline [25]. Long-term impact to specific muscles involved in deglutition has not been characterized in the literature. We did not record whether patients continued to train using the EMST device after the completion of the study.

We did not analyze information regarding disease onset, prior interventions, or comorbidities. Due to the variability in disease severity across patients and other variables such as current and prior treatment and treatment adherence, we could not observe differences between older versus younger patients in this cohort. Analysis of these patient variables may be interesting to examine in future studies and may highlight characteristics that predispose patients to functional improvements or to slow progression. There was a progression of pharyngeal phase findings (increased residue and reduced contact of soft palate and posterior pharyngeal wall) that suggests further decline in pharyngeal swallow function. With the more severe presentations of dysphagia, current measurement tools have a ceiling effect and do not detect change after a certain level of impairment.

MBSImP has refined our understanding of swallow function in a much more granular fashion and informs us about the impairment of specific physiological functions. However, comprehending how this information influences patient function and quality of life will require further study.

Major limitations of this study include the small sample size and lack of control arms. The recruitment was affected by the travel restrictions during COVID-19 pandemic. Future studies should include a control arm as well as more specific functional and physiologic assessments of swallowing mechanics.

Author Contributions

Stacey Sullivan: conceptualization, formal analysis, project administration, supervision. **Carina Stafstrom:** writing – review and editing, project administration. **Natalie Grant:** project administration. **William S. David:** investigation, writing – original draft, project administration. **Feodor Price:** conceptualization, investigation. **Lee Rubin:** conceptualization, investigation. **Florian Eichler:** conceptualization, investigation. **Reza Sadjadi:** conceptualization, investigation, funding acquisition, writing – original draft, methodology, validation, visualization, writing – review and editing, software, formal analysis, project administration, supervision, resources.

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Ethics Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.