Title: Dysphagia in Friedreich ataxia

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ABSTRACT

Objectives

To comprehensively characterise dysphagia in Friedreich ataxia (FRDA) and identify predictors of penetration/aspiration during swallowing. We also investigated the psychosocial impact of dysphagia on individuals with FRDA.

Methods

Sixty participants with FRDA were screened for dysphagia using a swallowing quality of life questionnaire (Swal-QOL). Individuals reporting dysphagia underwent a standardized oromotor assessment (Frenchay Dysarthria Assessment, 2, FDA-2) and videofluoroscopic study of swallowing (VFSS). Data were correlated with disease parameters (age at symptom onset, age at assessment, disease duration, *FXN* intron 1 GAA repeat sizes and Friedreich Ataxia Rating Scale (FARS) score). Predictors of airway penetration/aspiration were explored using logistic regression analysis.

Results

Ninety-eight percent (59/60) of participants reported dysphagia, of whom 35 (58.3%) underwent FDA-2 assessment, and 38 (63.3%) underwent VFSS. Laryngeal, respiratory, and tongue dysfunction was observed. A Penetration-Aspiration Scale score above 3 (deemed significant airway compromise based on non-clinical groups) was observed on at least one consistency in 13/38 (34.2%) participants. All of those who aspirated (10/38, 26.3%) did so silently, with no overt signs of airway entry such as reflexive cough. Significant correlations were observed between dysphagic symptoms and disease duration and severity. No reliable predictors of penetration or aspiration were identified.

Conclusion

Oropharyngeal dysphagia is commonly present in individuals with FRDA and worsens with disease duration and severity. Individuals with FRDA are at risk of aspiration at any stage of the disease and should be reviewed regularly. Instrumental analysis remains the only reliable method to detect aspiration in this population. Dysphagia significantly affects the quality of life of individuals with FRDA.

Key words:

Trinucleotide repeat diseases, Gait disorders/ataxia, Quality of life, Videofluoroscopy, swallowing

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INTRODUCTION

Friedreich ataxia (FRDA) is an autosomal recessive condition resulting from a deficiency of frataxin, most commonly due to homozygosity for a GAA trinucleotide repeat expansion in intron 1 of *FXN* (1). FRDA is a multisystem neurodegenerative disorder with a prevalence of approximately 1 in 29000 (2). No effective treatments known to reverse or halt disease progression (3, 4). Symptoms typically present in teenage years and patients become non-ambulant within 10-15 years of disease onset (5). Deficits include progressive gait and limb ataxia, auditory (6) and optic neuropathy (7), cardiomyopathy, scoliosis, dysarthria (8) and dysphagia (9). Cognitive function is characterised by subtle executive problems and parieto-temporal dysfunction (10). These impairments differentially combine to significantly restrict the health and quality of patients (11). Neuropathology has traditionally been described as restricted to the cerebellar dentate nucleus and spinal cord however recent evidence suggests involvement of the cerebral and cerebellar cortices (12). Pneumonia (a potential sequelae of

dysphagia) is reportedly the cause of death in approximately 10% of individuals with FRDA (13).

Dysphagia is associated with malnutrition, dehydration, and aspiration-related pneumonia, as well as reduced self-esteem and social isolation (14). In movement disorders dysphagia may be exacerbated by concurrent upper limb impairment, making feeding difficult (15). Swallowing is known to be impaired in FRDA (9) however the underlying mechanisms and characteristics FRDA-related dysphagia are not well described. The onset of dysphagia is related to GAA1 GAA1 (the shorter of the two GAA repeats) (16), however the influence of repeat length on dysphagia severity is unknown. The only investigation of swallowing in FRDA (n=36) to date reported dysphagia in 100% of affected individuals based on non-instrumental measures of severity, including a clinical bedside examination, the Royal Brisbane Hospital Outcome Measure for Swallowing (RBHOMS) (17), and the Australian Therapy Outcome Measure for Speech and Swallowing (AusTOMS) (18). Dysphagia symptoms included coughing and choking on liquids and solids (strongly suggestive of aspiration) and nasal regurgitation (9). Further, dysphagia was s shown to affect activity, participation, and well-being, with the degree of impairment correlating with disease duration (9).

This study aimed to comprehensively characterize swallowing function in individuals with FRDA using the gold standard of swallowing assessment. We also sought to determine the psychosocial impact of dysphagia in individuals with FRDA. Correlations were made between FRDA clinical parameters (including age at disease onset, disease duration, and GAA repeat length) and measures of dysphagia to determine the relationships between FRDA and swallowing. Behavioral and clinical data were analyzed to determine predictors of penetration/aspiration in FRDA.

METHODS

Participants

Sixty individuals (mean ($\bar{x}$) age 35.5 years, standard deviation (σ) 12.2) homozygous for *FXN* intron 1 GAA expansions were consecutively recruited through the Friedreich ataxia Clinic in Melbourne, Australia (see *Table I- Demographic and clinical characteristics of the FRDA cohort, and total assessment scores*). Participants were excluded if they presented with a neurological disorder other than FRDA or a speech and/or swallowing impairment prior to the onset of FRDA. Disease severity was determined via the Friedreich Ataxia Rating Scale (FARS; (19)) administered by a physician.

Participants were screened for dysphagia using a swallowing questionnaire (SWAL-QOL (20)) or clinical case history. If dysphagia was present on either assessment, the participant was invited to participate in oromotor assessment (Frenchay Dysarthria Assessment, 2nd edition; FDA-2) (21)) and videofluoroscopic evaluation of swallowing studies (VFSS). The FDA-2 and/or VFSS were conducted as soon as possible following clinical case history and SWAL-QOL assessment. On average, VFSS was conducted 22.8 days (SD16.6) after administration of the SWAL-QOL, and 32.7 days (SD 22.8) after administration of the FDA-2. It is unlikely the length of the time period between assessments affected the outcome of this study given the slowly progressing nature of the disease (22).

Fifty-nine participants completed the SWAL-QOL, 35/60 participated in FDA-2 and 38/60 underwent VFSS (Figure 1). Of the remaining 22 individuals, 12 did not participate in further assessment due to logistical reasons (such as transport issues and appointment scheduling), eight declined further assessment, and one participant did not present with signs of dysphagia on SWAL-QOL or case history, therefore did not meet criteria for administration of VFSS or FDA-2. One (1.67%) participant participated in VFSS only after not returning the SWAL-QOL, however had previously reported dysphagia on case history (*Figure 1*).

Fifty-nine age-matched ($\bar{x}$ age 35.30 years, σ 12.28 years, range 16.14 to 65.01 years; $p>0.05$) healthy controls (HC) were recruited via advertisement to complete a swallowing questionnaire (SWAL-QOL (20)) only. Exclusion criteria for the HC group included evidence of neurological impairment, pulmonary disease, or a history of neck surgery.

All experimental procedures were approved by the Human Research Ethics Committees of Monash Health and The University of Melbourne. All participants gave informed consent prior to inclusion in the study in accordance with the Declaration of Helsinki.

Assessments

SWAL-QOL

The SWAL-QOL (20) is a validated self-report questionnaire with 44 items covering 10 quality of life domains relating to dysphagia (Burden, Eating Duration, Eating Desire, Food Selection, Communication, Fear, Mental Health, Social, Fatigue, and Sleep) and a symptom frequency scale. Each item is scored on a scale from one to five, where 5 = optimal, and 1 = maximal impairment. Scores for each SWAL-QOL domain were expressed as a percentage of the maximum possible domain score. A total SWAL-QOL score is derived by summing each domain score and dividing by 11 giving a total SWAL-QOL score that ranges between 0 and 100 (worst–best).

FDA-2

The FDA-2 (21) is a clinician-administered assessment of oromotor function. It consists of 26 items across seven categories, including 'Reflexes', 'Respiration', 'Lips', 'Palate', 'Laryngeal function', 'Tongue', and 'Intelligibility'. Items are scored on a 9-point scale, where a score of 1 corresponds to normal oromotor function and a score of 9 indicates a complete absence of function (2 - 4 = mild, 5 - 6 = moderate, 7 - 8 =severe, 9 = profound impairment).

Videofluoroscopic Study of Swallowing (VFSS)

Three consistencies were trialled, including unmodified/regular fluids (5ml bolus and consecutive sips), puree (up to five teaspoons of Foster Clark Custard®), and biscuit (Arnott's Savoy® Biscuits with a thin spreading of jam mixed with barium powder). The barium powder was MCI Forrest X-OPAQUE-HD barium sulphate suspension formulation. For water, a desired weight to volume percentage between 20 and 30 was reached by mixing 250ml of fluid with approximately 60 to 80 grams of barium formulation. For the custard, 140ml was mixed with approximately 80 grams of barium formulation, and thee teaspoons of jam was mixed with the equivalent in barium power. Of the 38 participants who underwent VFSS, two did not trial puree consistency due to intolerance to custard. A consistent recipe was used for each VFSS procedure and substances were presented in a random order to control for fatigue, and other possible effects related to bolus presentation. Participants were encouraged to self-feed during the procedure to replicate everyday feeding practice. VFSS was interpreted using the Bethlehem Assessment Scale (BAS) (23) and the Penetration-Aspiration Scale (PAS) (24). The BAS is broken down into 10 anatomical domains, including lip function, tongue function, jaw function, soft palate function, reflex initiation, aspiration, residue in the valleculae, residue in the pyriform sinuses, pharyngeal function, and cricopharyngeal function. Each of these parameters was rated using a four point scale, where 1 equates to no impairment and four is severe impairment. The PAS is an 8-point scale describing penetration and aspiration events where higher values indicate more severe penetration and aspiration.

Statistical analysis

Statistical analysis was performed using SPSS Statistical Software Version 22.0 (SPSS® IBM Corporation, Armonk, New York, USA). Mann-Whitney U tests were used to investigate differences between individuals with FRDA and HCs on the SWAL-QOL. Mann-Whitney U tests were also used to explore individuals with FRDA on the VFSS as pertaining

to the presence or absence of significant airway entry during swallowing. Effect size was interpreted as 0.1=small effect, 0.3=medium effect, and 0.5=large effect (25). Data from participants undergoing VFSS were split into two groups: individuals with and without evidence of penetration and/or aspiration, as determined by the PAS score > 3. Spearman's rho (ρ) was used to investigate the relationship between swallowing function and other FRDA clinical parameters including GAA repeat length, disease severity and disease duration. Logistic regression was used to determine predictors of significant penetration and/or aspiration (PAS score > 3) in individuals with FRDA.

VFSSs were rated by MK and IG; Speech Pathologists with 5and 6 years of experience with VFSS respectively at the commencement of data collection. Overall agreement between raters was kappa 0.60 (p=<0.01).

RESULTS

Insert Table I- Demographic and clinical characteristics of the FRDA cohort, and total assessment scores

Insert Figure I- Venn diagram demonstrating participation across three assessments

Swallowing-related QOL

Fifty-nine individuals with FRDA (mean age 35.5 years SD 12.2 years, range 15.5-57.1 years) and 59 age matched HCs ($\bar{x}$ age 35.30 years, σ 12.28 years, range 16.14 to 65.01 years; p>0.05) completed the SWAL-QOL. The FRDA group scored significantly lower in all SWAL-QOL domains compared to the HC group (Figure 2), with effect sizes ranging from 0.31 (small) for *Sleep* to 0.97 (large) for *Communication* (see *Insert Table II - SWAL-QOL subsections and total SWAL-QOL for individuals with FRDA and healthy controls*). Fatigue was the most affected domain (mean percentage score 59.75 SD 27.82%), followed by eating duration (mean64.19% SD 30.39%), sleep (71.19% SD 27.68%) with social functioning being the least affected domain (mean 92.46% SD 15.74%). Overall swallowing-related QOL

correlated with disease severity (ρ=0.4, $p<0.01$) and disease duration (ρ=0.4, $p<0.05$). Refer to Online Resource *Supplementary Table I* for correlations between SWAL-QOL domains and clinical parameters.

Insert Table II - SWAL-QOL subsections and total SWAL-QOL for individuals with FRDA and healthy controls

Oromotor function

Mean scores were calculated for each FDA-2 domain. Laryngeal function was the most affected domain (mean 4.0 SD 1.65), followed by tongue function (mean 3.0 SD 1.2), respiration (mean 2.8 SD 1.4), reflexes (mean 2.7 SD 1.2), intelligibility (mean 2.5 SD 1.5), lips (mean 2.3 SD 0.6), and palate (mean 1.9 SD 0.6) (Online Resource *Supplementary Table II*). Oromotor function as assessed by accumulated FDA-2 score positively correlated with disease duration (ρ=0.74, $p<0.01$), FARS score (ρ=0.64, $p<0.05$), GAA1 (ρ=0.40, $p<0.05$), and age at disease onset (ρ=0.37, $p<0.05$). A negative correlation was observed between total FDA-2 score and age at disease onset (ρ=-0.37, $p<0.05$). FARS and disease duration correlated with all FDA-2 domains. Tongue function correlated with GAA1 length (ρ=0.45, $p<0.01$) and age at onset (ρ=-0.52, $p<0.01$) (Online Resource *Supplementary Table III*).

Videofluoroscopic Study of Swallowing (VFSS)

Of the 38 participants who underwent VFSS, two did not trial puree consistency under VFSS due to intolerance to custard. We deemed a PAS score ≥ 3 to be clinically significant based on results of non-clinical populations where 99% of healthy individuals (n=95) scored <3 on VFSS [15]. Ten participants (26.3%) aspirated (scoring PAS ≥ 6) on at least one consistency. An additional three (7.9%) participants demonstrated penetration (PAS score ≥ 3) on at least one consistency. The cumulative total of participants with a compromised airway was 13 (34.2%). Aspiration occurred most frequently with fluid (8/38 (21.1%) of participants). Refer to *Table I* for PAS scores of each participant.

Analysis of VFSS data using the BAS revealed impairment in the oral and pharyngeal phases of swallowing. Oral residue (a manifestation of lingual dysfunction) was observed with all consistencies (fluid mean 1.5 SD 0.6; puree mean 2.1 SD 0.6; biscuit mean 2.9 SD 0.8). Reflex initiation was delayed across all consistencies (fluid mean 3.1 SD 0.7, puree mean 3.1 SD 0.5, and biscuit mean 3.1 SD 0.5) (*Figure 2 A*). Residue in the pharyngeal structures was also observed across all consistencies, with biscuit appearing the most severe (*Figure 2 B*) (for BAS results refer to Online Resource *Supplementary Table IV*).

Insert Figure II - VFSS of a 50 year old male with Friedreich ataxia

Relationship between FRDA clinical parameters and dysphagia

No significant correlations were observed between FRDA clinical parameters and aspiration of fluid or puree. Deficits in the oral phase parameters of the BAS correlated with FARS score (lip function with fluid: $\rho=0.48$, $p<0.01$; jaw function with biscuit:, $\rho=0.38$, $p<0.05$), age at assessment (lip function with fluid: $\rho=0.44$, $p<0.01$; jaw function with biscuit: $\rho=0.34$, $p<0.05$), and disease duration (lip function with fluid: $\rho=0.58$, $p<0.01$; jaw function with puree, $\rho=0.44$, $p<0.01$; and biscuit, $\rho=0.46$, $p<0.01$). There was a trend between disease duration and pharyngeal phase deficits with solid food (biscuit) (reflex initiation $\rho=0.43$, $p<0.01$; Aspiration $\rho=0.45$, $p<0.01$; valleculae $\rho=0.35$, $p<0.05$; pharyngeal $\rho=0.33$, <0.05). Disease duration correlated with soft palate elevation ($\rho=0.50$, $p<0.01$), reflex initiation ($\rho=0.43$, $p<0.01$), aspiration ($\rho=0.45$, $p<0.01$), vallecular residue ($\rho=0.35$, $p<0.05$), and pharyngeal function ($\rho=0.33$, $p<0.05$). GAA1 length positively correlated with vallecular residue of biscuit ($\rho=0.42$, $p<0.01$). GAA2 length positively correlated with vallecular ($\rho=0.35$, $p<0.05$) and pharyngeal residue ($\rho=0.45$, $p<0.01$) (Online Resource *Supplementary Table V* and *VI).*

Predictors of aspiration in FRDA

The cohort who underwent VFSS (n=38) was dichotomized into two groups according to the presence and severity of barium entry into the airway on one or more consistency: 1) those with adequate airway protection (PAS scores all < 3) (n=25), and 2) those who demonstrated penetration/aspiration of the airway on any consistency (at least one PAS score > 3) (n=13). Direct logistic regression was performed to assess the predictive ability of the clinical and behavioral data on the occurrence of matter entry into the airway when swallowing. The independent variables included GAA2, FDA-2 Reflexes, and FDA-2 Intelligibility (determined by running logistic regression for each independent variable and identifying the independent variables that most relate to the model, Online Resource *Supplementary Table VII*). The full model containing all independent variables was statistically significant, X^2(3, N=30)=8.971 (p=0.03), indicating that the model was able to distinguish between participants who demonstrated penetration and/or aspiration on at least one consistency and those who did not. The model as a whole explained between 25.8% (Cox and Snell R square) and 35.9% (Nagelkerke R Square) of cases, and correctly classified 76.7% of cases. Sensitivity was 60% and specificity was 85%, indicating a tendency towards under-prediction. As highlighted in *Insert Table III - Logistic regression predicting likelihood of airway entry of barium*, none of these variables made a unique significant contribution to the model. The strongest predictor of penetration/aspiration in individuals with FRDA was FDA-2 Reflexes, with an odds ratio of 1.26.

Insert Table III - Logistic regression predicting likelihood of airway entry of barium

DISCUSSION

In this study 98% (59/60) of participants reported symptoms of dysphagia, and 100% had their concerns verified on VFSS. Delayed pharyngeal swallowing reflex was the most pertinent factor of FRDA-related dysphagia, followed by lingual dysfunction and reduced

clearance of solid foods from the pharyngeal structures. Significant entry of barium into the airway was observed in 34.2% of the cohort, and aspiration in 26.3%. All of those who aspirated did so silently, necessitating the need for instrumental analysis for accurate identification of aspiration in this population.

This is the first study to systematically describe swallowing function in individuals with FRDA. Previous research using non-instrumental assessment reported a plethora of dysphagia symptoms in FRDA, including coughing/choking on thin fluids, coughing/choking on dry, crumbly or solid foods, oral residue, and nasal regurgitation (9). In the present study coughing/choking was not observed on VFSS, however was reported on the SWAL-QOL (by 41/59 [80.4%] and 44/59 [74.6%] participants on solids and liquids respectively). All participants who underwent VFSS presented with a degree of oral residue on at least one consistency. Nasal regurgitation was not observed on VFSS however palatal elevation was notably reduced. Oral and pharyngeal phase swallowing deficits correlated with disease severity and duration, with a trend between disease duration and reduced tolerance of solid food (biscuit).

More than a quarter of participants silently aspirated and more than a third of participants demonstrated penetration or aspiration. These rates are well beyond those observed in non-clinical groups where 97% of individuals score 1 (material does not enter the airway) or 2 (material enters the airway, remains above the vocal folds, and is ejected from the airway) on the PAS (26). Of note, the volume of aspirated material observed in individuals with FRDA was trace amounts, and thus the amount of aspirated material may not have been enough to elicit a cough response (27). This may explain the discrepancy seen between subjective reports of coughing with oral intake and the aspiration observed on VFSS.

There were no significant clinical or behavioural differences found between individuals who maintained a clear airway and those who penetrated or aspirated on VFSS. Interestingly,

dysarthria severity (as measured by the FDA-2) did not correlate with penetration and aspiration of the airway. Attempts to find clinically meaningful outcomes that assist in predicting penetration or aspiration in individuals with FRDA were not fruitful. The predictability of aspiration in other neurodegenerative populations is inconclusive. A clinical neurological examination is reported to predict aspiration in individuals with myasthenia gravis (n=20) with 71% sensitivity and 77% specificity (28), whilst in the ischemic stroke population (n=96), objective measures of cough are reported to predict aspiration with 82-91% sensitivity and 81-92% specificity (29). These figures demonstrate a trend of over and under-prediction of aspiration in these cohorts. We do not definitively know the incidence of aspiration pneumonia in FRDA, and thus the clinical implications of FRDA-related aspiration remains unclear. Ten percent of deaths in FRDA are reportedly due to pneumonia (13) yet little evidence of overt aspiration was observed in this study Together these two points suggest we need more work investigating the potential causal link between aspiration and pneumonia in individuals with FRDA in individuals with more severe clinical profiles. Beyond the physical complications of dysphagia in FRDA, the significant impact dysphagia has on QOL is notable. Participants reported significant dysphagia-related burden, difficulty finding foods they can both eat and enjoy, and extended mealtimes (possibly exacerbated by upper limb dysfunction and difficulty feeding independently). These factors may in turn limit eating desire. Dysphagia-related burden and lengthy mealtimes worsen with the implementation of safe swallowing strategies and increased effort associated with preparing appropriate foods. Both of these strategies have been identified as commonplace practice in the FRDA population (9, 30). Issues with self-perception (including a change in the individual's role within family and social groups) was reported by the FRDA group, as well as reduced participation in social events and gatherings, in line with earlier studies (14).

Dysphagia in FRDA likely arises due to mistiming and incoordination of the swallow arising from cerebellar degeneration and exacerbated by spasticity and weakness. Postural difficulties (scoliosis) and associated respiratory compromise may impact on coordination between breathing and swallowing (31, 32), increasing risk of aspiration (33). Deficits observed during the oral voluntary phase of the swallow may be related to corticobulbar and corticopontine degeneration (a hallmark feature of FRDA) (34). Diminished pharyngeal and laryngeal sensitivity may be a manifestation of sensory peripheral neuropathy (also a sequela of FRDA) (35). Future research could consider measures of laryngeal sensitivity in the FRDA population (via cough reflex testing, for example), as well as the reliability of other non-instrumental measures of swallowing in predicting aspiration in this population, including pulse oximetry.

Clinical implications of this research

This research informs the nature of swallowing assessment appropriate for the FRDA population, as well as management. Swallowing function and swallowing perception do not correlate in individuals with FRDA, and therefore open-ended questions enquiring about swallowing function during a scheduled clinical visit should not be considered reliable. More informed specific questioning pertaining to swallowing function may be a reliable indicator, however it is recommended clinicians screen individuals with FRDA for dysphagia using a standardised questionnaire such as the SWAL-QOL. Results of the SWAL-QOL will inform the clinician on the impact dysphagia may have on the QOL of the individual, and this information should be used to guide management and rehabilitation of swallowing function. Furthermore, a bedside swallowing assessment, and a judgement of aspiration based on the presence or absence of a cough on bedside assessment is not reliable given significant silent aspiration in the FRDA population. Instrumental analysis remains the only objective way to identify aspiration in this population, however recommendations made should consider the

significant limitations of VFSS. The management of FRDA-related dysphagia should be guided and informed via collaboration between the Speech Pathologist, Neurologist, the wider treating team, and the patient, to address the physical and psychosocial impacts of the condition.

Although this study proved aspiration to be present in a third of individuals with FRDA, the clinical implications of FRDA-related aspiration remain unclear. In the only study of mortality in FRDA, pneumonia accounted for almost 10% of deaths (13), yet data pertaining to the frequency of aspiration-related pneumonia in the FRDA population is limited. An important next step in this research would be to determine the causal relationship, if any, between aspiration and the presence of pneumonia in FRDA

The management of FRDA-related dysphagia should be guided and informed by collaboration with cross-disciplinary colleagues (including speech pathology, neurology, physiotherapy and occupational therapy) to address the physical and psychosocial impacts of swallowing impairment. Here we showed oral and pharyngeal dysphagia secondary to FRDA, characterised by reduced bolus control and clearance in the oral phase of swallowing, impaired pharyngeal constriction and clearance, and aspiration (including silent aspiration). FRDA may affect an individual's ability to consume solid foods, indicated by the pronounced difficulty clearing biscuit from the mouth and pharynx observed here. The aspiration observed was trace amounts only; a phenomenon also reported in 28% of otherwise healthy individuals (36). These data, coupled with adequate cognitive function and decision-making capacity characteristic of FRDA, points towards management that includes diet and postural modification, alongside the prescription of specialised feeding equipment such as controlled-flow containers. Drastic textural modifications to food and thickening fluids is not currently recommended given the impact these changes have on the QOL of individuals.

Limitations

The current study has some limitations. Despite being the largest cohort study of swallowing in FRDA to date, the relatively small sample size may have impacted our capacity to identify predictors of aspiration. The small sample size made distribution and division of the data difficult, especially as the sample was dichotomised to identify predictors of aspiration. The non-significant result (in the identification of predictors of aspiration) is possibly due to a Type II error due to the small sample size. The lack of an associated predictive parameter does not mean that one does not exist. It would be interesting to see if increasing the sample size would in turn increase the power of the statistical analysis. Furthermore, missing data (from the 22 participants who did not participate in assessment beyond a case history and SWAL-QOL, or the nine participants who did not participate in FARS) may have biased the results of this study. Another limiting factor is the limited number of pediatric participants (<18 years) included in this study (four in total completed the SWAL-QOL, two completed the FDA-2, and one participated in VFSS), meaning the spectrum of FRDA disease severity may not be completely captured in this study.

CONCLUSION

Oral and pharyngeal phase dysphagia is prevalent in FRDA and appears to worsen with disease duration and severity. Aspiration is not predictable in this population and appears to occur at any stage of disease, necessitating the need for regular monitoring and evaluation of swallowing function. Dysphagia significantly impacts QOL in individuals with FRDA, and management should reflect and address the significant burden associated with swallowing impairment in these individuals. This characterization work lays the foundation for future targeted clinical trials given there is an absence of high quality evidence supporting the use of *any* dysphagia treatment in ataxia (37).

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Table I- Demographic and clinical characteristics of the FRDA cohort, and total assessment scores

ID	*Age at onset (y)*	*Gender*	*GAA1*	*GAA2*	*FARS*	*Total assessment score*				
						SWAL-QOL (total)	*FDA-2 (total)*	*VFSS (PAS score)*		
								F	*P*	*B*
FA001	13	f	706	811	106.5	88	56	1	1	1
FA002	5	m	1099	1099	n/a	60	102	1	2	2
FA003	24	m	682	1041	96	94	42	2	1	1
FA004	25	f	284	984	78	53	n/a	1	1	1
FA005	14	m	720	720	66	95	64	1	1	1
FA006	15	m	720	720	68	85	70	1	1	1
FA007	3	m	645	771	127.5	49	115	1	2	1
FA008	14	f	760	1020	117	76	n/a	n/a	n/a	n/a
FA009	14	m	471	590	74.5	80	60	2	2	1
FA010	14	m	552	552	71.5	71	84	8	2	2
FA011	11	f	444	526	70.5	66	56	2	1	1

FA012	14	m	650	900	129	83	84	1	1	1
FA013	18	f	447	967	102	72	56	2	2	1
FA014	18	m	374	985	66.0	84	n/a	n/a	n/a	n/a
FA015	8	f	642	1132	136.0	54	94	2	2	1
FA016	28	m	606	986	102.5	83	60	1	2	1
FA017	20	f	646	1293	115.7	68	76	1	1	1
FA018	11	f	659	865	108.5	71	n/a	n/a	n/a	n/a
FA019	9	f	694	1000	1190	72	n/a	n/a	n/a	n/a
FA020	23	m	291	912	37.5	92	n/a	n/a	n/a	n/a
FA021	7	m	780	980	138.5	60	124	8	n/a	4
FA022	34	m	126	924	71.5	94	n/a	n/a	n/a	n/a
FA023	10	m	659	822	109.5	54	120	1	n/a	1
FA024	12	m	850	850	n/a	72	126	8	n/a	1
FA025	13	f	471	707	130.5	81	n/a	n/a	n/a	n/a
FA026	32	m	320	320	70.5	100	n/a	n/a	n/a	n/a
FA027	26	m	560	989	n/a	83	80	2	1	1

FA028	19	m	476	545	76.5	74	60	4	4	1
FA029	14	f	833	835	95.5	84	84	1	8	1
FA030	6	m	815	856	n/a	91	36	n/a	n/a	n/a
FA031	12	f	685	1064	41	100	n/a	n/a	n/a	n/a
FA032	14	m	569	884	77	92	54	1	2	1
FA033	30	m	323	1046	66	96	n/a	n/a	n/a	n/a
FA034	21	f	462	462	84.5	21	62	8	1	1
FA035	14	f	727	727	90.5	87	72	n/a	n/a	n/a
FA036	30	f	414	590	63.5	92	34	1	1	1
FA037	3	m	800	800	109.5	82	76	2	2	1
FA038	21	f	437	611	n/a	87	n/a	n/a	n/a	n/a
FA039	8	m	733	943	117.5	100	74	1	1	1
FA040	14	m	505	1345	119.5	71	n/a	1	1	1
FA041	10	m	593	957	48.5	96	n/a	n/a	n/a	n/a
FA042	10	f	706	706	n/a	72	81	n/a	n/a	n/a
FA043	13	f	747	875	98.5	98	n/a	8	1	1

FA044	6	m	713	875	111	95	n/a	8	1	1
FA045	12	m	818	818	78	100	n/a	2	1	1
FA046	18	f	489	1207	140	81	n/a	8	4	8
FA047	17	m	589	589	n/a	68	118	8	4	4
FA048	14	m	853	853	n/a	79	86	4	1	1
FA049	10	m	779	932	70	89	39	4	4	1
FA050	7	m	998	998	96.5	69	n/a	1	1	1
FA051	4	f	556	733	66	86	n/a	n/a	n/a	n/a
FA052	16	f	690	690	109.7	80	70	n/a	n/a	n/a
FA053	11	m	647	915	n/a	70	n/a	n/a	n/a	n/a
FA054	32	f	674	803	84	78	56	4	8	4
FA055	13	m	558	784	101.5	85	38	n/a	n/a	n/a
FA056	16	m	630	850	55.5	80	34	1	1	1
FA057	28	m	383	942	69.5	n/a	n/a	2	1	1
FA058	17	m	1050	1050	62.5	78	n/a	n/a	n/a	n/a
FA059	6	m	1015	1015	125	63	n/a	n/a	n/a	n/a

FA060	21	m	527	1058	79	72	n/a	n/a	n/a	n/a
mean	15.4		627.5	863.7	91.1	184.2	72.1	3.0	2	1.5
SD	7.7		193.1	197.0	35.6	26.0	26.2	2.8	1.8	1.4
Range	3-34		126-1099	320-1345	37.5-140	85-220	34-126	1-8	1-8	1-8

f Female, m Male, SD Standard Deviation, F fluid, P puree, B biscuit, n/a Not Applicable

Table II - SWAL-QOL subsections and total SWAL-QOL for individuals with FRDA and healthy controls

	FRDA (n=59)		*HC (n=59)*		*Mann-Whitney U test*
SWAL-QOL Domain	*Mean*	*SD*	*Mean*	*SD*	
Burden	85.17	19.90	99.58	3.25	U=886.00, z=-5.95, p=0.00, r=-0.77
Eating Duration	64.19	30.39	89.41	18.10	U=828.00, z=-5.12, p=0.02, r=-0.67
Eating Desire	89.55	16.78	96.19	8.52	U=1383.00, z=-2.34, p=0.00, r=-0.30
Symptom Frequency	77.33	16.06	91.80	9.85	U=757.50, z=-5.32, p=0.00, r=-0.69
Food Selection	89.62	17.39	98.94	5.82	U=1213.00, z=-4.18, p=0.00, r=-0.54
Communication	74.15	21.76	98.09	6.06	U=634.00, z=-6.81, p=0.00, r=-0.89
Fear	78.39	20.48	97.03	7.19	U=718.00, z=-6.01, p=0.00, r=-0.78
Mental Health	85.76	18.45	99.41	2.95	U=859.00, z=-5.88, p=0.00, r=-0.77
Social	92.46	15.74	99.83	0.91	U=1313.50, z=-3.67, p=0.00, r=-0.48
Fatigue	59.75	27.82	76.27	22.84	U=1152.50, z=-3.67, p=0.00, r=-0.41
Sleep	71.19	27.68	82.20	19.59	U=1152.50, z=-3.67, p=0.04, r=-0.27
Total	78.87	15.03	93.49	5.64	U=612.00, z=-6.08, p=0.00, r=-0.79

Table III - Logistic regression predicting likelihood of airway entry of barium

						95% confidence interval for odds ratio	
Variables	B	Wald	df	p	Odds ratio	Lower	Upper
GAA2	-0.00	2.60	1	0.11	0.99	0.99	1.00
FDA-2 Reflexes	0.23	1.26	1	0.26	1.26	0.84	1.89
FDA-2 Intelligibility	0.07	0.23	1	0.63	1.07	0.81	1.42

Figure 1- Venn diagram demonstrating participation across three assessments

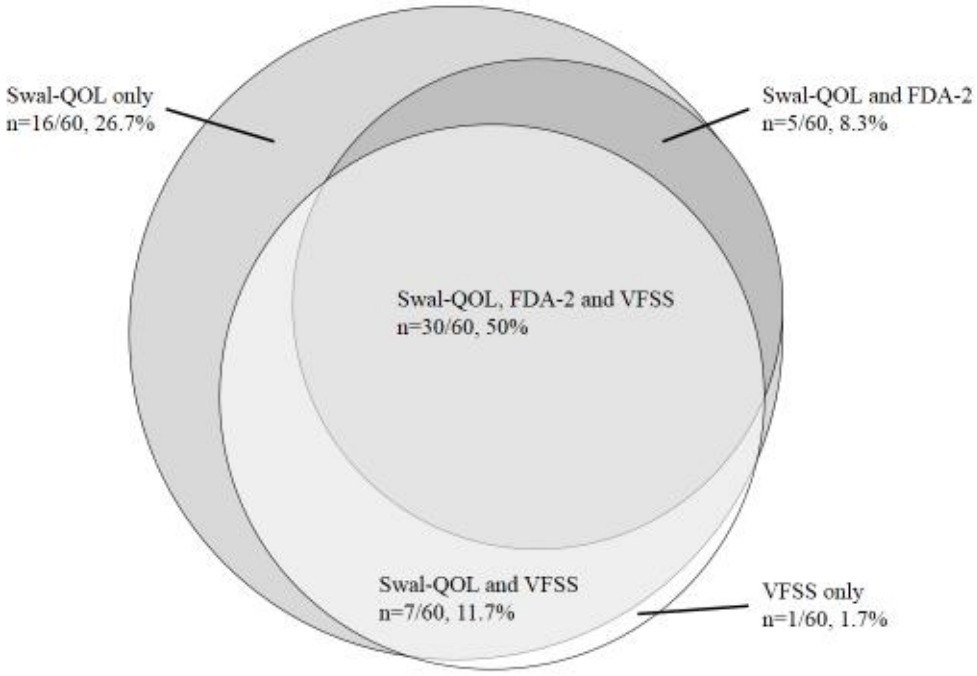
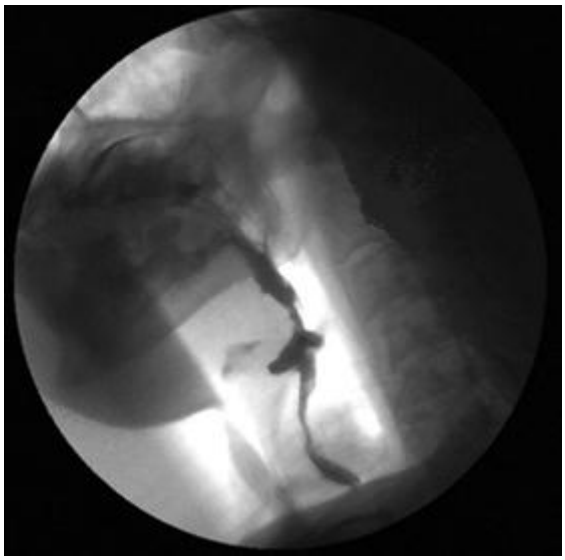
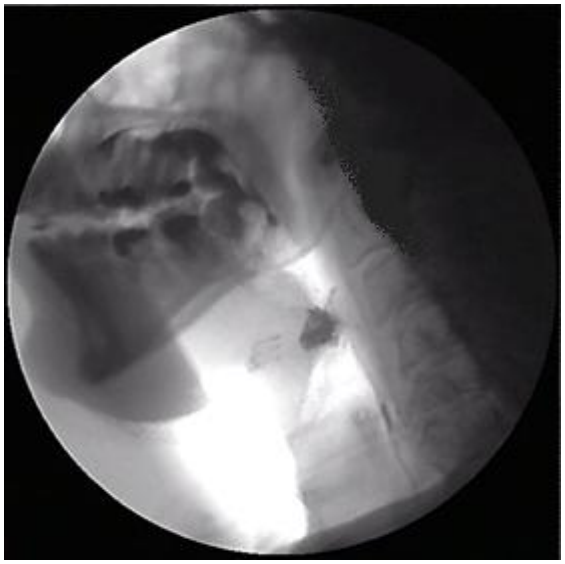


Figure 2 - VFSS of a 50 year old male with Friedreich ataxia (age at onset - 7 years, disease duration– 43.7 years, FARS - 138.5) demonstrating (A) a delayed pharyngeal swallow with unmodified fluid, and (B) pharyngeal residue in the valleculae and above the cricopharyngeal sphincter following swallow of biscuit

A.



B.



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Supplementary material

Supplemental Table I – Relationships between Swal-QOL and FRDA clinical parameters

	Burden	*Eating duration*	*Eating Desire*	*Symptom Frequency*	*Food selection*	*Communication*	*Fear*	*Mental Health*	*Social*	*Fatigue*	*Sleep*	*Total*
GAA1	-0.05	-0.01	-0.01	-0.06	0.05	0.00	-0.04	-0.02	0.19	0.00	0.00	-0.03
GAA2	-0.09	-0.09	0.06	-0.02	-0.07	-0.02	0.01	-0.06	0.13	-0.01	0.00	-0.05
FARS	-0.3*	-0.3	-0.14	-0.4**	-0.3*	-0.4**	-0.4**	-0.3*	-0.20	-0.19	-0.18	-0.4**
Age at disease onset	0.15	0.07	0.05	0.18	0.03	0.20	0.08	0.15	0.05	0.19	0.18	0.20
Age at assessment	-0.21	-0.1	-0.03	-0.20	-0.22	-0.26*	-0.29*	-0.19	-0.18	0.08	-0.07	-0.21
Disease duration	-0.38*	-0.34*	-0.07	-0.30	-.334*	-.513**	-0.29	-.352*	-0.17	0.07	-0.12	-0.36*

**Significant at p<0.0.1

* Significant at p<0.05

Supplemental Table II - FDA-2 results

						Arithmetic domain score	
		Min	Max	*Mean*	*Standard deviation*	*Mean*	*Standard deviation*
Reflexes	Cough	1	7	2.9	1.5	2.7	1.2
	Swallow	1	5	3.3	1.4		
	Dribble/Drool	1	5	2.0	1.4		
Respiration	Rest	1	7	2.8	1.6	2.8	1.4
	In Speech	1	7	2.8	1.4		
Lips	Rest	1	3	1.2	0.6	2.3	0.6
	Spread	1	3	1.2	0.6		
	Seal	1	5	2.6	1.3		
	Alternate	1	5	3.1	1.0		
	In Speech	1	5	3.1	1.1		
Palate	Fluids	1	3	1.2	0.6	1.9	0.6
	Maintenance	1	3	1.2	0.6		

	Speech	1	5	3.3	1.2		
Laryngeal	Time	1	9	3.2	2.1	4.0	1.6
	Pitch	1	9	4.7	2.2		
	Volume	1	7	4.7	1.9		
	In speech	1	7	3.3	1.6		
Tongue	rest	1	5	2.1	1.3	3.0	1.2
	protrusion	1	7	2.8	2.0		
	elevation	1	7	3.2	1.8		
	lateral	1	7	2.4	1.7		
	alternate	1	7	3.7	1.5		
	speech	1	5	3.7	1.3		
Intelligibility	words	1	5	2.3	1.5	2.5	1.5
	sentences	1	7	2.6	1.7		
	conversation	1	7	2.5	1.5		
Total FDA2 score		34.00	126.0	72.7	26.2		

Supplemental Table III – Relationships between FDA-2 and FRDA clinical parameters

	Reflexes	*Respiration*	*Lips*	*Palate*	*Laryngeal*	*Tongue*	*Intelligibility*	*Total*
GAA1	0.13	0.26	0.25	0.09	0.32	0.45**	0.22	0.40*
GAA2	-0.07	0.15	0.09	0.12	0.14	0.19	0.00	0.11
FARS	0.48**	0.54**	0.52**	0.66**	0.63**	0.48**	0.55**	0.64**
Age at disease onset	-0.18	-0.27	-0.34*	-0.17	-0.32	-0.52**	-0.25	-0.37*
Age at assessment	0.37*	0.38*	0.18	0.45**	0.36*	0.03	0.39*	0.34
Disease duration	0.60**	0.53**	0.57**	0.67**	0.71**	0.58**	0.66**	0.74**

**Significant at p<0.0.1

* Significant at p<0.05

Supplemental Table IV - Results of VFSS as rated by the BAS

		Min	*Max*	*Mean*	*Standard deviation*
Lip function	Fluid	1	2	1.1	0.3
	Puree	1	3	1.4	0.5
	Biscuit	1	3	1.5	0.6
Tongue function	Fluid	1	3	1.5	0.6
	Puree	1	3	2.1	0.6
	Biscuit	2	4	2.9	0.8
Jaw function	Fluid	1	3	1.1	0.4
	Puree	1	3	1.1	0.4
	Biscuit	1	3	1.2	0.5
Soft palate function	Fluid	1	4	1.7	0.9
	Puree	1	4	1.7	0.9
	Biscuit	1	4	1.8	0.9
Reflex initiation	Fluid	2	4	3.1	0.7
	Puree	2	4	3.1	0.5
	Biscuit	2	4	3.1	0.5
Aspiration	Fluid	1	4	1.7	0.8
	Puree	1	3	1.5	0.6
	Biscuit	1	3	1.2	0.4
Residue in valleculae	Fluid	1	3	1.6	0.7
	Puree	1	4	2.7	0.9
	Biscuit	1	4	3.0	1.0

Residue in pyriform sinuses	Fluid	1	3	1.4	0.5
	Puree	1	3	2.1	0.8
	Biscuit	1	4	2.0	0.8
Pharyngeal function	Fluid	1	3	1.4	0.6
	Puree	1	4	2.4	0.9
	Biscuit	1	4	2.4	0.9
Cricopharyngeal function	Fluid	1	3	1.5	0.7
	Puree	1	4	2.4	0.9
	Biscuit	1	4	2.6	1.0

Supplemental Table V – Relationships between VFSS (BAS) and FRDA clinical parameters

	Lips			*Tongue*			*Jaw*			*Soft palate*			*Reflex*			*Aspiration*			*Valleculae*			*Pyriform*			*Pharyngeal*			*Cricopharyngeal*		
	F	P	B	F	P	B	F	P	B	F	P	B	F	P	B	F	P	B	F	P	B	F	P	B	F	P	B	F	P	B
GAA1	0.07	-0.32	-0.11	-0.09	0.03	0.14	-0.11	0.12	0.00	-0.14	-0.17	-0.07	-0.08	-0.14	-0.01	-0.07	0.08	0.10	-0.15	0.03	0.42**	-0.19	-0.20	0.08	-0.21	0.00	0.18	0.00	0.00	0.18
GAA2	-0.01	0.08	0.16	-0.18	0.05	0.11	-0.02	0.08	0.09	0.16	0.17	0.21	0.04	-0.19	0.15	-0.16	-0.03	0.14	0.12	0.09	0.35*	0.15	0.13	0.26	0.05	0.37*	0.45**	0.04	0.11	0.21
FARS	0.48**	0.20	0.13	0.18	0.03	0.26	0.17	0.31	0.38*	0.45**	0.41*	0.46**	0.21	0.05	0.42*	0.11	0.18	0.32	0.14	0.03	0.30	0.06	-0.01	0.17	0.17	0.16	0.29	0.07	0.00	0.25
Age at disease	-0.18	0.01		-0.00	0.0		0.00	-0.0	-0.0	-0.0	-0.0	-0.0	-0.0	-0.0	-0.0	0.01	-0.0	0.02	0.06	0.03	-0.0	0.00	0.14	-0.0	-0.0	-0.0	-0.0	-0.0	-0.0	-0.0

onset	17			05		28		16	12	14	10	20	05	02	04		08			30			21	02	17	30	12	06	24
Age at assessment	0.44**	0.31	0.25	0.10	0.11	0.06	0.14	0.28	0.34*	0.27	0.30	0.31	0.18	0.06	0.34*	0.14	0.09	0.46**	0.33*	0.23	0.14	0.19	0.26	0.08	0.31	0.10	0.14	0.17	0.08	0.11
Disease duration	0.58**	0.19	0.20	0.19	0.11	0.26	0.17	0.44**	0.46**	0.42**	0.45**	0.50**	0.21	0.13	0.43**	0.16	0.18	0.45**	0.26	0.27	0.35*	0.14	0.22	0.24	0.29	0.22	-0.33*	0.21	0.12	0.25

F- Fluid, P – Puree, B – Biscuit,

**Significant at p<0.0.1

* Significant at p<0.05

Supplemental Table VI – Relationships between penetration/aspiration and FRDA clinical parameters

	Penetration-Aspiration Scale		
	Fluid	Puree	Biscuit
GAA1	-0.02	0.03	0.04
GAA2	-0.20	-0.12	0.03
FARS	0.06	0.10	0.21
Age at disease onset	0.01	-0.03	0.04
Age at assessment	0.11	0.09	0.41*
Disease duration	0.12	0.16	0.38*

**Significant at $p<0.01$

* Significant at $p<0.05$

Supplemental Table VII - Logistic regression between significant airway entry (PAS > 3) and independent variables

		Equation	Cox and Snell R square	Nagelkerke R squared	Whole model	Wald	Sig
FRDA clinical parameters	GAA1	X2(1, N=38)=0.57 (p=0.45)	0.02	0.02	63.2%	0.56	0.45
	GAA2	X2(1, N=38)=2.33 (p=0.13)	0.06	0.08	68.4%	2.13	0.15
	FARS	X2(1, N=38)=0.09 (p=0.76)	0.00	0.00	69.7%	0.09	0.76
	Age at disease onset	X2(1, N=38)= 0.00 (p=0.98)	0.00	0.00	65.8%	0.00	0.99
	Disease duration	X2(1, N=38)= 1.32 (p=0.25)	0.03	0.05	71.1%	1.29	0.26
Swal-QOL	Total score	X2(1, N=37)= 0.22 (p=0.64)	0.01	0.01	64.9%	0.22	0.64
	Burden	X2(1, N=37)= 0.25 (p=0.64)	0.01	0.01	64.9%	0.26	0.61
	Eating desire	X2(1,	0.00	0.00	64.9%	0.02	0.89

		N=37)=0.02 (p=0.88)					
	Eating duration	X2(1, N=37)= 0.42 (p=0.52)	0.01	0.02	64.9%	0.42	0.52
	Symptom frequency	X2(1, N=37)=0.53 (p=0.47)	0.01	0.35	67.6%	0.53	0.47
	Food selection	X2(1, N=37)=0.27 (p=0.87)	0.00	0.00	64.9%	0.03	0.87
	Communication	X2(1, N=37)= 0.00 (p=0.97)	0.00	0.00	64.9%	0.00	0.97
	Fear	X2(1, N=37)= 0.00 (p=0.78)	0.00	0.00	64.9%	0.08	0.78
	Mental health	X2(1, N=37)= 0.02 (p=0.90)	0.00	0.00	64.9%	0.02	0.90
	Social	X2(1, N=38)= 0.12 (p=0.73)	0.00	0.00	64.9%	0.12	0.73
	Fatigue	X2(1, N=38)=0.84 (p=0.77)	0.00	0.00	64.9%	0.08	0.77
	Sleep	X2(1, N=38)= 1.28 (p=0.26)	0.03	0.05	64.9%	0.26	0.84
FDA-2	Total score	X2(1, N=30)= 1.78 (p=0.18)	0.06	0.08	70.0%	1.70	0.19

	Reflexes	X2(1, N=30)=5.98 (p=0.01*)	0.18	0.25	80.0%	4.59	0.03*
	Respiration	X2(1, N=30)= 1.36 (p=0.24)	0.04	0.06	73.3%	1.31	0.25
	Lips	X2(1, N=30)= 2.88 (p=0.09)	0.09	0.13	73.3%	2.56	0.11
	Palate	X2(1, N=30)= 1.11 (p=0.29)	0.04	0.05	70.0%	1.05	0.31
	Laryngeal	X2(1, N=30)= 0.22 (p=0.64)	0.01	0.01	66.7%	0.22	0.64
	Tongue	X2(1, N=30)= 0.30 (p=0.58)	0.01	0.01	66.7%	0.30	0.59
	Intelligibility	X2(1, N=30)= 3.11 (p=0.08)	0.10	0.14	60.0%	2.82	0.09

**significant at p<0.0.1, *significant at p<0.05

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