

Subclinical Dysphagia in Persons With Prader–Willi Syndrome

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Prader–Willi Syndrome (PWS) is caused by a genetic imprinting abnormality resulting from the lack of expression of the paternal genes at 15q11–q13. Intellectual disability, low muscle tone, and life-threatening hyperphagia are hallmarks of the phenotype. The need for the Heimlich maneuver, death from choking, and pulmonary infection occur in a disproportionately high number of persons with PWS. The widely held belief is that eating behaviors are responsible for choking and aspiration; yet, no investigation had sought to determine if swallowing impairments were present in persons with PWS. To address this research and clinical gap, simultaneous videofluoroscopy and nasal respiratory signals were used to record swallowing function and breathing/swallowing coordination in 30 participants with PWS. Subjects consumed thin liquid and barium cookies under two randomized conditions as follows: (i) controlled (cues to swallow and standardized bolus sizes); (ii) spontaneous (no cues or bolus size control). Under videofluoroscopy, the cohort showed disordered pharyngeal and esophageal swallowing in both conditions with disturbances in timing, clearance, and coordination of swallowing with the respiratory cycle. No participant showed a sensory response such as attempting to clear residue or coughing; thereby supporting the lack of overt symptoms. We conclude that the high death rate from choking and pulmonary infection in children and adults with PWS may be related, in part, to underlying, asymptomatic dysphagia. The combination of rapid eating and dysphagia would increase the risk of aspiration-related morbidity and mortality. © 2016 Wiley Periodicals, Inc.

Key words: Prader–Willi syndrome; dysphagia; deglutition disorders; esophageal dysmotility; choking; swallowing disorders; aspiration pneumonia

INTRODUCTION

Prader–Willi Syndrome (PWS) is a rare neurogenetic disorder that affects approximately one in every 10,000–22,000 Live births. Prader–Willi Syndrome is caused by a genetic imprinting abnormality resulting from the lack of expression of the paternal genes at 15q11–q13. Both paternal deletion and maternal

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uniparental disomy (UPD) of this region produce symptoms consistent with PWS [Sahoo et al., 2008]. The absence of expression of the *necdin* gene (*NDN*), one of the protein encoding genes located in the deletion, has been linked to several sensory-motor deficits in PWS such as severe hypotonia at birth, failure to thrive, and developmental delay [Jay et al., 1997; MacDonald and Wevrick, 1997; Lee et al., 2005; Pagliardini et al., 2005]. *NDN* is important to the development of neurons in the hypothalamus [Muscatelli et al., 2000; Nakada et al., 2000], and its absence has been associated with other features of the syndrome, such as temperature instability, hypogonadism, pain insensitivity, decreased thirst, viscous saliva, and several endocrine abnormalities [Angulo et al., 2015]. Hyperphagia, combined with increased adiposity and decreased lean muscle mass, may be a function of unexpressed *NDN* [Bush and Wevrick, 2012], making PWS the most common cause of genetic obesity [Butler, 2011]. Intellectual disability and low muscle tone are characteristic of the phenotype resulting in functional impairments associated with daily living. Unfortunately, mortality risk is increased for those with PWS and deaths are often unexpected [Whittington and Holland, 2004; Lioni et al., 2015].

It is well-established that death rates are higher in persons with intellectual disability [Heslop and Glover, 2015; Lauer and

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McCallion, 2015; McCarron et al., 2015; Arvio et al., 2016]. When matched for similar intellectual levels, the PWS death rate is four times greater, and when compared to groups with mild intellectual impairment or average IQ, PWS death rate was found to be greater by a factor of 20 [Einfeld et al., 2006]. Several descriptive studies provided summary data in relation to mortality in PWS, and premature deaths from choking appear to occur at alarmingly high rates [Eiholzer, 2005; Nagai et al., 2005; Einfeld et al., 2006]. In response to the unexplained high death rate in PWS, Stevenson et al. [2007] surveyed families whose loved ones with PWS had died prematurely. They reported that respiratory compromise and pneumonia were listed as the cause of death in 24% of 152 decedents. Choking was listed as the cause of death in twelve persons (8%) who ranged in age from 3 to 52 years. Thirty-four percent of the decedents had a history of choking at mealtimes with six percent requiring the Heimlich maneuver. Moreover, in 78%, death was reported as sudden and/or unexpected. Tauber et al. [2008] provided additional support for Stevenson's findings. In their review of 64 cases of death in children with PWS, respiratory infection was the most common cause of death in nearly half (44%), with five percent (5%) caused by food-related asphyxiation. Numerous reports of premature deaths from choking and pulmonary infection have been published [Butler et al., 2002; Schrandt-Stumpel et al., 2004; Stevenson et al., 2004; Vogels et al., 2004; Eiholzer, 2005; Nagai et al., 2005; Grugni et al., 2008; Jacob et al., 2008; Tauber et al., 2008].

Probable causes for the increased choking risk in persons with PWS are thought to be related to neurobehavioral factors such as eating too quickly (gorging) and/or incomplete chewing that could cause solid food to block the airway [Stevenson et al., 2007; Guthrie et al., 2015]. The high incidence of pulmonary infection in PWS is considered to be related to "unrecognized aspiration" where liquids or food enter the airway below the level of the true vocal folds and into the lungs. Indeed, an association between intellectual disabilities, fast eating, and increased choking risk has been reported [Samuels and Chadwick, 2006; Thacker et al., 2008; Guthrie and Stansfield, 2015]. Furthermore, children and persons with intellectual disabilities and swallowing impairments (dysphagia) are at even greater risk for asphyxiation from food or silent aspiration [Samuels and Chadwick, 2006; Weir et al., 2011]. Based upon what is currently understood about the functional consequences associated with the deletion, a genetic predisposition to impairments in complex functions that rely on sensory-motor integration, such as swallowing function, should be suspected.

Swallowing is not a simple, segmental reflex, but rather a highly complex motor pattern that emanates from bilateral, brainstem central pattern generators that receive and process sensory input from the cortex and periphery [Lowell et al., 2008]. Medullary centers for swallowing and breathing are adjacent to one another, and some neurons serve both functions. Because gross anatomy for breathing and swallowing also overlap, proper coordination between the two functions is crucial to safe passage of food and drink. Interestingly, studies using *Ndn* nil mice have revealed atypical development of medullary respiratory neurons as indicated by recording irregular, rather than rhythmic, discharge patterns [Ren et al., 2003] and this could imply that unsafe coordination between the two functions may be present in

persons with PWS. Furthermore, axonal abnormalities such as defasciculations and altered pattern growth, that can ultimately impair neural transmission, have been observed in prenatal *Ndn* deficient mice [Pagliardini et al., 2005].

Impairments in sensory input, muscle weakness, respiratory insufficiency, cortical, and subcortical damage are among the many factors that can disrupt sensory-motor integration and cause dysphagia [Logemann, 1998]. Since many known impairments related to dysphagia exist within PWS, it seemed plausible that subclinical (without symptoms) disordered swallowing could be a significant, yet unknown, contributing risk factor to frequent choking and high pulmonary infection rates. For that reason, we conducted a thorough review of the literature; however, we could not find an investigation that examined swallowing function in persons with PWS. Therefore, to begin to address this research and clinical gap, the purpose of this investigation was to determine if dysphagia and/or risk factors for aspiration are present in persons with PWS. We also sought to determine if eating behaviors contribute to choking and aspiration risk, as had been suggested. We hypothesized that dysphagia and risk factors for oropharyngeal aspiration would be revealed under videofluoroscopy and that the risk factors for choking and aspiration would increase when persons with PWS ate and drank spontaneously.

MATERIALS AND METHODS

Experimental Design

This experiment employed a prospective, repeated measures design. Swallowing function was measured in a single cohort (PWS) under two conditions that were randomized. This research study was approved by The Children's Institute Institutional Review Board. Signed, informed consent was provided by all parents and guardians. All participants gave written assent prior to study procedures.

Inclusion/Exclusion Criteria

Because no prior work had been done in the area of dysphagia, persons with PWS from age 4 to 55 were eligible to enroll. Children under age four were excluded because younger children may not have been able to follow directions for the study procedures. The upper age limit of 55 years was set as the cut-off, since age-related swallowing changes can occur after this age in typical persons. Individuals with a history of surgical treatment for obstructive sleep apnea (uvulopalatopharyngoplasty) were excluded because of the potential effects on pharyngeal swallowing function. Participants without adequate dentition for mastication (defined as occlusion molars on at least one side of the mouth) were excluded. Medication use was documented, but not used as criteria for inclusion or exclusion.

To limit radiation exposure time, we elected to study the two consistencies that were most likely to uncover dysphagia: thin liquids because they are easily aspirated, and a solid consistency that would require mastication, because solids have the potential to occlude the airway. The thin liquid was taken from a standardized mixture of 100 cc of water and 25 g of flavored powdered barium

(Varibar[®] barium sulfate, EZ EM Canada, Inc. 40% wt/vol). The viscosity of this mixture is very low (approximately four centipoise) making it similar to liquids that are commonly consumed. For a uniformly solid consistency that would require mastication, cookies that were baked with barium in the dough (Wanda's Barium Cookies, Calumet, MI, product #200) were used. Each cookie was approximately 1.5" diameter and weighed about 12 g.

To assess if neurobehavioral factors such as rapid eating or taking large mouthfuls had an influence on swallowing function, two randomly assigned conditions were employed for comparison, controlled and spontaneous. In the *controlled* condition, the size of each bolus and the rate of oral delivery were controlled by the investigator. In this condition, two 5 cc and two 10 cc boluses of thin liquid were delivered to the oral cavity using a small syringe. Subjects were instructed to "hold it in your mouth until I tell you to swallow." The two different liquid sizes were selected with the aim of making within-group comparisons and to determine if the size of the swallowed liquid bolus was related to aspiration risk. Also, 5 and 10 cc volumes are commonly used in dysphagia research and we planned to compare the data from those with PWS to the available literature. The bolus size of the cookie in this condition was controlled by splitting each cookie into two near-equal parts. Each half cookie was handed to the participant. The average weight of cookie halves was 5.81 g. The order of delivery of cookie halves and liquids was randomized within the controlled condition.

In the *spontaneous* condition, each participant ate and drank a fixed amount without cues or external controls. It was expected that the spontaneous condition would promote larger bolus sizes when drinking [Lawless et al., 2003] and/or that bigger bites of the cookie would be taken by the subjects when the amount was not controlled by the investigators. For this condition, a tray was placed in front of the participant with the remaining 70 cc of thin liquid contained in a Styrofoam cup and a whole cookie. Participants were told to "have a snack" and to "eat any way that they would like" and to "pretend that no one is here."

Participants

Thirty volunteers with PWS met the inclusion/exclusion criteria and participated in the research procedures. Twenty-three of the participants were recruited from an in-patient behavioral health and weight loss program; the remainder responded to IRB approved advertisements. There were 15 males and 15 females. Twenty-four subjects were Caucasian (80%), five were African American (17%), and one person was Hispanic. The average age of the participants was 18.6 years (range 5–35 years). According to medical records or family report, the deletion genotype was present in 19 subjects, maternal UPD in 10 subjects; and genotype in one person was unknown. There was no single medication taken by all subjects. Calcium carbonate was most commonly prescribed (21/30 subjects or 70%). Human growth hormone (HGH) was the second most commonly prescribed medication (11/30 or 37% of the participants). Ten subjects had never received HGH, eleven persons were receiving HGH at the time of data collection, and nine had received HGH in the past, but were not receiving it at the time of the study. The average body mass index (BMI) was 38.1 (range 17.2–70.3). Table I contains the brand name of medications

TABLE I. Medications Taken by Three or More Subjects at Time of Study

Brand/generic medications	% of subjects
Calcium carbonate	70
Human growth hormone	37
Metformin	23
Antibiotics	17
Topamax [™] /topiramate	17
Risperdal [™] /risperidone	13
Prozac [™] /fluoxetine	13
Geodon [™] /ziprasidone	13
Abilify [™] /aripiprazole	10
Lamictal [™] /lamitrigine	10
FeoSol [™] , Feratab [™] /iron	10
Aldactone [™] /spironolactone	10
Intuniv [™] /guanfacine	10

that were taken by three or more participants and shows the percentage of subjects who were on the medication at the time of data collection.

Simultaneous swallowing physiology and nasal respiratory signals, were observed directly in real-time using radiographs digitally recorded with a C-arm fluoroscope (Siemens, Compact L, Erlangen, Germany) connected to a KayPentax (Lincoln Park, NJ) Swallowing Workstation (Model 7200). The C-arm was set on continuous fluoroscopy and frame rate was 30/sec. Breathing cycle was tracked and recorded using a nasal cannula connected to the workstation's thermistor. The KayPentax software was used to obtain temporal measurements and frame by frame analyses of swallowing physiology. The analyses of all swallowing measures were conducted by the speech pathology co-investigators (RRG, KH) trained by the principal investigator (RDG), who has over 20 years of dysphagia research experience. RGG and KH have specialty training in dysphagia and each has at least 8 years of experience in videofluoroscopic swallowing evaluation and measurement using KayPentax analysis software. RDG performed all measurements and judgments for the inter-rater reliability measures.

Each participant was seated comfortably in a chair throughout data collection. The principal investigator, RDG, conducted all procedures on all subjects. The image intensifier was set so that the oral cavity, pharynx, larynx, and upper trachea were in lateral view (Fig. 1). For anterior-posterior (AP) views of the esophagus, the upper margin of the field was set just below the level of the mandible to ensure that as much of the esophagus as possible could be viewed.

Measurements

Five predetermined swallowing measurements were chosen because they are widely used and indicative of dysphagia or risks for aspiration/airway occlusion. To determine if aspiration and risk factors for aspiration were present, the depth of entry into the airway was rated using the highly reliable Penetration-Aspiration Scale (PAS) [Rosenbek et al., 1996; Robbins et al., 1999]. The PAS

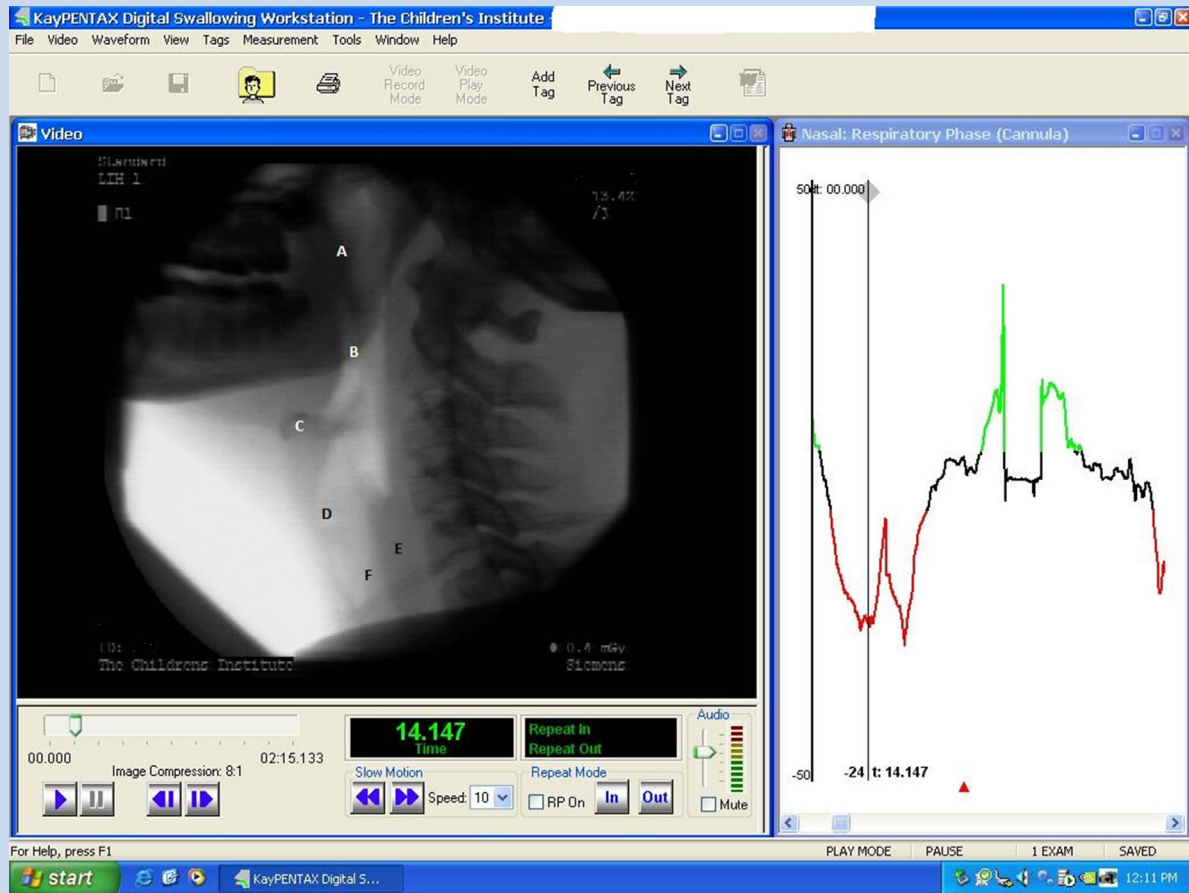


FIG. 1. X-ray image: [A] Soft palate at rest. [B] Ramus of the mandible. [C] Hyoid bone. [D] Level of the true vocal folds. [E] Upper portion of the esophagus. [F] Trachea. The inverted peaks (red) represent inhalation and the upright peaks (green) are exhalation. [Color figure can be viewed at wileyonlinelibrary.com].

is an eight-point interval-appearing scale that assigns a value to each swallow dependent upon whether or not swallowed material enters the larynx and trachea. The PAS also considers whether or not material in the airway is cleared or not (Fig. 2).

The second measure for risk of aspiration is called “oral to pharyngeal stage transition time (OPST).” OPST is an important measurement for risk of aspiration because should delay exist between the two stages, the airway is open and vulnerable. OPST begins when the head of the liquid bolus reaches the point where the tongue base crosses the ramus of the mandible. The end-point was taken at the onset of the anterior thrust of the hyoid that occurs during the onset of the pharyngeal phase [Nagaya et al., 1998; Huggins et al., 1999; Ishida et al., 2002]. OPST was measured only in the controlled bolus sizes so that comparisons could be made with published normative data for this variable.

The third measurement was the determination of the presence or absence of solid or liquid within the pharynx after the swallow (residue). Pharyngeal residue is a risk factor for aspiration because food material or drink remaining in the throat after the swallow has the potential to enter the airway while breathing, or during a subsequent swallow. Pharyngeal residue was defined

as any easily visible material remaining in the pharynx after the swallow [Ludlow et al., 2007].

A preferred breathing and swallowing coordination exists in humans where swallows occur most often during early to mid-exhalation, and exhalation almost always follows a swallow. Exhalation after the swallow can reduce aspiration risk by clearing the laryngeal vestibule via positive airflow should any material enter during the swallow [Martin et al., 1994; Klahn and Perlman, 1999; Hardemark Cedborg et al., 2009; Wheeler Hegland et al., 2011]. To determine the percentage of swallows that were immediately followed by inhalation, respiratory signals were identified by the combined fluoroscopic observation of the swallow and the simultaneous flat, black line visible when there is no respiratory signal [Martin-Harris et al., 2005; Gross et al., 2008].

For the final measure, an anterior to posterior (AP) view of the chest was used to observe swallowed material remaining within the esophagus (stasis). Esophageal stasis can accumulate and redirect back into the pharynx and larynx, resulting in prandial aspiration. In the upright position, the esophagus should transport swallowed food and liquid in 3–10 sec [Diamant, 2012]. The esophageal image was taken randomly

1. Material does not enter the airway.
2. Material enters the airway, remains above the vocal folds, and is ejected from the airway.
3. Material enters the airway, remains above the vocal folds, and is not ejected from the airway.
4. Material enters the airway, contacts the vocal folds, and is ejected from the airway.
5. Material enters the airway, contacts the vocal folds, and is not ejected from the airway.
6. Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway.
7. Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort.
8. Material enters the airway, passes below the vocal folds, and no effort is made to eject.

FIG. 2. Eight-point penetration-aspiration scale.

Source: Rosenbek et al. [1996].

after one swallow of the cookie by repositioning the C-arm fluoroscope; a process that took approximately 20 sec.

Statistical Analyses

In addition to descriptive statistics, within-group comparisons and comparisons between the two conditions were made. Normality testing of OPST between 5 and 10 cc boluses and PAS data failed (Shapiro–Wilk test); therefore, the Wilcoxon Signed rank test was employed. McNemar’s Chi-square tests were used for paired, categorical pharyngeal residue data. The level of significance was pre-set at $P < 0.05$ for all tests. Intrarater and interrater reliability were calculated on 10% of randomly selected data from each dependent measure using Cohen’s kappa for categorical variables and intraclass correlation coefficients for temporal measures. Analyses were conducted at the level of the individual swallow as well as at the subject level using IBM SPSS version 22 (Armonk, NY). Table II shows the reliability data across the different measures.

RESULTS

Out of the possible 120 controlled thin liquid swallows, 57 swallows of the 5 cc liquid boluses and 54 of the 10 cc boluses could be analyzed. During spontaneous drinking, 131 swallows were obtained. The total number of liquid swallows recorded was 242. A total of 69 controlled swallows of cookie and 78 spontaneous swallows of cookie were available for analyses. The total number of cookie swallows was 147. Not all of the recorded swallows could be used in the final analyses because subjects sometimes moved within the radiographic field, or swallowed before the radiograph was

TABLE II. Reliability Data

Measurement	Intra-rater	Inter-rater
PAS thin liquid controlled and spontaneous conditions	1	1
PAS solid controlled and spontaneous conditions	1	1
Stage transition time	0.99	0.96
Pharyngeal residue	0.75	0.85
Post-swallow respiratory phase	0.92	0.83
Esophageal stasis	1	1

turned on. Some of the younger and smaller participants found the 10 cc liquid bolus too large to hold in their mouth.

Penetration-Aspiration

Penetration ratings that could indicate the possible risk of aspiration (PAS score of 3 or higher) were observed infrequently as indicated by the mean PAS scores for the 5 and 10 cc liquid bolus sizes. PAS score group mean for 5 cc boluses was 1.2 (SD 0.44, range 1.0–3.0) and mean PAS for the 10 cc bolus was 1.4 (SD 1.02, range 1.0–8.0). The difference in PAS between the bolus sizes was not significant ($P = 0.497$). When drinking spontaneously, the mean PAS was 1.31 (SD 0.1, range 1.0–8.0). Silent aspiration (PAS score of 8) was observed in one subject (3%), and occurred on one swallow of a 10 cc thin liquid bolus and twice during spontaneous drinking. Since the difference in PAS scores between the 5 and 10 cc boluses was not significant, the controlled liquid data were collapsed into one group and compared to the spontaneous drinking condition. The difference in PAS scores between the two conditions was not significantly different ($P = 0.600$).

Aspiration was not observed with the cookie swallows within the cohort in either condition. Mean PAS scores between controlled and spontaneous eating of the cookie were low at 1.03 (SD 0.17, range 1–2) and 1.0 (SD 0), respectively.

Stage Transition Time

The mean OPST for 5 cc thin liquid bolus was 0.26 sec (SD 0.26, range -0.03 to 1.58), and for the 10 cc bolus size, the mean was 0.29 sec (SD 0.27, range -0.06 to 1.29). The difference in OPST between the bolus sizes was not significant ($Z = -0.592$, $P = 0.554$).

Pharyngeal Residue

In our cohort, 67% (20/30) of the subjects had liquid residue after at least one swallow. Residue remained in the pharynx after 19% of 5 and 10 cc volumes, and therefore, the difference was not significant ($P = 1.0$). After drinking spontaneously, residue was present following 11% of the swallows. A comparison between the two conditions for the presence of liquid residue found that the difference between the two drinking conditions was not statistically significant ($P = 0.25$).

Overall, 97% of the participants (29/30) had easily visible residue after at least one swallow of the cookie. Residue was

observed in the pharynx after 51% of the controlled cookie swallows and after 47% of the spontaneous cookie swallows. The difference between the two conditions was not significant ($P=0.560$). There was substantial agreement for both intra-rater and inter-rater reliability for thin liquid judgments ($k=0.61$).

Post-Swallow Respiratory Phase

The difference in the proportion of swallows followed by inhalation for 5 cc (0.58) and 10 cc boluses (0.42) was not significant ($P=0.332$), therefore, the data were collapsed into one set called the *controlled condition*. Thus, for the controlled condition, 21% (22/104) of liquid swallows were followed by inhalation. When drinking from the cup, 30% (25/84) of spontaneous liquid swallows showed post-swallow inhalation. The difference in the proportion of post-swallow inhalation between controlled and spontaneous liquids was not significant ($P=0.391$). Inhalation occurred after 42% (25/59) of the controlled cookie swallows and after 30% (20/66) of the spontaneous cookie swallows. There was no significant difference between the controlled and spontaneous cookie boluses for post-swallow inhalation ($P=0.391$).

Esophageal Clearance

All subjects (30/30) had plainly visible esophageal stasis with the cookie. To further describe the finding, the relative location and amount of stasis was subjectively rated by the radiology co-investigator (RM) who specializes in esophageal dysmotility and abdominal imaging. RM was blinded to the bolus size and condition. The location of the stasis was variable with 50% (15/30) of participants showing stasis in the proximal 1/3 of the esophagus, 27% (8/30) in the middle 1/3 esophagus, 13% (4/30) in the distal 1/3 of the esophagus, and in 10% (3/30), the entire esophagus contained stasis. In 63% of the subjects (19/30), stasis was judged as moderate, and in 37% (11/30) of the participants, the stasis was rated as severe.

DISCUSSION

Our study revealed that children and adults with PWS can have important physiologic signs of dysphagia and key risk factors for choking and aspiration. In addition, no participant showed overt signs of dysphagia such as coughing and/or throat clearing or complaints of swallowing difficulty such as feeling that food is sticking in the throat or chest. The lack of typical clinical signs of dysphagia in the presence of direct fluoroscopic evidence indicates that the dysphagia is subclinical and cannot be detected without instrumentation. Furthermore, symptoms of dysphagia and risk factors for aspiration were present within the cohort regardless of whether the swallowed materials were controlled for bolus size and rate of delivery or taken spontaneously. The lack of significant differences between the two conditions suggests that the impairments are physiological and not solely related to neurobehavioral factors.

Penetration-Aspiration

We expected to observe more frequent aspiration and to measure higher (worse) mean penetration scores than obtained in our sample. All mean PAS scores for both liquids and solids in both conditions were below two, which is considered essentially within normal limits [Robbins et al., 1999; Daggett et al., 2006; Allen et al., 2010]. It is possible that the rate of penetration and aspiration is low because of the small number of swallows in our protocol. The use of videofluoroscopy and the importance of keeping radiation exposure to a minimum prevented our study from more closely resembling an actual meal. An alternate method for the evaluation of swallowing function uses a flexible nasoendoscope to provide direct views of the pharynx, larynx, and proximal trachea before and after each swallow. Fiberoptic endoscopic evaluation of swallowing (FEES) does not use radiation, and therefore, poses no time limitations. Furthermore, there is some evidence that FEES is more sensitive to penetration and aspiration than videofluoroscopy [Wu et al., 1997; Butler et al., 2009a,b]. Our use of videofluoroscopy may have reduced our ability to identify all episodes of penetration and aspiration; yet, had we used FEES in this investigation, swallowing physiology and esophageal clearance could not have been observed.

Stage Transition Time

In our PWS cohort, mean OPST values of 0.26 sec (5 cc) and 0.29 sec (10 cc) were measured. The positive values revealed that our participants had a delay between the offset of the oral phase and the onset of the pharyngeal phase. A temporal difference is a risk factor for aspiration because the airway is open and vulnerable to aspiration during this time. In fact, aspiration without coughing (silent) occurred in one subject when the liquid entered the airway during the time lag between the phases. For comparison, Kim et al. [2005] used the same measure of stage transition in a group of healthy participants (ages 21–51) and reported overlap between the two phases with -0.06 sec for 5 cc volumes and -0.08 sec for 10 cc volumes. Recently, Molfenter and Steele [2013a] reported positive mean OPST values of 0.03 sec for 5 cc and 0.06 sec for 10 cc in a healthy group (mean age was 31.5); however, the durations measured in PWS are approximately 5–8 times longer.

Pharyngeal Residue

Pharyngeal residue after swallowing liquid and solid consistencies was present in the majority of our subjects, and this is a significant risk factor for aspiration. Furthermore, no participant had awareness of their pharyngeal residue or attempted to clear the material until asked. For example, one teen (age 13) confirmed that the cookie was “all gone” when, in fact, the majority of the bolus had remained in his pharynx after he swallowed (Fig. 3). Healthy people, regardless of age, do not have pharyngeal residue beyond a slight coating of structures [Kelly et al., 2008; Butler et al., 2009a]. Perlman et al. [1994] retrospectively reviewed the videofluoroscopic studies of 330



FIG. 3. Example of post-swallow cookie residue in the pharynx of a 13-year-old participant.

patients of various diagnoses and calculated odds ratios for several independent variables in order to help clinicians predict the risk of aspiration. Their calculations showed that the risk of aspiration was greater with increased amounts of residue. Eisenhuber et al. [2002] reported that the risk of aspiration increases with the amount of pharyngeal residue. In their retrospective review of 386 patients who had undergone videofluoroscopic examinations of swallowing function, aspiration was present in 83% who had pharyngeal residue after swallowing liquid boluses, and aspiration was found in only 3% who did not have liquid pharyngeal residue. The presence of liquid residue also increased the risk of aspiration on the subsequent swallows [Molfenter and Steele, 2013b].

Post-Swallow Respiratory Phase

A large percentage of swallows were followed by inhalation, rather than exhalation. Post-swallow airflow direction is important to swallowing safety because expiratory airflow has the potential to expel unwanted material from the laryngeal vestibule; whereas inspiratory effort is more likely to draw material into the airway. The predilection for exhalation after each swallow has been documented extensively in healthy controls of all age groups [Paydarfar et al., 1995; Nilsson et al., 1996; Klahn and Perlman, 1999; Martin-Harris et al., 2005; Hardemark Cedborg et al., 2009, 2010] and disordered coordination of breathing and swallowing patterns have been identified in disorder groups that have high rates of lung infection including aspiration pneumonia [Pinnington et al., 2000; Gross et al., 2008, 2009]. Breathing and swallowing patterns were tracked during this investigation because persons with PWS have impaired pulmonary function, small chest size, and reduced thoracic muscle strength [Hakonarson et al., 1995]. Furthermore, lack of *NDN* expression could be responsible for breathing disorders in PWS [Zanella et al., 2009]. Irregular respiratory rhythms have been recorded in the medulla and from the diaphragm and hypoglossal nerve roots in *Ndn* deficient mice

[Ren et al., 2003; Zanella et al., 2008, 2009] and neuromodulation of respiratory rhythm generators must be intact in order to adapt to behavioral demands such as swallowing.

Esophageal Clearance

Given that this was the first prospective investigation of swallowing function in persons with PWS, we thought that it was essential to document esophageal clearance. The possibility that some participants would have esophageal stasis was anticipated because obesity is common in PWS and has been linked to esophageal dysmotility [Cote-Daigneault et al., 2014]. A significant finding of our investigation was the high frequency and severity of esophageal stasis observed regardless of age or BMI (Figs. 4 and 5). While esophageal stasis can be found in healthy research subjects [Pouderoux et al., 1999; Bogte et al., 2014], incomplete esophageal clearance is indicative of ineffective, weak peristalsis. The relationship between complete esophageal clearance and normal peristaltic contraction force was demonstrated by Tutuian et al. [2003] in an investigation of 43 healthy male and female volunteers who ranged in age from 21 to 72 years. They employed simultaneous multichannel impedance and manometry while subjects swallowed 10 boluses of viscous fluid similar to applesauce. Their results showed that 96.1% of swallows with normal manometry had complete bolus clearance.

When questioned, none of our 30 participants had any sensation of esophageal stasis, regardless of location and severity. The lack of correlation between perception of bolus clearance and instrumental assessment of bolus clearance is not fully understood. In some studies, patients are hypersensitive and perceive stasis where none is present [Dalmazo et al., 2012; Bogte et al., 2014]; whereas, in other cases, ineffective motility can be asymptomatic [Pouderoux et al., 1999; Lazarescu et al., 2010; Dalmazo et al., 2015]. It cannot be concluded from our study that the lack of awareness of stasis is abnormal; however, our random examination of the esophagus revealed that, in some cases, the stasis was cumulative and resulted in moderate and severe



FIG. 4. Example of esophageal stasis in a 7-year-old participant.



FIG. 5. Example of esophageal stasis in a 35-year-old participant.

amounts of retention. Inefficient afferent input may be responsible for inadequate motor output and the lack of residue or stasis sensation increases the probability of silent aspiration [Paydarfar, 2011].

In light of the esophageal stasis, it is interesting to consider that emesis is rare in persons with PWS [Cassidy et al., 2012] yet, there are reports of rumination occurring in these individuals [Alexander et al., 1987; Sloan and Kaye, 1991]. Rumination is a volitional behavior where gastric contents are brought up to the mouth and the food is either spit out or re-swallowed. When questioned, our subjects with the most severe stasis confirmed that there were times when *undigested* (did not reach the stomach) food “came back up.” Cote-Daigneault et al. [2014] found that esophageal dysmotility was present in 51% of asymptomatic obese patients ($n = 52$), and regurgitation was the only symptom that correlated with abnormal manometry. The results of this investigation show that it is reasonable to consider that many children and adults with PWS may be misdiagnosed with rumination syndrome or even gastroesophageal reflux disease (GERD). Our supposition is strengthened when considering the work of Herregods et al. [2015] who reviewed 106 patients diagnosed with GERD and determined that approximately one-third were misdiagnosed. We cannot conclude that all persons with PWS have non-obstructive dysphagia; however, we have enough preliminary evidence to justify the need to more fully characterize esophageal transport during typical deglutition.

Study Limitations

There are two primary limitations of this study. The first is that our spontaneous condition did not simulate actual eating behaviors likely to occur when food is eaten covertly, such as rapidly stuffing food into the mouth, or swallowing with minimal chewing. Also, sufficient saliva is important for adequate mastication and salivary flow is reduced in PWS. Since there was no time restriction, we observed prolonged chewing in many participants. In addition, participants were given liquid as part of

the protocol which kept the oral cavity moist. Our design did not replicate the amount of food normally consumed during a meal because we had to limit the radiation exposure. It is plausible that residue and stasis may accumulate during actual meals and result in silent aspiration.

A second important limitation is that our original intent was to examine the esophagus and ensure that boluses were fully transported into the stomach. We did not fully anticipate the high frequency of esophageal stasis that was observed. The determination of eosinophilic esophagitis and achalasia were not part of our investigation, and these could be possible causes for the esophageal findings. Furthermore, some individuals were receiving psychotropic medications and these may have had an effect on esophageal motility.

CONCLUSIONS

In conclusion, this investigation was not designed to determine a causal relationship between swallowing function and choking; however, the well-documented high death rate from choking and pulmonary infection in children and adults with PWS may be related to the underlying, asymptomatic dysphagia that our experiment revealed. Under videofluoroscopy, persons with PWS showed disordered pharyngeal and esophageal swallowing with disturbances in timing, clearance, and coordination of swallowing with the respiratory cycle. While *NDN* is only one of several inactivated genes in PWS, it is not unreasonable to speculate that the absence of *NDN* in persons with PWS might be related to the sensory-motor impairments of dysphagia. The combination of dysphagia with rapid eating and intellectual disability can increase the risk of aspiration and asphyxiation in persons with PWS. Food impaction within the esophagus and/or unexpected regurgitation of food retained within the esophagus may increase the risk of aspiration and/or airway occlusion. Moreover, aspiration in persons with PWS may be particularly dangerous because the syndrome characteristics include a high pain threshold and lack of fever, both would act as barriers to detecting an infection [Priano et al., 2009; Angulo et al., 2015]. Without overt symptoms of dysphagia, it is possible that many pulmonary infections, such as aspiration pneumonia, go undetected.

Because dysphagia in this population appears to be primarily occult, it is recommended that persons with PWS receive videofluoroscopic swallowing evaluations, particularly those who have a history of rumination, regurgitation, choking, or pulmonary infection. The swallowing evaluation should be conducted with the patient in their natural seated position, use solid food items that require mastication, and include esophageal views. Future research will focus on fully characterizing esophageal motility in PWS and explore treatments that can improve swallowing safety.

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