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Videofluororadiographic Descriptors of Swallowing Physiology in Typical Rett Syndrome: Post-Regression Stabilization During Early Childhood

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Typical or classic Rett syndrome (RTT) is the only pervasive neurodevelopmental disorder with a known chromosomal abnormality. Despite differences in clinical phenotype of girls with RTT who share the same gene mutation on chromosome X, there is commonality in the stages and core features of this profoundly disabling disorder, including the deterioration of acquired vocal behaviors and meaningful speech during the regression stage. The purpose of this article is to ascertain any commonality in the swallowing neurophysiology of a select sample of girls with typical RTT who were under the age of 5 years and had undergone the devastating effects of developmental regression.

Approximately 30,000 individuals in the United States have diagnosed Rett syndrome (RTT), a debilitating neurodevelopmental disorder predominantly affecting females (National Institutes of Health [NIH], 2011). Afflicted males are likely to experience early, severe postnatal encephalopathy or early death (Kankirawatana et al., 2006). An estimated 1 in every 10,000 live female births worldwide are affected with typical RTT. Despite the fact that 95%–97% of these females will have a mutation in the transcription regulating gene Methyl-CpG binding protein 2 (MECP2) located on chromosome Xq28, RTT remains a clinical diagnosis (Amir & Zoghbi, 2000; Neul et al., 2010). More than 200 MECP2 mutations have been identified (Percy, 2005). Although there are differences in clinical phenotype of patients who share the same mutation, there is commonality in stages and features of RTT. Newborn females with typical RTT present as well-babies, appearing to develop normally during their first 6 months of life despite subtle abnormalities. Between 6 and 18 months of age, they undergo a period of developmental stagnation, acquiring autistic features and microcephaly. Developmental regression follows with onset occurring between 12 and 48 months of age. Vocal development, acquired oral expressive lexicon, purposeful hand skills, and fine motor finger function are partially or completely lost during the regression stage. Hand stereotypies, the clinical hallmark of typical RTT, emerge, taking the form of repetitive wringing/squeezing, clapping/tapping, washing, or mouthing. Ambulation becomes dyspraxic or absent. Onset of dysfunctional respiratory patterns, such as hyperventilation and breath-holding episodes, can occur as well. Eye contact is characteristically preserved. The clinical course becomes more stable during the pseudo-stationary stage that follows regression. Potential for partial recovery of skills and unapparent, slow neuromotor regression lasting years to decades characterize this period (Charman et al., 2002; Hagberg, 2002; Hoffbuhr et al., 2001; Neul et al., 2010).

Feeding Abnormalities in Young Girls With RTT

Feeding difficulties are complex, multifactorial, and associated with problematic nutrition and growth in RTT (Morton, Bonas, Minford, Kerr, & Ellis, 1997; Oddy et al., 2007). Cass et al. (2003) evaluated 87 females ages 2;1 to 44;10 (years;months) with RTT using the Schedule for Oral Motor Assessment (Reilly, Skuse, Mathisen, & Wolke, 1995) and found moderate-severe oromotor dysfunction in 72% of their cohort. Oromotor function for semi-solids and solids was poorer than for purees and liquids. Oddy et al. (2007) surveyed families of 201 females with RTT ages 2–29 years. They reported 61.5% of the participants had difficulty with or were not able to eat particular food items, and 60.2% required their food to be modified to puree, mashed, or chopped. Twenty-one percent were coughing on liquids with 7.6% coughing on purees and 11.2% coughing on solids. Thirty-four percent of the families worried that their daughters were not ingesting adequate fluid. Twenty percent required enteral nutritional support. Motil et al. (2012) surveyed 983 parents who had female children with RTT ages 0–40+ years. Chewing problems and swallowing difficulties were reported by 56% and 43% of the parents, respectively. Choking and gagging during feeding was less frequent at 27%. Sixty-two percent of the parents indicated prolonged feeding time to 60 minutes.

Despite the high frequency of feeding issues indicative of swallowing problems in large cohorts of females with RTT, there is a paucity of instrumental data detailing swallowing physiology. Two studies have provided videofluororadiographic swallowing data. Morton et al. (1997) reported reduced mid- and posterior tongue movements, premature spillage, and delayed pharyngeal swallows in their 20 subjects ages 1.5–33 years. The 13 patients, ages 3.7 to 25.7 years, evaluated by Motil, Schultz, Browning, Trautwein, & Glaze (1999) had poor bolus formation, posterior bolus loss, pharyngeal pooling, vallecular and pyriform sinus residua, and airway compromise during the swallow for thin liquid. The broad age ranges utilized by Morton, Motil, and their colleagues precluded assessment of age or stage effects on swallowing in RTT.

Videofluororadiographic Descriptors of Swallowing in Young, Post-Regression Girls With RTT

We do not know if female infants who go on to be diagnosed with typical RTT have subtle deviations in the stages of swallowing for bottle or breast during their early months of life, nor do we know if swallowing is affected during the period of developmental stagnation. To begin to determine the effects of developmental regression on swallowing in RTT, we selected 18 young females ages 1;11 to 4;9 (mean age = 3;0) who were evaluated through the Rett Center at the Children's Hospital at Montefiore, Bronx, NY. All had diagnosed typical RTT with positive MECP2 mutation testing. The subjects had undergone developmental regression and were now in the pseudo-stationary stage as confirmed by a pediatric neurologist specializing in RTT. Onset of regression ranged from 4 to 33 months (mean = 12 months). The subjects' overall clinical severity as measured by the Rett Syndrome Severity Scale (Neul et al., 2010) was classed as mild (n = 4) or moderate (n = 14). In addition to hand stereotypies, 15 of the subjects had movement disorders adversely affecting upper body positioning; the remaining 3 had significant trunkal hypotonia. None of the subjects had meaningful vocal behaviors or expressive lexicon. They were unable to vocalize on request, and could not imitate nonspeech movements of the orofacial structures. All were oral-only feeders with no enteral nutrition via nasogastric or gastrostomy tube. Ten subjects were off the bottle using a spout or straw cup. All had transitioned to puree from a spoon. Fifteen subjects had transitioned to moist ground or solid food items. Oral stage swallowing dysfunction characterized the entire sample in the clinical milieu. The 18 subjects underwent videofluororadiographic study of swallowing as a component of their work-up for dysphagia. The Institutional Review Board #12-07-240 of the Montefiore Medical Center and the Albert Einstein College of Medicine in New York approved use of the subject information.

Liquid Ingestion

Oral Stage. No subject was using an open cup in the home for liquid ingestion despite age or severity level. Eight of the girls utilized a bottle with a nipple in the home milieu, whereas 10 used a cup with a spout or an attached straw. Impairments to volitional motor control and coordination of the lips and tongue were observed across subjects. Concomitantly, 6 bottle users and 8 spout/straw users displayed involuntary repetitive tongue movements during liquid ingestion. Yet, 7 of the 8 bottle users were able to sustain organized suck-swallow patterning for a short series under fluoroscopy. Only 3 of the 10 spout/straw users were able to maintain consecutive liquid bolus swallows. Erratic liquid expression and variable bolus size were common for the subjects using a spout or straw cup. The subjects' movement disorders affecting the upper body further exacerbated their attempts to grasp a straw or spout with their lips and tongues.

Liquid ingestion using a bottle with a nipple was found to be more efficacious for the young subjects with RTT than drinking from a cup that had a spout or straw. There was a difference noted in the use of the oral tongue when ingesting liquids for various utensil types. Nipples were positioned on the tip/blade/front of the oral tongue with the lingual stripping wave utilized for liquid expression. Spouts were positioned between the dentition with minimal to no positioning on the tip/blade of the oral tongue. Short, thin, rigid spouts were positioned against the oral tongue tip with the tongue bunched posterior to the spout. Cups with a spout or straw appeared to restrict or prevent effective use of the lingual pulsion wave. Once liquid was expressed from a spout or straw, bolus loading onto the tongue was either absent or reduced, as was labial closure with consequent anterior spillage.

Pharyngeal Stage. Timing delays were the most frequent pharyngeal stage deficit for liquid ingestion. Fifteen subjects displayed delayed initiation of the swallow response and/or delayed closure of the laryngeal vestibule. All of these subjects penetrated the supraglottic airway with 4 covertly aspirating. Three subjects had mild pharyngeal dysmotility for small volume liquid ingestion with no airway contamination risks secondary to post-swallow residua.

Food Ingestion

Oral Stage. All 18 subjects with RTT demonstrated oral stage deficits for solid, moist ground, and puree bolus ingestion. *Dysmotility* (Leopold & Kagel, 1997) of the oral tongue was the primary deficit identified under fluoroscopy, significantly affecting food bolus ingestion in 17 of the 18 subjects studied. Oral tongue dysmotility interacted with involuntary repetitive tongue movements in 14 of the 17 subjects. Oral preparation and transport for puree, moist ground, and solid boluses appeared arduous, especially chewable solids. Bolus loading by the oral tongue for single puree boluses was incomplete or nonexistent for 11 of the 18 subjects. Ten of the 11 subjects that had transitioned to hard chewable solids displayed absent or ineffective labial seal for anterior containment of pieces. Their restrictive or absent tongue motility and vertical, rigid mandibular movements for bolus manipulation and lateralization resulted in partial mastication of a single solid bolus with bolus formation either incomplete or nonexistent.

Pharyngeal Stage. Twelve of the 18 subjects with typical RTT had mild pharyngeal dysmotility. Supraglottic penetration and silent aspiration of post-swallow residua secondary to pharyngeal dysmotility for puree was confirmed in 1 subject. Delayed initiation of the primary swallow response for at least one food texture was evidenced in 7 of the 18 subjects studied here with involuntary repetitive tongue movements implicated in 4 of these cases. Delayed closure of the laryngeal vestibule was confirmed in 1 subject. Four of the 8 subjects with timing delays penetrated the supraglottic airway with 1 covertly aspirating.

Involuntary Repetitive Tongue Patterns Affecting Swallowing in Young, Post-Regression Girls With RTT

Aberrant, involuntary tongue movements in females with RTT have been reported by Morton and colleagues in 1997 and by Abraham, Djukic, and Loizides in 2010. The impairment to motor control in RTT is considered apraxic in nature (NIH, 2011). The highly restrictive, groping, delayed, absent functional tongue and lip movements in the young subjects with RTT were consistent with an oral apraxia. In-depth analysis of their videofluororadiographic swallowing studies revealed dystonic and dyskinetic tongue movements co-occurring with apractic movements during bolus swallowing in 14 of the 18 subjects. These involuntary movements were rapid and repetitive or repeated, disrupting and interfering with neuromotor and temporal aspects of oral preparation, transport, and transfer.

The most unusual and dramatic finding was repeated retroflexion of the oral tongue. The tongue tip moved superior and posteriorly to the level of the soft palate, oropharynx, or hypopharynx, then returned to rest in the floor of mouth. Oral tongue retroflexion was confirmed in two subjects studied here. One repeatedly retroflexed the tongue tip to the soft palate and back to resting position, whereas the other subject repeatedly retroflexed the tongue tip to the hypopharynx and filled the pharyngeal airspace prior to returning to resting position.

Six subjects with RTT displayed a rocking tongue pattern, appearing as rapid, repetitive to-fro motion of the bolus on the oral tongue. Rolling tongue pattern was confirmed in 2 other subjects with 1 displaying a rolling pattern during collection. These tongue patterns in the subjects with RTT were similar to the rocking-rolling lingual pattern described by Logemann (1998) as the pathognomonic sign of Parkinson's disease. Morton and colleagues (1997) suggested a similarity between the swallowing abnormalities in RTT and those observed in Parkinson's disease.

Ten subjects with RTT displayed a lingual pattern that took the form of multiple anterior to posterior (A-P) lingual pulsion waves prior to the actual lingual pulsion wave associated with oral bolus transfer-swallow response initiation. This multi-wave transfer pattern was confirmed in 10 subjects. Six of them displayed two to five A-P transfer waves with each wave having an abrupt "stop," thus appearing as "false starts" prior to actual initiation of the swallow response. Three subjects had base of tongue spasticity and/or velar spasticity associated with this multi-wave transfer pattern.

Other repeated tongue patterns observed in at least 2 subjects were sudden posterior tongue "drops" and untimely, elevated posturing of a thickened oral tongue tip. Of note, 1 subject who presented clinically with recurrent "spit out" of oral bolus was found to have rapid retrograde bolus movement from the tongue base to the oral tongue and beyond, escaping through the lips to the chin.

Concluding Remarks

Hapberg (2002) states that swallowing dysfunction could not be considered among the supportive criteria in the clinical diagnosis of RTT because "the clinical pattern is unspecific in type and has been difficult to delineate" (p. 63). This study is an initial step toward characterizing dysphagia in RTT by stage and age. The focus here was specifically the Early Pseudostationary Stage III. The girls had experienced the devastating effects of Developmental Regression Stage II and were now considered stable from a neurological point of view. Findings here support a commonality in the swallowing deficits of post-regression girls with RTT who are under the age of 5 years. Although stabilization of the disease process did follow developmental regression, these girls with RTT were left with overall severe neuromotor-based dysphagia affecting the oral and oral transfer stages, more so than the pharyngeal stage of swallowing. Their impaired volitional motor control of orofacial structures for oral ingestion, coupled with their provisionally unique patterns of involuntary repetitive tongue movements, created an

ominous task for them to remain oral feeders. In turn, their motor deficits and unique differences created a complex task for the treating clinicians.

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