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Potocki-Lupski Syndrome: A Microduplication Syndrome Associated with Oropharyngeal Dysphagia and Failure to Thrive

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Abstract

Objective—Failure to thrive (FTT) is a feature of children with Potocki-Lupski syndrome (PTLS) [duplication 17p11.2]. This study was designed to describe the growth characteristics of 24 subjects with PTLS from birth through age 5 years in conjunction with relevant physical features and swallow function studies.

Study design—We evaluated 24 individuals with PTLS who were ascertained by chromosome analysis and/or array comparative genome hybridization. Clinical assessments included review of medical records, physical examination, otolaryngological examination, and swallow function studies. Measures of height and weight were converted to Z-scores.

Results—The mean weight-for-age and weight-for-length Z-scores at birth were lower ($P < .01$) than the reference standard and did not change with age. A history of poor feeding, hypotonia, and FTT were reported in 92%, 88%, and 71%, respectively. Individuals with hypotonia had lower weight-for-age and body mass index-for-age Z-scores ($P = .01$). Swallow function studies demonstrated at least one abnormality in all subjects.

Conclusions—FTT is common in children with PTLS. We hypothesize that oropharyngeal dysphagia and hypotonia likely contribute to FTT in patients with PTLS and recommend that once a diagnosis is established, the individual be assessed for feeding and growth issues and be availed of oromotor therapy and nutritional services.

Potocki-Lupski syndrome (PTLS) (MIM 610883) is a chromosomal microduplication syndrome that results from an interstitial duplication of chromosome 17 at band p11.2 [dup(17) (p11.2p11.2)].¹⁻³ Because the duplication in PTLS can be submicroscopic, this chromosomal aberration often is undetected on routine chromosome analysis. Until the utilization of array-based comparative genomic hybridization in the clinical laboratory, many individuals with PTLS were undiagnosed.⁴ Practitioners generally associate chromosomal abnormalities with dysmorphic features and multiple congenital anomalies; thus, another factor contributing to delayed diagnosis in PTLS is the lack of strikingly dysmorphic craniofacial features in the majority of patients. Clinical features associated with PTLS include infantile hypotonia, congenital heart disease, sleep disordered breathing,

developmental delay, intellectual disability, and autism; not all of these features are present in every patient.^{2,3,5,6}

Failure to thrive (FTT), defined as weight-for-age less than 2 standard deviations (SD) below the mean diagnosed by observation of growth over time, has been reported in children with PTLS.² Initial clinical observations of children with PTLS suggested that poor oral motor skills and hypotonia may lead to FTT. This report describes linear and ponderal growth patterns of 24 subjects with PTLS and delineates relevant clinical features of oral-pharyngeal structure and function. We hypothesize that oropharyngeal dysphagia and hypotonia may contribute to FTT in PTLS.

Methods

From June 1997 to December 2008, 24 individuals identified with 17p11.2 duplication, diagnosed by chromosome analysis and/or array-based comparative genomic hybridization, were enrolled in a multidisciplinary clinical study at the General Clinical Research Center (GCRC), Texas Children's Hospital, Houston, under a protocol approved by the Institutional Review Board for Human Subject Research at Baylor College of Medicine. Cytogenetic and molecular methods confirming the chromosomal microduplication in these individuals were reported previously.^{2,3} Written permission was obtained from the parent or legal guardian of each subject; assent was waived because of the age of the children. The clinical evaluations performed as part of this study included a physical examination, otolaryngological examination, electrocardiography, and echocardiography. Growth measurements, including height or length, weight, and head circumference, were obtained by direct measurement upon admission to the GCRC; historical growth measurements and neurological examination reports were collected by review of available medical records. A swallow function study, obtained in conjunction with a radiologist and speech pathologist, was performed to evaluate the oral and pharyngeal phases of swallowing.

Procedures

Height measurements, standing without shoes, were obtained on children 2 years of age and older; values were recorded to the nearest 0.1 cm. Length measurements, reclining without shoes, were obtained on children younger than 2 years of age; values were recorded to the nearest 0.5 cm. Weight measurements were obtained using an electronic scale; values were recorded to the nearest 0.1 kg. Heavy clothing and shoes were removed before weighing. Head circumferences were measured from the maximum occipital protuberance through the glabella. The method of measurement for values obtained from medical records provided by private physicians was unknown. Body mass index (BMI) was calculated as the ratio of weight divided by height squared (kg/m^2) for children 2 years of age and older. Weight-for-length was determined for children younger than 5 years of age. Height, length, weight, weight-for-length, BMI, and head circumference measurements were converted to age-appropriate Z-scores. The number of measurements, as well as the age at which each measurement was obtained, varied for each subject. The Z-scores (SD units) for height-for-age, length-for-age, weight-for-age, weight-for-length, BMI-for-age, and head circumference-for-age were calculated from the reference growth standards for the US population established by the National Center for Health Statistics and the Centers for Disease Control and Prevention.⁸

Swallow function studies were conducted per protocol as established by the Departments of Speech, Language and Learning, and Diagnostic Imaging. All children were offered age-appropriate, barium-laced thin liquids and pureed and solid foods consumed in the home. Children were seated in an upright position for the evaluation. Lateral radiographic views of chewing and swallowing were obtained.

Statistical Analysis

Statistical analysis was performed with MiniTab statistical software (Version 13.0, MiniTab, Inc, State College, Pennsylvania) and SPSS software (Chicago, Illinois). Descriptive statistics were used to determine the mean (SD) length-for-age, weight-for-age, weight-for-length, and head circumference-for-age Z-scores at birth for the PTLs cohort. One-sample *t* tests were applied to detect differences in length-for-age, weight-for-age, weight-for-length, and head circumference Z-scores at birth between the PTLs cohort and reference standards. Height-for-age, weight-for-age, weight-for-height, BMI-for-age, and head circumference Z-scores were truncated after 65 months of age because these data were not available for most children after this time point. However, the progression of height and weight through adolescence was summarized where appropriate. The incremental changes (slopes) in height-for-age, weight-for-age, weight-for-height (length), BMI-for-age, and head circumference Z-scores over time, as measured by age, were calculated by fitting regression lines through their respective Z-scores for each individual who had at least 2 data points for each outcome variable. The formula for these lines was $y = a + bx$, where *y* indicates height-for-age, weight-for-age, weight-for-length, BMI-for-age, or head circumference Z-scores, *a* is their respective intercepts, *b* is their respective slopes as change in Z-scores per month, and *x* is age. Descriptive statistics were used to determine the mean (SD) changes in height-for-age, weight-for-age, weight-for-length, BMI-for-age, and head circumference Z-scores. One sample *t* tests were applied to detect differences between the mean slopes for each outcome variable for the PTLs cohort and the reference value. One-way analysis of variance was applied to detect differences in the change over time in height-for-age, weight-for-age, weight-for-height, BMI-for-age, and head circumference Z-scores after adjustment for sex and enteral tube feeding status. Kruskal-Wallis tests were applied to detect differences in weight-for-age and BMI-for-age Z-scores in subjects with and without hypotonia and chewing and swallowing abnormalities. Significance was determined at $P < .05$.

Results

The characteristics of 12 female and 12 male subjects with PTLs are listed in Table I (available at www.jpeds.com). The majority of subjects were diagnosed after age 2 years. Only 7 individuals were diagnosed in their first year of life. The racial and ethnic distribution of the cohort was predominantly Caucasian. Table II shows the prevalence of clinical features associated with feeding in the cohort. Specific characteristics included infantile hypotonia as documented in medical records and/or by physical examination at the time of GCRC admission was observed in 88% and mild micrognathia in 58%. Sixteen (67%) subjects had normal palate anatomy, and the remainder had various abnormalities including high arched palate, submucosal cleft palate, and bifid uvula. Microcephaly was noted in two patients; developmental delay and/or intellectual disability were consistent features in all subjects. Ventricular and atrial septal defects, as well as aortic root dilation, were the most common cardiovascular anomalies found in 42% of these subjects. Sinus arrhythmia was observed in one subject (2745) and hypoplastic left heart requiring heart transplant was noted in another subject (1838). Early feeding problems including poor suck, difficulty latching onto the breast, and easy fatigability were reported in 92%. A diagnosis of FTT in infancy or early childhood was ascribed to 71%. A history of gastroesophageal reflux was reported in 42% and chronic constipation was noted in 46% of the subjects.

Nasogastric or gastrostomy tube feedings were implemented in 29% of the cohort. Review of medical records indicated that the duration for nasogastric tube intervention observed in four subjects was 2 weeks (1838), 9 weeks (2695), 6 months (2211), and an undetermined duration (1618). The three subjects that received a gastrostomy tube still had it in place upon admission to the GCRC. The duration of gastrostomy tube intervention was 5 months (1579), 17 months (2440), and 12.5 years (1913). Subject 1913, who was more than 2 SD

below the mean for height, was receiving growth hormone; however, her linear growth was not altered by this therapy. Specific data regarding dietary intake was not available for review.

Growth Data

Weight-for-age, length-for-age, and weight-for-length Z-scores at birth for children with PTLs were plotted against the normative values for the general population (Figure 1). Although the majority of subjects plotted within normal percentiles for age at birth, 8% of subjects were small for gestational age). As a group, the mean weight-for-age and weight-for-length, but not length-for-age, Z-scores at birth were lower ($P < .01$) than the reference standard. Mean weight-for-age, weight-for-length, and length-for-age Z-scores did not change over time during the first 5 years of age. Weight-for-age Z-scores in the older subjects were below the mean through adolescence. Although the mean BMI-for-age Z-score tended to increase with increasing age this value did not achieve significance ($P < .06$). Seven subjects had a nasogastric or gastrostomy tube placed for nutritional support. The change in weight-for-age Z-scores over time, when adjusted for birth weight, was not different between individuals who were tube fed and those who were not (data not shown). Figure 2 (available at www.jpeds.com) illustrates the growth pattern of one subject (2695) who received nutritional support via a nasogastric tube which was placed at 1 month of age when her weight was persistently in the 3rd percentile for age. Her weight improved with nasogastric tube feedings yet remained in the 3rd percentile throughout infancy following the removal of the nasogastric tube at age 2 months.

Swallow Function Study Data

One or more elements of oral phase dysfunction were evident in all 18 subjects (Table III). Abnormal lingual function, including reduced bolus formation, piecemeal deglutition, reduced tongue elevation, and reduced anterior-posterior tongue movement, was observed in 67% of individuals. Reduced or immature chewing was observed in 39%. Residue after oral phase completion was seen in 78%. The most common features observed during the pharyngeal phase were a mild delay in the initiation of swallowing in 61% and residue in the valleculae and/or pyriform sinus after swallowing in 72%. Laryngeal penetration was seen in 39% of the subjects; tracheal aspiration was not observed. Median weight-for-age (-0.9 versus 0.1 , $P < .05$) and BMI-for-age (-0.9 versus 0.8 , $P < .04$) Z-scores were lower in subjects with than without hypotonia. Median weight-for-age and BMI-for-age Z-scores were not significantly different between those individuals who had oropharyngeal dysfunction, measured as residue after completion of oral and pharyngeal phases of swallowing, than those who did not.

Molecular Data

Molecular analyses were reported previously in all of the subjects,^{2,7} and are summarized in Table I. Seventy-one percent of subjects (17/24) harbored the common PTLs microduplication in chromosome 17p11.2 (~3.7 Mb)^{2,7}; 21% (5/24) had a microduplication size larger than ~3.7 Mb^{2,7}; one subject was found to have a microduplication smaller than 3.7 Mb² and one subject had a mosaic marker chromosome 17.7

Discussion

Chromosomal rearrangements including microdeletion and microduplication are a common cause of morbidity and mortality in the pediatric population.⁹ Array-based comparative genomic hybridization has revolutionized the early diagnosis and management of these chromosomal abnormalities that often were undetected by routine cytogenetic analysis.⁴

This report describes the growth pattern, swallow function studies, and associated clinical features in PTLs.

FTT is a frequent finding in individuals with chromosomal disorders and neurological impairment. FTT was diagnosed in 71% of our cohort. Our observations provide additional understanding into the mechanisms that may account for the feeding difficulties and FTT associated with PTLs. Abnormalities of swallowing function were universally present in this cohort suggesting that oropharyngeal dysfunction plays an important role in FTT and PTLs. It is known that hypotonia causes problems with feeding due to the inability to suck or masticate for prolonged periods of time. The observation of infantile hypotonia in 88% of the individuals suggests that hypotonia contributes to the etiology of FTT in PTLs. In addition, other features in PTLs that may influence feeding, such as structural abnormalities of the palate, were observed in 46% of the subjects. Our data also demonstrated that weight but not length deficits were present at birth and persisted throughout infancy and early childhood in persons with PTLs, suggesting that intrinsic genetic factors may also affect growth.

PTLS results from microduplication of chromosome 17 band p11.2.³ The common microduplication is the homologous recombination reciprocal of the 3.7Mb common Smith-Magenis syndrome (SMS) (MIM 182290) microdeletion (deletion 17p11.2).¹¹ Although PTLs and SMS share the same molecular mechanism, the clinical characteristics of individuals with these disorders are distinct. Mouse models of PTLs demonstrate that the growth patterns of these animals are similar to those of human subjects as the heterozygous duplication PTLs mice are underweight from approximately 3 months of age and homozygous duplication animals have more severe weight and growth impairment; however, evidence of inadequate suck or feeding in these animals is lacking.^{12,13} In contrast, the SMS deletion animal model and the heterozygous *Rai1*[±] knockout animals are overweight compared with wild-type controls,¹⁴ a feature common to older children and adults with SMS. Thus, the data derived from animal models of PTLs support that intrinsic genetic factors may also have a major impact on growth in this newly characterized chromosomal microduplication syndrome.

Medical intervention for FTT typically includes nutritional support and feeding therapy. Of the three subjects wherein the duration of nasogastric tube intervention was known, nutritional support ranged between 2 weeks and 6 months. Individuals with gastrostomy tubes had them placed for longer periods, yet details of caloric intake in these subjects are not available. The seven subjects with PTLs who underwent nasogastric or gastrostomy tube feedings remained on their respective linear growth curves and failed to resolve their weight deficits. The short-term intervention and lack of longitudinal data in this cohort precludes establishment of firm conclusions regarding these findings.

Although these are descriptive data and causation cannot be proven, we hypothesize that hypotonia and oropharyngeal dysphagia probably contribute to FTT in PTLs. Although we lack longitudinal follow-up of nutritional, developmental, cognitive, and behavioral outcomes, our preliminary data delineate the growth profile and abnormal swallowing function of individuals with PTLs and substantiate the need for early intervention with nutritional and oromotor therapy. Based on our results, we recommend that patients diagnosed with PTLs undergo an evaluation of oral-motor function by a trained therapist, a swallow function study, and an examination by an otolaryngologist. We anticipate that oral-motor feeding therapies will favorably influence overall nutrition and development in these children.

We conclude that FTT and oropharyngeal dysfunction are common features associated with PTLs. Weight-for-age, weight-for-length, and BMI-for-age in PTLs are significantly lower than those of the reference population and 100% have an element of oropharyngeal dysfunction. Oropharyngeal motor dysfunction and hypotonia are likely to contribute to poor feeding and FTT in PTLs. Our data demonstrate the need for early intervention with nutritional, feeding, and oromotor therapy in PTLs.

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Glossary

BMI	Body mass index
FTT	Failure to thrive
GCRC	General Clinical Research Center
PTLS	Potocki-Lupski syndrome
SD	Standard deviation
SMS	Smith-Magenis syndrome

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Figure 1. Distribution of Z-scores at birth in PTLS. Z-scores for individual patients with PTLS are plotted against the reference Z-score values for the general population.

Figure 2. Patient 2695 growth charts. Weight and length percentiles at birth were 25th percentile and 50th percentile, respectively. The arrows located in the weight for age chart indicates the time interval of approximately 9 weeks in which this patient received nasogastric tube feedings.

Table 1

Summary of study patients with PTLs

Subject [*]	Sex	Age at diagnosis (months)	Age at enrollment (months)	Type of duplication	Size (Mb)	Race
990	Male	72	118	Common	3.7	Caucasian/Hispanic
1006	Female	144	144	Common	3.7	Caucasian
1579 ^{//}	Male	11	50	Common	3.7	Caucasian
1618 [§]	Male	72	174	Common	3.7	Caucasian
1838 [§]	Male	48	118	Common	3.7	Caucasian
1913 ^{//}	Female	144	156	Common	3.7	Caucasian
2167	Female	9	39	Common	3.7	Caucasian
2211 [§]	Male	36	58	Large, complex	8.7	Caucasian
2306	Female	29	33	Common	3.7	Caucasian
2343 [†]	Female	112	144	Mosaic marker	5.5	Caucasian
2362	Male	8	69	Large	7.0	Hispanic
2414	Male	34	113	Common	3.7	Caucasian
2440 ^{//}	Female	9	25	Large	4.9	Caucasian
2543	Male	91	97	Small, complex	1.5	Caucasian
2555	Female	23	32	Common	3.7	Caucasian
2581 [†]	Male	58	65	Common	3.7	Caucasian
2634 [‡]	Male	18	69	Common	3.7	Caucasian
2695 ^{‡, §}	Female	6	49	Large, complex	4.4	Caucasian
2708 [‡]	Female	11	96	Common	3.7	Caucasian
2711 [‡]	Female	14	37	Large, complex	11.1	Caucasian
2724 [‡]	Female	52	87	Common	3.7	Hispanic
2738 [‡]	Male	8	17	Common	3.7	Hispanic
2745 [‡]	Male	33	46	Common	3.7	Caucasian
2767 [‡]	Female	157	163	Common	3.7	Caucasian

^{*} Laboratory numbers are given, and citations of references are included if the subject was described elsewhere. Unless otherwise noted, subjects published in Potocki et al. 2007.²

[†] Yatsenko et al, 2005.⁷

[‡] Zhang et al, 2010.³

[§] Subjects who had a nasogastric tube placed for nutritional support.

^{||} Subjects who had a gastrostomy tube placed for nutritional support.

Clinical features of PTLs

Table II

Clinical feature	Total* (n = 24)	Common duplication [†] (n = 17)	Large duplication [‡] (n = 5)	Small duplication [§] (n = 1)	Marker [¶] (n = 1)
Small for gestational age at birth	2 (8%)	2	-	-	-
Infantile hypotonia	21 (88%)	14	5	1	1
Microcephaly	2 (8%)	2	-	-	-
Developmental delay and/or intellectual disability	24 (100%)	17	5	1	1
Micrognathia	14 (58%)	9	4	1	-
Normal palate	16 (67%)	11	3	1	1
High arched palate	7 (29%)	5	2	-	-
Submucosal cleft palate	2 (8%)	2	-	-	-
Bifid uvula	2 (8%)	2	-	-	-
Cardiovascular abnormalities	10 (42%)	7	3	-	-
Poor feeding in neonatal period and infancy	22 (92%)	15	5	1	1
Failure to thrive in infancy or early childhood	17 (71%)	13	3	1	-
Enteral feeding tube					
Nasogastric tube ^{**}	4 (17%)	2	2	-	-
Gastrostomy tube ^{††}	3 (12%)	2	1	-	-
History of chronic constipation	11 (46%)	8	2	1	-

* Total number of subjects with growth data available.

[†] 3.7-Mb duplication.[‡] Duplication larger than 3.7 Mb.[§] Duplication smaller than 3.7 Mb.[¶] Markers: Mosaic marker chromosome 17p.^{||} Cardiovascular abnormalities: Including ventricular septal defects, atrial septal defects, hypoplastic left heart, valvular disease, and aortic root dilation.^{**} Duration of nasogastric tube intervention for these 4 subjects was: 2 weeks, 9 weeks, 6 months, and one of undetermined duration.^{††} Duration of gastrostomy tube intervention was 5 months, 17 months, and 12.5 years.

Table III

Swallow function studies in PTLs

Clinical features	Total* (n = 18)	Common duplication [†] (n = 11)	Large duplication [‡] (n = 5)	Small duplication [§] (n = 1)	Marker ^{//} (n = 1)
Oral phase					
Abnormal lingual function ¹	12 (67%)	8	4	-	-
Abnormal mastication ²	7 (39%)	4	3	-	-
Residual component after oral phase completion ³	14 (78%)	9	4	-	1
Pharyngeal phase					
Mild delay in swallow ⁴	11 (61%)	8	2	1	-
Laryngeal penetration	7 (39%)	3	3	1	-
Tracheal aspiration	-	-	-	-	-
Residual component after pharyngeal phase completion ⁵	13 (72%)	8	3	1	1

¹ Reduced bolus formation, piecemeal swallow, reduced elevation, and reduced anteroposterior motion.

² Absent or incomplete mastication, vertical, diagonal, circular, or anterior mastication pattern.

³ Residue on hard palate, soft palate, and/or posterior surface of the tongue.

⁴ Pooling of food in the valleculae before swallow.

⁵ Trace/mild residue after swallow on valleculae and/or pyriform sinuses.

* Total number of subjects with swallow function study available.

[†] 3.7-Mb duplication.

[‡] Duplication larger than 3.7 Mb.

[§] Duplication smaller than 3.7 Mb.

^{//} Marker: Mosaic marker chromosome 17p.