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Symptoms of Pediatric Feeding Disorders Among Individuals with 3q29 Deletion Syndrome: A Case-Control Study

Addam J. Wawrzonek, PhD,*† William Sharp, PhD,*† Teresa Lindsey Burrell, PhD,*†
Scott E. Gillespie, MS, MSPH,* Rebecca M. Pollak, PhD,‡ The Emory 3q29 Project,§
Melissa M. Murphy, PhD,§ Jennifer G. Mulle, MHS, PhD§‖

ABSTRACT: *Objective:* The goal of this study was to evaluate symptoms of pediatric feeding disorder in a sample of individuals with 3q29 deletion syndrome (3q29Del). Previous research has found that individuals with 3q29Del may experience elevated feeding concerns in early childhood; however, the specificity of these feeding concerns is not well understood. *Methods:* We compared individuals with 3q29Del (N = 83) with controls (N = 59) using an 11-item survey that assessed commonly reported symptoms associated with pediatric feeding disorders. An exploratory analysis also examined individuals with 3q29Del with and without a comorbid global developmental delay (GDD) or an autism spectrum disorder diagnosis. *Results:* Caregivers of 3q29Del cases reported higher incidences of feeding concerns on 10 of the 11 items included in the survey. This included statistically significant differences in food refusal behaviors, rejection of 1 or more food groups, and a history of failure to thrive. Parents of children with comorbid GDD were more likely to report concerns regarding food selectivity and problem behaviors during mealtime. *Conclusion:* The results suggest individuals with 3q29Del experience increased symptoms of pediatric feeding disorder that may require targeted evaluation and intervention for optimal outcomes. Future research should include a more thorough multidisciplinary evaluation to further elucidate symptom severity and optimal treatment strategies.
(J Dev Behav Pediatr 43:e170–e178, 2022) **Index terms:** 3q29 deletion syndrome, feeding disorders, genomic disorder, feeding problems, 3q29 registry, ARFID.

From the *Department of Pediatrics, Emory University School of Medicine, Atlanta, GA; †Multidisciplinary Pediatric Feeding Disorders Program, Marcus Autism Center, Children's Healthcare of Atlanta and Emory University School of Medicine, Atlanta, GA; ‡Genetics and Molecular Biology Program, Laney Graduate School, Emory University, Atlanta, GA; §Department of Human Genetics, Emory University School of Medicine, Atlanta, GA; ‖Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA.

3q29 deletion syndrome (3q29Del) is caused by a 1.6 Mb heterozygous deletion on chromosome 3,[1] with an estimated prevalence of 1 in 30-40,000 in the general population.[2] The syndrome is associated with a range of neurodevelopmental and neuropsychiatric phenotypes, including mild to moderate intellectual disability (ID), increased risk of autism spectrum disorder (ASD), increased prevalence of anxiety disorders, and a 40-fold increased risk of schizophrenia.[1,3] Individuals with 3q29Del are also at higher risk of failure to thrive, reduced birth weight, and significant growth deficits.[1,4] In addition to evidence of ID, ASD, and growth concerns, a recent systematic survey of a large 3q29Del cohort also found significantly higher rates of global developmental delays (GDDs) and gastrointestinal complications compared with the general population.[1] Together, high prevalence of these co-occurring conditions suggest individuals with 3q29Del may also be at increased risk of pediatric feeding disorders.

The phenotype of 3q29 deletion syndrome continues to emerge from case reports[4] and systematic evaluation in deliberately curated cohorts.[1,5,6] Medical manifestations common to the syndrome include congenital heart defects (25%) and gastrointestinal symptoms (81%), with a large proportion of mild, nonspecific musculoskeletal findings (81%) seen on physical examination.[26]

Neurodevelopmental phenotypes account for a significant burden of disability and include intellectual disability (34%), ASD (38%), executive function deficits (46%), and graphomotor weakness (78%). Psychiatric illness manifests across the life span with psychosis prodrome (15%), psychosis (20%), anxiety disorders (40%), and attention-deficit/hyperactive disorder (63%).[6] Neuroimaging studies revealed structural anomalies of the posterior fossa, without accompanying motor symptoms. A recent evaluation of craniofacial dysmorphology reveals that many subjects have a prominent forehead (48.4%), prominent nose tip (35.5%), and thin upper lip vermillion (25.8%), but there is no characteristic facies that would permit clinical identification in the absence of a genetic test.[7] Deficits in cognitive ability, though present, are generally mild to moderate and do not correlate with the overall burden of neurodevelopmental and psychiatric comorbidity.[8]

Pediatric feeding disorder involves severe disruptions in nutritional and caloric intake exceeding ordinary variations in hunger, food preference, and/or interest in eating.[9] Restriction in food intake may present as food selectivity (i.e., eating a narrow variety of foods and/or rejecting one or more food groups) and/or food refusal (i.e., eating a restricted volume of food resulting in formula or feeding tube dependence).[10] Individuals who severely restrict the volume and/or variety of foods consumed during meals meet the diagnostic criteria for Avoidant and Restrictive Food Intake Disorder (ARFID).[11] Manifestations of ARFID include faltering growth, nutritional deficiencies, and the need for oral nutrition supplementation or tube feeding to support growth and meet energy and nutrient needs. Many complex factors contribute to the development of this level of feeding concern in pediatric populations, including behavioral and environmental variables, oral motor skill deficits, and/or medical or anatomical abnormalities.[12,13] Case in point, it is well-established that there is a higher incidence of feeding disorders among individuals with ASD and GDD, as well as children with predisposing medical conditions (e.g., congenital or acquired respiratory, cardiac, and gastrointestinal problems).[9,14-16] Children with ARFID and food selectivity most often present with comorbid developmental conditions including ASD and/or GDD[7,17]; children with ARFID and formula or feeding tube dependence most often present with complex medical histories.[12,16] In both cases, problem behaviors during meals (tearful protests or tantrum) often maintain restricted intake of food.[18]

Provisional evidence suggests that as many as 64% of children with 3q29Del experience elevated feeding problems during the first year of life.[1] Available evidence, however, does not provide specific detail regarding the nature of feeding problems in this pediatric population. The purpose of this study was 2-fold. The primary aim was to evaluate symptoms of pediatric feeding disorders in a sample of individuals with 3q29Del relative to a control sample. A secondary aim was to analyze pediatric feeding symptoms among individuals with 3q29Del and comorbid GDD or ASD, relative to individuals with 3q29Del without GDD or ASD. In the process, this study provides insight into the topography and prevalence of feeding problems associated with 3q29Del.

METHODS

Recruitment

Individuals with a diagnosis of 3q29 deletion syndrome (3q29Del) were ascertained through the existing 3q29 registry housed at Emory University (3q29.org), as previously reported.[1] In brief, recruitment of study subjects, informed consent, assent, Health Insurance Portability and Accountability Act authorization, and data collection are all enabled by the registry website. Recruitment is multifactorial and targeted to reach the stakeholder community. On launch of the registry in 2013, e-mails bearing information about the registry were sent to health care providers, medical geneticists, genetic counselors, and support organizations. The registry is also advertised through an internet campaign (Google AdWords), wherein a series of specific keywords were chosen to target the website. Registry information may also be included in the clinical genetics report that is returned to families on a positive genetic test. Individuals who register and complete informed consent have a personal profile page, in which they can complete data collection instruments. Answers may be submitted by an individual with 3q29Del or a family member (usually a parent or guardian) if the 3q29 deletion patient is underage or not capable of submitting answers. Documents can be uploaded to the registry website, and it is requested but not required that participants upload their clinical genetics report indicating a diagnosis of 3q29Del. For the current study, the inclusion criteria were as follows: clinical documentation or parent report of 3q29Del and a completed medical history and feeding questionnaire. The exclusion criterion was nonfluency in English. Study subjects of any age and with any comorbid condition were eligible to participate.

The goal of this study was to assess whether feeding problems in 3q29Del are elevated as compared with the general population; we therefore recruited a typically developing sample of control study subjects. These individuals were recruited through e-mails sent to intramural CDC and Emory University Listservs that invited a community sample to fill out surveys in an identical fashion to cases. The exclusion criterion for controls involved a clinical diagnosis of a neurodevelopmental disorder. Emory University's Institutional Review Board (Emory University) approved this study.

Measurement

Data collection instruments exist within the registry; answers may be submitted by an individual with 3q29Del or a family member (usually a parent or guardian) if the patient is underage or not capable of submitting answers. At

Table 1. Characteristics of Study Participants With 3q29Del and Controls

Variable	Control, N = 59 (41.5%)	3q29Del, N = 83 (58.5%)	p
Age, yr, mean (range)[b]	10.5 (1.70–41.6)	9.4 (0.19–64.0)	0.456
Sex, male, n (%)	30 (50.8%)	48 (57.8%)	0.410
Comorbid diagnosis, n (%)[a]			
Autism	0 (0%)	20 (24.1%)	**<0.001**
Gastrointestinal concerns	9 (15.3%)	55 (66.3%)	**<0.001**
Global developmental delay	0 (0%)	41 (49.4%)	**<0.001**
Intellectual disability	0 (0%)	18 (21.7%)	**<0.001**
None of the above	50 (84.8%)	13 (15.7%)	**<0.001**

[a]Will not add up to 100% as participants could have more than 1 comorbid diagnosis. [b]p value for age based on 2-sample t test; p values for sex and diagnoses based on χ^2 tests of independence or Fisher's exact tests, as appropriate. Bold indicates statistically significant results at $p < 0.05$.

enrollment, the 3q29 registry collects baseline information about the participant (i.e., the individual with 3q29Del), including sex and birthdate, and contact information for both the participant and the informant. Additional characterization occurs through a custom medical and demographic questionnaire deployed within the registry that includes 7 health-related domains that were intentionally prioritized for data collection based on medical issues previously noted in 3q29Del individuals, including self-report of autism spectrum disorder (ASD) and global developmental delays.[4,19]

In 2016, we developed and deployed into the registry an 11-item questionnaire that covered common symptoms associated with pediatric feeding disorder, manifestations of Avoidant and Restrictive Food Intake Disorder, and/or signs of malnourishment based on our clinical and research experience supported by a review of the extant literature (see supplement 1: Feeding Questionnaire, Supplemental Digital Content 1, http://links.lww.com/JDBP/A325). Items included in the questionnaire covered signs of food refusal (e.g., "The participant relies on a feeding tube to meet his/her nutritional needs." "The participant accepts little or no food by mouth."), food selectivity ("The participant is highly selective about the foods he/she consumed during meals." "The participant rejects most items from one or more food group (i.e., fruits, vegetables, protein, or starch)."), current or previous malnutrition (e.g., "The participant is currently failure to thrive." "The participant has been diagnosed with anemia, now or at any time in the past."), and feeding skill concerns ("The participant does not feed himself/herself." "The participant only consumes smooth (e.g., yogurt) or pureed foods."). All 11 items involve a "yes" or "no" response format. Item 7 involved a stem that allowed respondents to provide further detail about food group rejection in response to a positive response; item 9 involved a stem that provided more detail regarding specific behavior problems encountered during meals.

Analysis

We coded variables from the medical questionnaire (age at completion, sex, and autism diagnosis) as follows: age at completion, numerical value in years; sex, male yes/no; and autism diagnosis, yes/no. For the feeding questionnaire, we coded the 9 of 11 core variables as yes/no. For item 7, we coded the stem of total food group rejection as a count (range 0–4) to reflect the total number of rejected groups. For item 9, we coded the stem of food refusal behaviors as a count (range 0–8) to reflect the total problem behaviors. We first summarized continuous and discrete variables in a univariate fashion, comparing cases with controls using t tests for continuous data and χ^2 or Fisher's exact test for discreet data. We then performed multivariate analysis, adjusting for age and sex. Specifically, analyses for total food group refusals and food refusal behaviors involved negative binomial regression, assessing each outcome as a count. We calculated rate ratios as unadjusted and adjusted for covariates (i.e., age and sex). We analyzed the remaining outcome variables involving dichotomous (yes vs no; e.g., picky eater and tube dependency) variables using binary logistic regression. We calculated odds ratios unadjusted and adjusted for covariates. When expected frequency counts were less than 5, we used exact binary logistic regression. When odds ratios could not be calculated because of zero observations in a 2×2 contingency table cell, we reported Fisher's exact p values. To assess the effect of ASD as a potential comorbidity in participants with 3q29Del, we conducted a subanalysis comparing 3q29Del study subjects with and without a self-report ASD diagnosis. We performed all analyses in SAS v.9.4 (Cary, NC) or R version 4.0.2.

RESULTS
Participant Characteristics

Table 1 provides a description of the study sample. Eighty-three 3q29 deletion syndrome (3q29Del) registrants (50.8% male) were included in this study, ranging in age from 0.19 to 64 years (mean = 9.4 years). Of the 83 responses, 81 (97.6%) were contributed by a parent or caretaker; 2 (2.4%) were completed by the 3q29 proband. Fifty-nine control participants (50.84% male) were included in the study, after excluding 1 control participant reporting a clinical diagnosis of a neurodevelopmental disorder. The sample of participants with

Table 2. Adjusted Risks and Odds of Outcomes for Patients with 3q29Del vs. Control Patients (N = 142)

Outcome, N (row %)	Control, N = 59 (41.5%)	3q29Del, N = 83 (58.5%)	Unadjusted Ratio (95% CI)	Adjusted Ratio (95% CI)	p^a
Signs of food refusal					
Tube dependency[b]					
No	59 (100%)	76 (92.7%)	Reference	Reference	**0.040**
Yes	0 (0%)	6 (7.3%)	NA	NA	
Formula dependency[b]					
No	59 (100%)	73 (87.9%)	Reference	Reference	**0.005**
Yes	0 (0%)	10 (12.1%)	NA	NA	
No food by mouth[b]					
No	58 (100%)	70 (84.3%)	Reference	Reference	**0.001**
Yes	0 (0%)	13 (15.7%)	NA	NA	
Signs of food selectivity					
Highly selective eater					
No	49 (83%)	34 (41%)	Reference	Reference	**<0.001**
Yes	10 (17%)	49 (59%)	7.04 (3.14, 15.9)	6.94 (3.08, 15.6)	
Food group refusal, mean ± SD	0.2 ± 0.6	0.8 ± 1.1	3.61 (1.76, 7.38)	3.50 (1.71, 7.18)	**0.001**
Signs of behavioral concerns					
Food refusal behaviors, mean ± SD	0.1 ± 0.5	1.7 ± 2.0	17.2 (6.80, 43.4)	15.5 (6.15, 38.9)	**<0.001**
Signs of malnutrition					
History failure to thrive[b]					
No	58 (100%)	45 (56.2%)	Reference	Reference	**<0.001**
Yes	0 (0%)	35 (43.8%)	NA	NA	
Currently failure to thrive[b]					
No	59 (100%)	72 (86.7%)	Reference	Reference	**0.003**
Yes	0 (0%)	11 (13.3%)	NA	NA	
History anemia					
No	56 (96.5%)	55 (66.3%)	Reference	Reference	**<0.001**
Yes	2 (3.5%)	28 (33.7%)	14.3 (3.24, 62.5)	16.9 (3.72, 76.9)	
Signs of feeding skill concern					
Smooth food only					
No	56 (98.2%)	76 (91.6%)	Reference	Reference	0.266
Yes	1 (1.8%)	7 (8.4%)	5.15 (0.62, 43.5)	3.44 (0.39, 30.3)	
Does not feed self					
No	58 (98.3%)	64 (77.1%)	Reference	Reference	**0.011**
Yes	1 (1.7%)	19 (22.9%)	17.2 (2.23, 125)	14.7 (1.88, 111.1)	

N (%) unless otherwise noted. Analyses of N (%) involved odds ratio (OR); count items involved rate ratio (RR); RR is the rate ratio based on negative binomial regression and assesses the rate of outcome in 3q29 versus the rate of outcome in control; OR is the odds ratio based on binary logistic regression and assesses the odds of outcome in 3q29 versus the odds of outcome in control. When the expected count is <5, exact binary logistic was used. ^{a}p values based on sex-adjusted and age-adjusted generalized regression model ratios. ^{b}Cannot estimate odds ratio because of 0 cells; presented p values based on Fisher's exact test. NA, not applicable.
Bold indicates statistically significant results at $p < 0.05$.

3q29Del reported high rates of gastrointestinal concerns (66.3%), global developmental delays (GDDs) (49.4%), autism spectrum disorder (ASD) (24.1%), and intellectual disability (21.7%).

Feeding Concerns in 3q29 Deletion Syndrome Versus Controls

Participants with 3q29Del indicated more feeding concerns on 10 of the 11 items on the questionnaire when compared with the control cohort (Table 2). Six of the 83 participants with 3q29Del (7.3%) reported relying on feed-ing tube supplementation, and 10 (12.1%) reported relying on oral formula supplementation; neither issue was pre-sented with controls (p values 0.04 and 0.005, respectively). Thirty-five children with 3q29Del (43.8%) reported a history of failure to thrive; this concern was also absent in controls (p value < 0.001). After controlling for age and sex, statis-tically significant differences between the groups were found on 10 of the 11 questionnaire items. This included a significantly greater number of 3q29Del respondents in-dicating concerns regarding lack of consuming food by mouth (15.7% in cases vs 0% in controls, p value < 0.001),
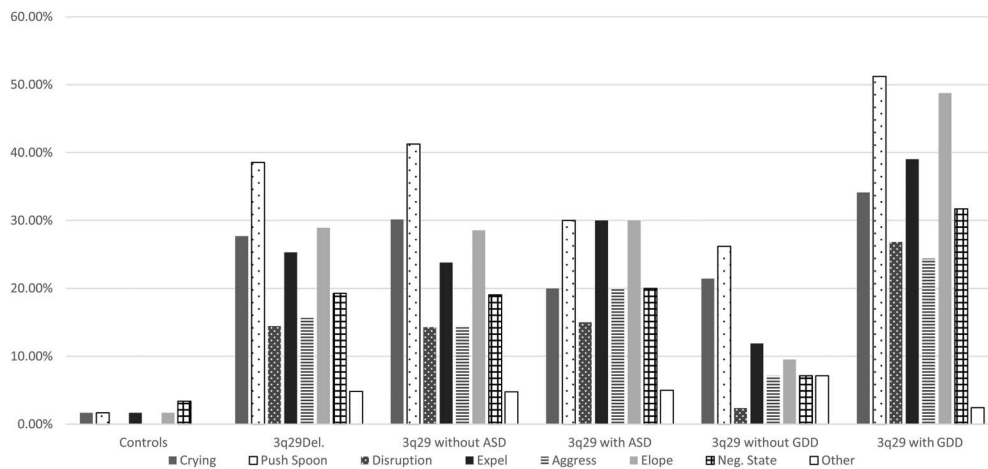
Figure 1. Food refusal behaviors among participants with 3q29Del (with and without ASD/GDD) and controls. ASD, autism spectrum disorder; GDDs, global developmental delays.

as well as significantly higher odds of participants with 3q29Del being reported as a selective eater (odds ratio [OR] = 6.94; confidence interval [CI] = 3.08, 15.6, p value < 0.001), not self-feeding (OR = 14.7; CI = 1.88, 111.1, p value = 0.011), and having a history of anemia (OR = 16.9; CI = 3.72, 76.9, p value < 0.001), relative to control participants. The number of food refusal behaviors in participants with 3q29Del was 15.5 times higher (mean ± SD: 1.7 ± 2.0) than that of controls (mean ± SD: 0.1 ± 0.5, p value < 0.001). Similarly, the number of food groups refused in participants with 3q29Del was 3.50 times higher (mean ± SD: 0.8 ± 1.1) than controls (mean ± SD: 0.2 ± 0.6, p value < 0.001). The specific topography of each behavior and food group are presented in Figures 1 and 2, respectively.

Age-Related Feeding Problems in 3q29Del

We also performed a descriptive analysis within the 3q29 deletion sample by age, grouped using a modified version of the age stages defined according to National Institute of Child Health and Human Development pediatric terminology, as cited in Ref. 29, shown in Supplementary Table 1 (Supplemental Digital Content 1, http://links. lww.com/JDBP/A325). These data reveal that some feeding problems are at their highest prevalence in the youngest age groups and diminish as study subjects age (tube dependency, formula dependency, no food by mouth, eats smooth foods only, or does not feed self). Other feeding problems manifest with equal frequency across the life span (highly selective eater, history of failure to thrive, currently failure to thrive, and history of anemia). In addition, the mean number of food groups refused and the mean number of food refusal behaviors are stable across age groups. These data indicate that while specific feeding symptoms may wax and wane with age, feeding problems in general are a persistent manifestation of 3q29Del.

Feeding Concerns in 3q29 Deletion Syndrome with and Without Comorbid Global Developmental Delays

Forty-one participants with 3q29Del (49.4%) reported a comorbid GDD diagnosis (Table 3). After controlling

for age and sex, we identified a significantly higher number of food refusal behaviors for individuals with 3q29Del and comorbid GDD compared with those without GDD. The number of food refusal behaviors reported in participants with 3q29Del and comorbid GDD was 2.69 times higher (mean ± SD: 2.6 ± 2.3) than those without comorbid GDD (mean ± SD: 0.93 ± 1.4, p value < 0.001). In addition, individuals with GDD were 2.54 times more likely to be described as a highly selective eater (p = 0.046) relative to those without GDD and were 3.21 times more likely to have a history of failure to thrive (p = 0.01).

Feeding Concerns in 3q29 Deletion Syndrome with and Without Comorbid Autism Spectrum Disorder

Twenty participants with 3q29Del (24.1%) reported a comorbid ASD diagnosis (Table 4). Age differed significantly between these groups: Individuals with a comorbid ASD diagnosis were of age 7.1 years on average (p = 0.018). After controlling for age and sex, individuals with ASD were 9.58 times more likely to report eating smooth foods only (p = 0.022). No other significant differences were found between the 2 groups.

DISCUSSION

Previous research has found that individuals with 3q29 deletion syndrome (3q29Del) report significant challenges with feeding in the first years of life.[1] The purpose of this study was to conduct a preliminary analysis of the specific behavioral and nutritional concerns related to pediatric feeding disorder within this population relative to a control sample. We obtained data in a systematic fashion using a targeted instrument in the largest sample of 3q29 deletion cases available. The initial data indicate a significantly higher proportion of individuals with 3q29Del experience symptoms related to pediatric feeding disorder, with higher rates of concerns on 10 of the 11 survey items. This includes concerns regarding total refusal of 1 or more food groups and increased food refusal behaviors during mealtimes. Of note, reported risk of most variables
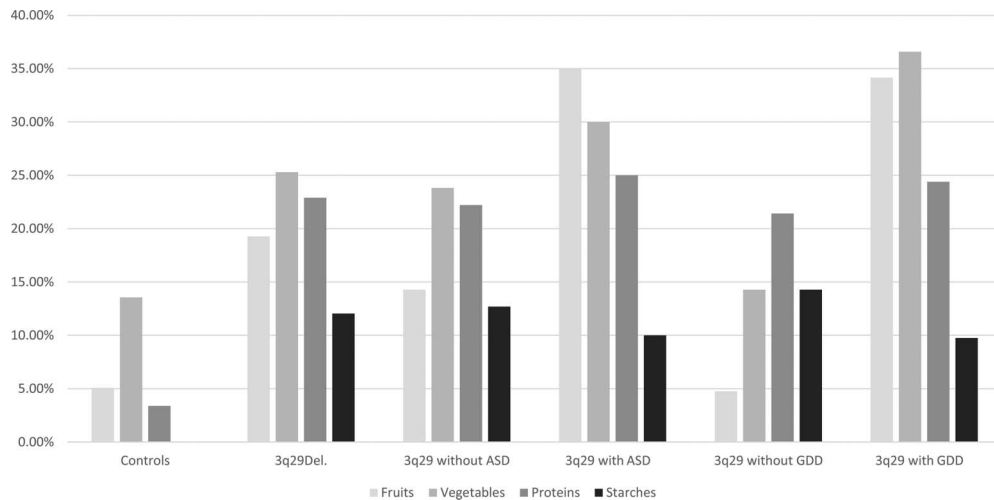
Figure 2. Food group rejection by participant group. ASD, autism spectrum disorder; GDD, global developmental delay.

was substantial; individuals with 3q29Del were 15 times more likely to report food refusal behaviors, including crying, negative statements, throwing food and utensils, spitting food, elopement, and aggression. Similarly, rates of total refusal of all foods from 1 or more food groups were 3.5 times higher in this population, with 40% of participants refusing all items from at least 1 food group. Finally, individuals with 3q29Del reported higher rates of tube and formula dependence and poorer self-feeding skills and were more likely to have a history of anemia or failure to thrive. This is the first systematic survey of feeding behaviors in study subjects with 3q29Del.

Food selectivity occurs frequently among children with global developmental delays (GDDs) and autism spectrum disorder (ASD)[9,14]; these are both common comorbid diagnosis within the 3q29Del population.[1] Understanding how feeding concerns differ across individuals in this population with and without GDD or ASD can help practitioners better identify those at greater risk within the 3q29Del population. The data indicate that, within the 3q29Del sample, individuals with GDD were more likely to show symptoms of food selectivity and engage in food refusal behaviors during mealtimes. Interestingly, although GDD was more indicative of a number of feeding concerns, individuals with ASD only reported higher incidences of consuming soft or puree foods. Although both of these groups are at increased risk of developing a feeding disorder, GDD seems to be a stronger risk factor of feeding concerns within our 3q29Del sample.

Implications

This study has a number of important implications for children with 3q29Del. Participants with 3q29Del are already at increased risk of neurodevelopmental deficits. Micronutrient deficiency, insufficient caloric intake, and poor growth can have significant impacts on cognitive development and may exacerbate the neurodevelopmental concerns in this population. Children who

present with feeding problems also frequently experience compromised immune functioning, may require recurrent hospitalizations, or in the most severe cases, may need placement of medically costly and invasive nasogastric or gastrostomy tubes to maintain caloric and nutritional intake.[21,22] In addition, parents of children with pediatric feeding disorder report high rates of emotional distress,[23] which can directly affect the socioemotional functioning of caregivers and children[24,25] and cause disruption in the overall parent-child relationship.[26,27]

Given the cognitive, developmental, and psychosocial implications of pediatric feeding disorder for participants with 3q29Del, it is essential that screening for feeding concerns be a part of the standard assessment protocol for this population. Effective treatments for treating feeding problems are available. In severe cases, current best practice recognizes intensive multidisciplinary intervention as a standard of care to expand oral food intake and reduce dependence formula or enteral nutrition supplementation.[28] A systematic review of these practices found an average 70% success rate for a full wean from enteral feeding and a 74% increase in oral consumption of foods.[16] Better screening and triage to treatment can help prevent or reduce the negative impact of poor nutrition on childhood growth and development and therefore should be a high priority for pediatricians working with children with 3q29Del.

Limitations

This study, although conducted on the largest known sample of individuals with 3q29Del, is not without limitations. The data were collected through self-report from parents or caregivers; self-report data can have poor reliability and validity.[29] Because this was an initial survey of pediatric feeding concerns in 3q29Del, no data were collected on the intensity or frequency on reported behaviors, and the severity of the feeding symptoms remains unknown. The participants in the control group were screened out for neurodevelopmental disorders, which are associated with

Table 3. Adjusted Risks and Odds of Outcomes for Patients with 3q29Del, GDD+ Versus GDD− (N = 83)

Characteristic, N (Row %)	Without GDD, N = 42 (50.6%)	With GDD, N = 41 (49.4%)	Unadjusted Ratio (95% CI)	Adjusted Ratio (95% CI)	pª
Sex					
Female	18 (42.9%)	17 (41.5%)	—	—	0.898
Male	24 (57.1%)	24 (58.5%)			
Age, mean ± SD	10.5 ± 12.2	8.3 ± 5.9	—	—	0.300
Signs of food refusal					
Tube dependency					
No	39 (95.1%)	37 (90.2%)	Reference	Reference	0.633
Yes	2 (4.9%)	4 (9.8%)	2.09 (0.28, 24.4)	2.36 (0.28, 30.4)	
Formula dependency					
No	38 (90.5%)	35 (85.4%)	Reference	Reference	0.426
Yes	4 (9.5%)	6 (14.6%)	1.62 (0.35, 8.48)	2.46 (0.43, 17.0)	
No food by mouth					
No	36 (85.7%)	34 (82.9%)	Reference	Reference	0.572
Yes	6 (14.3%)	7 (17.1%)	1.24 (0.38, 4.05)	1.47 (0.39, 5.61)	
Signs of food selectivity					
Highly selective eater					
No	22 (52.4%)	12 (29.3%)	Reference	Reference	
Yes	20 (47.6%)	29 (70.7%)	2.66 (1.08, 6.57)	2.54 (1.02, 6.35)	**0.046**
Food group refusal, mean ± SD	0.5 ± 1.0	1.0 ± 1.2	1.92 (0.97, 3.80)	1.92 (0.96, 3.83)	0.067
Signs of behavioral concerns					
Food refusal behaviors, mean ± SD	0.9 ± 1.4	2.6 ± 2.3	2.78 (1.58, 4.93)	2.69 (1.56, 4.63)	**0.001**
Signs of malnutrition					
History failure to thrive					
No	28 (70%)	17 (42.5%)	Reference	Reference	**0.014**
Yes	12 (30%)	23 (57.5%)	3.16 (1.26, 7.94)	3.22 (1.26, 8.17)	
Currently failure to thrive					
No	39 (92.9%)	33 (80.5%)	Reference	Reference	0.119
Yes	3 (7.1%)	8 (19.5%)	3.15 (0.77, 12.9)	3.09 (0.75, 12.8)	
History anemia					
No	27 (64.3%)	28 (68.3%)	Reference	Reference	0.859
Yes	15 (35.7%)	13 (31.7%)	0.84 (0.34, 2.08)	0.92 (0.35, 2.38)	
Signs of feeding skill concern					
Smooth food only					
No	40 (95.2%)	36 (87.8%)	Reference	Reference	0.148
Yes	2 (4.8%)	5 (12.2%)	2.75 (0.42, 30.5)	6.47 (0.63, 281)	
Does not feed self					
No	34 (81%)	30 (73.2%)	Reference	Reference	0.263
Yes	8 (19%)	11 (26.8%)	1.56 (0.55, 4.39)	1.99 (0.60, 6.60)	

N (%) unless otherwise noted. Analyses of N (%) involved odds ratio (OR); count items involved rate ratio (RR); RR is the rate ratio based on negative binomial regression and assesses the rate of outcome in 3q29 + GDD versus the rate of outcome in 3q29-GDD; OR is the odds ratio based on binary logistic regression and assesses the odds of outcome in 3q29 + GDD versus the odds of outcome in 3q29-GDD. When expected counts <5, exact binary logistic was used. ªp values based on sex-adjusted and age-adjusted generalized regression model ratios. GDD, global developmental delay; NA, not applicable.
Bold indicates statistically significant results at p < 0.05.

increased risk of developing a feeding disorder. When this study was launched, it was not known that GDD would amplify the risk of feeding problems in our study sample. As such, we did not include a GDD comparison group. Given our results indicating that participants with 3q29Del with GDD are at higher risk of feeding problems, this additional comparison is warranted in future research.

FUTURE DIRECTIONS

This is the first study specifically evaluating pediatric feeding concerns within the 3q29 deletion syndrome (3q29Del) population, benefiting from the largest cohort of 3q29 deletion study subjects available. Subsequent studies should conduct direct assessments of feeding

Table 4. Adjusted Risks and Odds of Outcomes for Patients with 3q29Del, ASD+ Versus ASD− (N = 83)

Characteristic, N (Row %)	Without ASD, N = 63 (75.9%)	With ASD, N = 20 (24.1%)	Unadjusted Ratio (95% CI)	Adjusted Ratio (95% CI)	p^a
Sex					
Female	29 (46%)	6 (30%)	—	—	0.206
Male	34 (54%)	14 (70%)			
Age, mean ± SD	7.5 ± 6.9	15.6 ± 13.7	—	—	**0.018**
Signs of food refusal					
Tube dependency[b]					
No	56 (90.3%)	20 (100%)	Reference	Reference	0.328
Yes	6 (9.7%)	0 (0%)	NA	NA	
Formula dependency[b]					
No	53 (84.1%)	20 (100%)	Reference	Reference	0.108
Yes	10 (15.9%)	0 (0%)	NA	NA	
No food by mouth					
No	52 (82.5%)	18 (90%)	Reference	Reference	1.000
Yes	11 (17.5%)	2 (10%)	0.53 (0.05, 2.79)	1.16 (0.09, 9.06)	
Signs of food selectivity					
Highly selective eater					
No	26 (41.3%)	8 (40%)	Reference	Reference	
Yes	37 (58.7%)	12 (60%)	1.05 (0.38, 2.94)	1.37 (0.44, 4.29)	0.593
Food group refusal, mean ± SD	0.7 ± 1.1	1.0 ± 1.2	1.37 (0.63, 2.99)	1.66 (0.73, 3.80)	0.231
Signs of behavioral concerns					
Food refusal behaviors, mean ± SD	1.8 ± 1.9	1.7 ± 2.5	0.96 (0.47, 1.99)	1.41 (0.65, 3.03)	0.376
Signs of malnutrition					
History failure to thrive					
No	35 (57.4%)	10 (52.6%)	Reference	Reference	0.559
Yes	26 (42.6%)	9 (47.4%)	1.21 (0.43, 3.41)	1.40 (0.46, 4.29)	
Currently failure to thrive					
No	55 (87.3%)	17 (85%)	Reference	Reference	0.746
Yes	8 (12.7%)	3 (15%)	1.21 (0.19, 5.81)	1.75 (0.23, 10.5)	
History anemia					
No	43 (68.3%)	12 (60%)	Reference	Reference	0.660
Yes	20 (31.7%)	8 (40%)	1.43 (0.51, 4.06)	1.31 (0.40, 4.27)	
Signs of feeding skill concern					
Smooth food only[c]					
No	59 (93.7%)	17 (85%)	Reference	Reference	**0.022**
Yes	4 (6.3%)	3 (15%)	2.57 (0.34, 16.8)	9.58 (1.50, NA)	
Does not feed self					
No	49 (77.8%)	15 (75%)	Reference	Reference	0.115
Yes	14 (22.2%)	5 (25%)	1.16 (0.28, 4.19)	4.66 (0.74, 35.5)	

N (%) unless otherwise noted. Analyses of N (%) involved odds ratio (OR); count items involved rate ratio (RR). RR is the rate ratio based on negative binomial regression and assesses the rate of outcome in 3q29 + ASD versus the rate of outcome in 3q29-ASD; OR is the odds ratio based on binary logistic regression and assesses the odds of outcome in 3q29 + ASD versus the odds of outcome in 3q29-ASD. When the expected count is <5, exact binary logistic was used. [a]p values based on sex-adjusted and age-adjusted generalized regression model ratios. [b]Cannot estimate odds ratio because of 0 cells; presented p values based on Fisher's exact test. [c]Upper bound could not be estimated because of few stratified observations within the adjusting covariates. ASD, autism spectrum disorder; NA, not applicable.
Bold indicates statistically significant results at $p < 0.05$.

issues to determine the severity and prevalence of feeding concerns. This should include a multidisciplinary approach aimed at identifying the behavioral, medical, nutritional, and skill-based profile of pediatric feeding disorder in this population.[12] A larger sample size would also permit well-powered subgroup analyses. Finally, because 3q29Del is comorbid with several other neurodevelopmental and medical disorders that are associated with pediatric feeding disorder, including intellectual disability, developmental delay, and various gastrointestinal conditions, having comparison groups with these conditions would add value to any future analysis.[9,14–16]

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CONCLUSION

This study found that participants with 3q29 deletion syndrome (3q29Del) report a number of concerns related to pediatric feeding disorder, including significant disruptive mealtime behaviors, total refusal of all foods from 1 or more food groups, picky eating, poor self-feeding skills, and a history of anemia and failure to thrive. Because this population is already at risk of developmental and physiological deficits and delays, it is essential that feeding problems be identified and addressed in early childhood. Early treatment of malnutrition or poor caloric intake holds benefit for health and overall development. For these reasons, clinicians working with patients with 3q29Del are encouraged to screen for symptoms associated with pediatric feeding disorder and, if warranted, refer for a multidisciplinary evaluation. Future research should evaluate specific nutritional, oral motor, and behavioral problems to identify the topography and severity of pediatric feeding disorder associated with 3q29Del.

REFERENCES

1. Glassford MR, Rosenfeld JA, Freedman AA, et al. Novel features of 3q29 deletion syndrome: results from the 3q29 registry. *Am J Med Genet C.* 2016;170:999–1006.
2. Stefansson H, Meyer-Lindenberg A, Steinberg S, et al. CNVs conferring risk of autism or schizophrenia affect cognition in controls. *Nature.* 2014;505:361–366.
3. Mulle JG, Dodd AF, McGrath JA, et al. Microdeletions of 3q29 confer high risk for schizophrenia. *Am J Hum Genet.* 2010;87:229–236.
4. Cox DM, Butler MG. A clinical case report and literature review of the 3q29 microdeletion syndrome. *Clin Dysmorphol.* 2015;24:89.
5. Pollak RM, Murphy MM, Epstein MP, et al. Neuropsychiatric phenotypes and a distinct constellation of ASD features in 3q29 deletion syndrome: results from the 3q29 registry. *Mol Autism.* 2019;1:1–5.
6. Russo RS, Gambello MJ, Murphy MM, et al. Deep phenotyping in 3q29 deletion syndrome: recommendations for clinical care. *Genet Med.* 2021;9:1–9.
7. Mak BC, Russo RS, Gambello MJ, et al. Craniofacial features of 3q29 deletion syndrome: application of next generation phenotyping technology. *medRxiv.* 2021;185:2094–2101.
8. Klaiman C, White S, Saulnier C, et al. A distinct cognitive profile in individuals with 3q29 deletion syndrome. *medRxiv.* 2021.03.05. 21252967. Available at: https://doi.org/10.1101/2021.03.05. 21252967.
9. Sharp WG, Berry RC, McCracken C, et al. Feeding problems and nutrient intake in children with autism spectrum disorders: a meta-analysis and comprehensive review of the literature. *J Autism Dev Disord.* 2013;43:2159–2173.
10. Volkert VM, Patel MR, Peterson KM. Food refusal and selective eating. In: *Behavioral Health Promotion and Intervention in Intellectual and Developmental Disabilities.* Cham: Springer; 2016:137–161.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. American Psychiatric Publishing, Inc: Arlington, VA; 2013.
12. Goday PS, Huh SY, Silverman A, et al. Pediatric feeding disorder: consensus definition and conceptual framework. *J Pediatr Gastroenterol Nutr.* 2019;68:124.
13. Silverman AH, Tarbell S. Feeding and vomiting problems in pediatric populations. In: *Handbook of Pediatric Psychology.* Guilford Press: New York, NY; 2009:429–445.
14. Babbitt RL, Hoch TA, Coe DA, et al. Behavioral assessment and treatment of pediatric feeding disorders. *J Dev Behav.* 1994;15:196–206.
15. Bandini LG, Anderson SE, Curtin C, et al. Food selectivity in children with autism spectrum disorders and typically developing children. *J Pediatr.* 2010;157:259–264.
16. Sharp WG, Volkert VM, Stubbs K, et al. Intensive multidisciplinary intervention for young children with feeding tube dependence and chronic food refusal: an electronic health record review. *J Pediatr.* 2020;223:73–80.
17. Sharp WG, Postorino V. Food selectivity in autism spectrum disorder. In: *Clinical Handbook of Complex and Atypical Eating Disorders.* Oxford, United Kingdom: Oxford University Press Oxford; 2017:126–148.
18. Volkert VM, Piazza CC. Pediatric feeding disorders. In: *Handbook of Evidence-Based Practice in Clinical Psychology.* John Wiley and Sons, Inc: Hoboken, NJ. Vol 25; 2012:1.
19. Ballif BC, Theisen A, Coppinger J, et al. Expanding the clinical phenotype of the 3q29 microdeletion syndrome and characterization of the reciprocal microduplication. *Mol Cytogenet.* 2008;1:8.
20. Williams K, Thomson D, Seto I, et al. Standard 6: age groups for pediatric trials. *Pediatrics.* 2012;1:S153–S160.
21. Cohen SA, Piazza CC, Navathe A. Feeding and nutrition. In: *Medical Care for Children and Adults with Developmental Disabilities.* Book News, Inc, Portland, OR; 2006:295–307.
22. Schwartz ID. Failure to thrive: an old nemesis in the new millennium. *Pediatr Rev.* 2000;21:257–264.
23. Budd KS, McGraw TE, Farbisz R, et al. Psychosocial concomitants of children's feeding disorders. *J Pediatr Psychol.* 1992;7:81–94.
24. Abidin RR. The determinants of parenting behavior. *Clin Child Psychol.* 1992;21:407–412.
25. Crnic KA, Greenberg MT. Minor parenting stresses with young children. *Child Dev.* 1990;61:1628–1637.
26. McKay JM, Pickens J, Stewart AL. Inventoried and observed stress in parent-child interactions. *Curr Psychol.* 1996;15:223–234.
27. Powers SW, Byars KC, Mitchell MJ, et al. Parent report of mealtime behavior and parenting stress in young children with type 1 diabetes and in healthy control subjects. *Diabetes Care.* 2002;25:313–318.
28. Lukens CT, Silverman AH. Systematic review of psychological interventions for pediatric feeding problems. *J Pediatr Psychol.* 2014;39:903–917.
29. Finlay WM, Lyons E. Methodological issues in interviewing and using self-report questionnaires with people with mental retardation. *Psychol Assess.* 2001;13:319.