Case Challenge:
Genetics

An Unusual Case of an Infant with Failure to Thrive
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CASE PRESENTATION

A 12-month-old black female, born at 39 weeks gestation, was seen in her primary care physician’s office for a routine examination. The mother’s chief concerns at that time were constipation beginning at age 4 months, delayed speech development, and poor weight gain. Prenatal history was remarkable for intrauterine growth retardation diagnosed at 7 months gestation via ultrasound. Her birth weight was 2.67 kg (10%), length was 49.53 cm (25% to 50%) and head circumference was 34.2 cm (25%). The newborn screen was negative. She was diagnosed with gastroesophageal reflux at age 5 weeks and was treated with ranitidine for 5 months. Her growth chart parameters are consistent with failure to thrive beginning at 9 months of age.

Family history was negative for food allergies, cystic fibrosis, inflammatory bowel or autoimmune disease, and congenital heart disease. Maternal height is 5 feet, 3 inches and paternal height is 5 feet, 8 inches. A maternal cousin has sickle cell disease. The child lives at home with her mother, the mother’s fiancé, and a female friend.

On physical examination, the infant was small but well-appearing, with a high-pitched cry when examined. Weight was 7.19 kg (<3%), length was 68.5 cm (3%), and head circumference was 42.5 cm (2%). Vital signs were within normal limits for age. Pupillary exam had red reflexes bilaterally. Ears were in normal position. The cardiac exam revealed regular rate and rhythm with no murmur. The patient’s abdomen was soft, nondistended, and without hepatosplenomegaly. The genitourinary exam revealed normal female genitalia with sexual maturity rating 1. The anus was patent without tags or fissures. Musculoskeletal exam showed normal muscle bulk, strength and tone, and range of motion. Gait with cruising, cranial nerves, sensation, and deep tendon reflexes were normal.

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Editor’s note: Each month, this department features a discussion of an unusual diagnosis in genetics, radiology, or dermatology. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at Pediatrics@Healio.com.
OUTPATIENT COURSE

The patient was evaluated for failure to thrive (FTT) over the next 4 months. Initial lead level was elevated at 13 mcg/dL, and a complete blood count (CBC) showed a picture consistent with iron-deficiency anemia with a hemoglobin of 10.7 g/dL, mean corpuscular volume of 76.6 fL, and a red cell distribution width of 16.7%.

She was started on ferrous sulfate; lead levels trended down over time. Basic metabolic panel (BMP) was only significant for a carbon dioxide level of 16 mmol/L. Thyroid-stimulating hormone (TSH) and T4 were normal, and a urinalysis was attempted but was unsuccessful.

The nutritionist saw the patient at 15 months of age. The working diagnosis was FTT secondary to inadequate caloric intake due to prolonged breastfeeding/grazing, attachment disorder to the mother, inappropriate food choices with varied textures, and an irregular feeding schedule. Treatment consisted of education and Pediasure (Abbott Laboratories) supplements daily.

The patient scored low in gross motor function on the Ages and Stages Questionnaire (ASQ) at 12 months: this, along with the concern for delayed speech, resulted in a referral to Early Intervention. Repeat ASQ testing at age 15 months showed global delays. She was referred to an FTT clinic and they agreed with the previous assessments regarding the etiology of the FTT.

At 17 months of age, she was also referred to a pediatric gastrointestinal (GI) specialist for evaluation of FTT, chronic intermittent constipation, and continued poor oral intake. At her first visit, the mother was advised to implement a high-calorie toddler diet, continue Pediasure supplements two to three times per day, eliminate junk food, consult with the GI dietician, keep a food diary, begin lansoprazole every morning for possible silent reflux, and follow up in 1 month. However, the patient was admitted to the hospital before all these interventions could be implemented.

INPATIENT COURSE

Less than 1 month after her GI evaluation, she was admitted to the hospital due to a marked decrease in oral intake, weight loss, dehydration, and for further evaluation of her FTT. On admission, her weight was 8.22 kg (only 68% of ideal body weight). A BMP showed an elevated anion gap of 17 (metabolic acidosis with bicarbonate of 17 mEq/dL with a low prealbumin of 15 mg/dL). This anion gap closed after administration of intravenous fluids, and the acidosis resolved before discharge. Liver function tests, CBC, and iron studies were normal. The smear revealed basophilic stippling; however, the lead level had trended down to 6 mcg/dL.

Urinalysis, urine for reducing substances, renal ultrasound, a metabolic workup (acetyl carnitine and amino acid profile, urine organic acids, and uric acid), TSH, free T4, erythrocyte sedimentation rate, C-reactive protein, tissue transglutaminase and immunoglobulin A, prothrombin time, partial thromboplastin time, International Normalized Ratio, and ImmunoCAP allergy testing (ThermoFisher Scientific) for common food allergens all proved negative. An upper GI and endoscopic evaluation were normal.

Neurology was consulted regarding the concern for mild developmental delay (DD), and although motor development was delayed at 17 months, it was still considered to be at the low-end of the normal. A brain MRI without contrast was normal.

An interdisciplinary team of speech therapy, nutrition, social work, and child protective services were involved in the diagnosis. They agreed with the previous outpatient diagnosis for the etiology of FTT and determined she had an oral aversion to liquids besides breast milk. There was no concern regarding potential abuse/neglect.

Due to lack of weight gain, persistent feeding difficulties, and a 3-day calorie count with inadequate oral intake, the patient received a gastrostomy tube and Nissen fundoplication. She eventually tolerated gastrostomy tube feedings and was discharged home with an outpatient genetics appointment.

The genetics team noted upslanting palpebral fissures and mild skin tags over left and right ears. They agreed the unexplained mild DD was at the lower end of normal but that she was making forward progress. Based on her clinical presentation, an array comparative genomic hybridization (microarray) was sent and demonstrated a terminal deletion of 346 oligonucleotide probes from 5pter to 5p15.31.

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Diagnosis:

Cri du Chat Syndrome

Cri du chat is a genetic disease resulting from a deletion of the short arm of chromosome 5 (5p-); 85% of cases are thought to occur de novo. 1 The classic presentation includes a high-pitched monochromatic cry, craniofacial abnormalities (microcephaly, broad nasal bridge, epicanthal folds, micrognathia, downsloping palpebral fissures), and severe psychomotor and mental retardation. 2 There are also associated cardiac abnormalities seen in a higher proportion than the general population.

The prevalence in the newborn is 1 in 50,000 live births, but can be as high
as 1 in 350 among those with a learning disability.\textsuperscript{3} In infancy, these children have low birth weight, hypotonia, feeding difficulties with poor suck, gastroesophageal reflux, and FTT.\textsuperscript{2,4} The mean of the growth curve for girls with cri du chat is at the 5th percentile on the Centers for Disease Control and Prevention (CDC) growth chart from birth to 9 months, after which it falls and remains below the 5th percentile.\textsuperscript{4}

The median head circumference for girls with this disorder drops below the 2nd percentile on the CDC curve by age 3 months. Consequently, compared with the standard population, most children with cri du chat syndrome are small with significant microcephaly and compromised weight for age, and to a lesser extent, compromised height for age.\textsuperscript{4}

There appears to be a spectrum of psychomotor and developmental disability in these patients. Hyperactivity, aggressiveness, self-injury, hypersensitivity to sound, and repetitive movements are seen.\textsuperscript{2} The typical IQ falls into the moderate-to-severe impairment range; however, the verbal skills progress (although delayed) and plateau at around 10 years.\textsuperscript{5} In the milder phenotype, this is manifest as learning difficulties, rather than disability, with an IQ often in the normal range, and defects in expressive language but intact receptive skills.\textsuperscript{5}

If not diagnosed based on dysmorphic features, these cri du chat patients with a milder phenotype are often given a diagnostic evaluation of FTT. In a classic study of hospitalized children with FTT, only 1.4% of laboratory tests were of diagnostic assistance.\textsuperscript{6} Similarly, in this group, abnormalities are seen in MRI in approximately 30% of cases; however, this leads to a specific diagnosis in up to 3.9% of patients.\textsuperscript{7} On the other hand, chromosomal abnormalities found on cytogenetic analysis range from almost 3% to 11.6% in a child with DD, even in the absence of dysmorphic features.\textsuperscript{7} The use of microarray, especially when no specific cause is clinically suggested for intellectual disability, has a diagnostic yield of 12%.\textsuperscript{8}

These newer diagnostic methods have resulted in a better understanding of the genotype-phenotype correlation in cri du chat. It is understood that the critical segment in all patients is 5p15.2, where severe intellectual impairment is mapped.\textsuperscript{1,5} Additionally, it is generally believed that speech delay is mapped to the distal part of 5p15.\textsuperscript{4,5} Thus, it appears that deletion of a small region proximal to 5p15.3 coincides with milder degree of cognitive impairment and with much improved prognosis than those that occur more upstream.\textsuperscript{9}

**CONCLUSION**

Although the etymology of the diagnosis comes from the French pediatrician Lejeune’s direct coinage of the main trait, “cry of the cat,” this symptom is not present in all cases of this syndrome. The patient here represents a nonclassical phenotype of cri du chat without the characteristic dysmorphic features, instead having been diagnosed because of persistent FTT and mild developmental delays.

Based on the literature, our patient’s chromosome deletion at the terminal end does fit with previous data mapping genotype-phenotype correlations. This case also illustrates the need for continued close follow-up in patients with FTT, especially where outpatient management has not yielded an underlying diagnosis for the cause and the patient fails to improve with standard FTT management. As genetic analysis becomes more sophisticated, the pediatrician will have to cast a broader net for diagnoses of these conditions.

The patient is now gaining weight with gastrostomy tube feedings. Although she is less than the 3% on the standard growth charts, she plots at the 50th percentile on the cri du chat growth charts. She began walking at 18 months of age, demonstrates self-feeding skills, has a vocabulary of 20 words, and can make three two-word phrases. Parental chromosome testing has been recommended to establish whether this is a de novo event or inherited. ■

**REFERENCES**