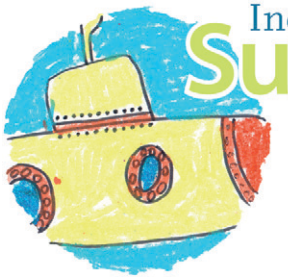

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1 Hypotonia and Failure to Thrive in a 3-month-old Boy

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EDITORS NOTE

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PRESENTATION

A 3½-month-old boy is seen in the general pediatric clinic for a weight check. He was delivered following induction at 36 weeks' gestation due to nonreassuring fetal heart tones. His birthweight was 2,300 g (3rd percentile) and he has been followed closely since birth for persistent feeding difficulty and poor weight gain. He has never successfully latched at the breast and has required syringe feedings of expressed breast milk (EBM) at home. Because of continued poor weight gain at 2 months of age, the EBM was fortified to 22 kcal/oz. With fortification, he is consuming approximately 140 kcal/kg per day, but his weight remains below the 3rd percentile for age. His length was at 40th percentile at birth but is now at the 1st percentile for age when plotted on the World Health Organization growth curves. His past medical history is otherwise unremarkable and without illness or hospitalizations. His mother has no history of medication use, substance abuse, or infections during pregnancy. The family history is noncontributory.

The boy's overall appearance is well, with normal vital signs. He has global hypotonia with poor suck reflex. He is unable to lift his head when prone and eliciting a Moro reflex is difficult. His grasp and plantar reflexes appear intact. He does not have any dysmorphic features. His heart has a regular rate and rhythm with no murmur. His abdomen is soft without evidence of organomegaly. Genital examination reveals a circumcised penis with a left testis that is palpated in the inguinal canal and a right testis that cannot be palpated. There are no areas of skin hypopigmentation and no increased work of breathing, tongue enlargement, or limb deformities.

DISCUSSION

Poor weight gain is a common problem among infants and has a broad differential diagnosis spanning all organ systems. The most common reason for failure to thrive is lack of sufficient energy consumption. Often, weight gain improves after provision of adequate energy and protein. The unique aspect of this patient was the persistent low weight despite adequate caloric consumption. In addition, he had global hypotonia, cryptorchidism, and poor linear growth. This constellation of findings narrowed the differential diagnosis toward a genetic cause. The differential diagnosis with a genetic cause remains vast and includes congenital myopathies (spinal muscle atrophy), inborn errors of metabolism (Pompe disease), or genetic disorders (Prader-Willi syndrome). This patient's lack of intact reflexes and dysmorphic features accompanied by cryptorchidism,

hypotonia, and failure to thrive made Prader-Willi syndrome (PWS) the most likely cause.

Diagnosis

A consultant from the genetics division recommended obtaining molecular testing for PWS. Although PWS has clinical diagnostic criteria, definitive genetic testing with molecular testing can confirm the diagnosis. The first-line genetic test for PWS is a DNA methylation analysis, which detects abnormal methylation within the critical region for PWS on 15q11.2-13. The test yields positive results in 99% of cases of PWS. Beyond confirming the diagnosis, further genetic testing is required to determine the genetic subtype: paternal deletion of 15q11.2-13 in 70% of patients, maternal uniparental disomy of chromosome 15 in 25%, and an imprinting defect in 5%. Knowledge of the genetic subtype is important for genetic counseling. This patient had positive methylation study results diagnostic for PWS, and subsequent florescence in situ hybridization documented a deletion of 15q11.2-13.

Condition

PWS is caused by the absent expression of genes in the paternally inherited 15q11-13 region of chromosome 15. It is the most common form of syndromic obesity.

Reduced fetal activity, polyhydramnios, and breech orientation are common prenatally. During infancy, hypotonia leading to feeding difficulty and failure to thrive are common. Hyperphagia manifests between 2 and 6 years of age. With time, hyperphagia becomes significant, with some patients eating garbage, consuming frozen foods, and stealing or hoarding food. Most patients have short stature and fail to have a pubertal growth spurt. Hypogonadism with cryptorchidism is noted in nearly all males. Development of secondary sexual characteristics is usually absent or delayed. Menarche is often delayed in girls.

Delayed developmental milestones become evident during the transition into early childhood. Affected children usually have a mild-to-moderate degree of cognitive impairment, with an average intelligence quotient of 70. Behavior issues and learning difficulties are typical. Younger children often have temper tantrums and display stubbornness and obsessive-compulsive type of behavior. Other issues, such as scoliosis (up to 80% of patients) and epilepsy (up to 25% of patients) become common as patients get older.

Management

Earlier diagnosis allows for anticipatory guidance and earlier access to care, which can substantially improve long-term health and developmental outcomes. The management of PWS is multidisciplinary, supportive, and aimed at associated comorbidities. The patient should be referred to "Early Intervention" for physical therapy, occupational therapy, and speech/feeding therapy. Management of feeding issues persists throughout life. During infancy, formal oromotor evaluation by a speech pathologist may be necessary, as might a swallow study. Assisted feeding is universally required and may include special nipples and nursing systems, fortification, thickening of feedings, or temporary nasogastric feeding. In older children, when hyperphagia dominates, strict food and caloric limitation is the focus of management. Access to food must be limited, with food often needing to be locked up because of the strong food-seeking drive in older children and adolescents. Currently there are no recommendations for pharmacotherapy or surgical intervention for weight loss or management for patients with PWS.

The patient should be referred to an endocrinologist soon after diagnosis. Many manifestations of PWS are believed to be due to hypothalamic and pituitary dysfunction. Growth hormone deficiency is considered to be universal. Growth hormone therapy has been approved by the U.S. Food and Drug Administration and is used routinely for PWS. Although growth hormone improves the short stature, its primary benefits are on muscle tone, motor function, and body composition. Due to concerns about the effect of growth hormone on sleep-disordered breathing, routine sleep studies are recommended. Obesity-related issues, such as type 2 diabetes, sleep apnea, and dyslipidemia, are prominent, as are hypogonadism and osteoporosis. Thyroid axis dysfunction can be seen in infants and young children with PWS, with total or free thyroxine values being low for age. Thyroid evaluation is appropriate during infancy, given the role of thyroid hormone on neurologic development.

Children should be referred to developmental pediatricians to ensure access to appropriate developmental resources and to address behavior issues.

The diagnosis of PWS can be stressful and sometimes devastating for the parents. Support services and resources for families and providers can be found through the Prader-Willi Syndrome Association USA (www.pwsausa.org), the Foundation for Prader-Willi Research (www.fpwr.org), and the International Prader-Willi Syndrome Organization (www.ipwso.org).

Lessons for the Clinician

- During infancy, Prader-Willi syndrome (PWS) presents with failure to thrive and hypotonia, even though hyperphagia is the dominant feature later in life. Clinicians

should consider PWS in all infants with failure to thrive, feeding difficulties, and hypotonia.

- Although clinical diagnostic criteria exist for PWS, genetic testing with methylation analysis should be performed when the diagnosis is suspected.
- Early diagnosis and multidisciplinary management of PWS facilitates improved long-term outcomes. Referrals should be made early to Early Intervention developmental services, a pediatric endocrinologist, and family support organizations.

Note: The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Army, Department of Defense, or the United States Government.

Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/37/1/39.

Parent Resources from the AAP at HealthyChildren.org

- Failure to Thrive: https://www.healthychildren.org/English/health-issues/conditions/Glands-Growth-Disorders/Pages/Failure-to-Thrive.aspx