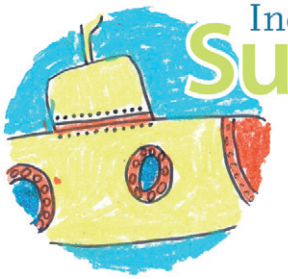

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6 Failure to Thrive with Congenital Glaucoma in a 2-month-old Girl

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PRESENTATION

A 2-month-old girl presents to her pediatrician for a regular checkup. Failure to gain weight, unmet developmental milestones, and hypotonia are observed, and the patient is admitted for evaluation for failure to thrive. The patient was born by spontaneous vaginal delivery at 39 weeks with a body weight of 2,690 g. Her newborn screening test result was normal. Shortly after birth, she was noted to have left buphthalmos associated with increased intraocular pressure (IOP) and underwent left eye trabeculotomy 10 days after birth. Postoperatively, she experienced hypothermia to 91.4°F (33.0°C), an elevated ammonia level to 126 μg/dL with mild metabolic acidosis, and difficulty regaining consciousness. She was admitted to the hospital for observation, and her ammonia level returned to normal without treatment. No further evaluation was initiated because the hyperammonemia self-corrected and was thought to be a postoperative complication related to anesthesia. She is currently followed by a glaucoma specialist. At home, she eats 2 to 3 oz of partially hydrolyzed cow milk formula every 3 hours, including overnight, an average of 101 to 151 kcal/kg per day. She has had no vomiting, diarrhea, or difficulty breathing. Her family history includes healthy parents, who both repeated a year of elementary school and received special education, and 2 healthy older brothers. Her extended family history includes a maternal grandmother who had 1 term stillbirth and 1 miscarriage and a developmentally normal 2-year-old maternal first cousin with a history of congenital cataracts. On physical examination, she is afebrile and her pulse is 152 beats/min, respiratory rate is 32 breaths/min, length is 20 in (52 cm) (2.20 percentile), weight is 3,170 g (0.09 percentile), and head circumference is 14.0 in (35.5 cm) (3.10 percentile). She has proportional features but is small for her age. She has mild proptosis of the left eye, with corneal clouding. She has a normal cry, normal muscle tone, 3+ right patellar reflex, and 2+ left patellar reflex. There are 3 round, hyperpigmented areas on the scalp, each with a diameter of less than 0.5 cm, and large areas of hypopigmentation with irregular borders on the upper chest and lower back. Heart, lung, and abdominal examination results are within normal limits.

Owing to the patient's history of difficulty with anesthesia and the concerning family history, metabolic studies are ordered and the genetics team is consulted.

Initial laboratory values for complete blood cell count, complete metabolic panel, and urinalysis are within normal limits. Other pertinent laboratory values include a lactic acid level of 22.5 mg/dL (reference range, 4.5–19.8 mg/dL [0.5–2.2 mmol/L]), an ammonia level of 28 μg/dL (reference range, 18-103 μg/dL), and a morning cortisol level of 24.4 μg/dL (673.2 nmol/L) (reference range, 2.8–23.0 μg/dL [77.3–634.5 nmol/L]). Additional questioning into family history reveals that the mother, maternal grandmother, and maternal great grandmother all have varying degrees of skin spots.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/38/4/189.

DISCUSSION

After admission to the children's hospital, the patient was continued on her home diet, with minimum intake set at 21 oz/day (132.5 kcal/kg per day). She was visited by the genetics team, who recommended echocardiography, abdominal ultrasonography, and skeletal survey, the findings of which were normal. Metabolic studies (very-long-chain fatty acid determination, serum amino acid quantification, acylcarnitine profile, total and free carnitine, and urine organic acids) and a single-nucleotide polymorphism microarray were sent for analysis, but most results remained pending throughout hospital admission. Her acylcarnitine profile returned to normal limits. Magnetic resonance imaging (MRI) of the brain revealed left macrophthlamia with asymmetry and hypoplasia of the sphenoid bone. Spinal MRI revealed a hyperintense, heterogenous lesion in T2-weighted images, which encased the spinal cord almost entirely as well as the lower spinal nerves and the distal aorta. Based on this classic appearance, the lesion was determined to be a plexiform neurofibroma. The National Institutes of Health (NIH) diagnostic criteria (discussed later herein) were used to make the clinical diagnosis of neurofibromatosis type 1 (NF1) based on the presence of a plexiform neurofibroma and sphenoid asymmetry/dysplasia in this patient; not present were the diagnostic number of café-au-lait spots, axillary/inguinal freckles, optic nerve glioma, iris hamartomas (Lisch nodules), or confirmed NF1 diagnosis in a first-degree relative, although it was presumed based on family history and maternal physical examination findings. If our patients' findings had not met the NIH criteria for a clinical diagnosis, genetics studies could have been sent to confirm the diagnosis. Based on the extent of lesion burden and patient status, surgery was not indicated. The patient continues to be managed medically.

During hospitalization, it was noted that the patient had significant feeding difficulties that limited her ability to meet the 21-oz/day goal. The feeding/swallowing team was consulted and taught the family proper chin/cheek support as well as various other feeding techniques to ensure adequate calorie intake. Even with this assistance, the patient gained only 0.2 kg throughout her 7-day hospitalization. A nasogastric tube and a gastrostomy button were discussed as possibilities in the near future.

The Condition

Neurofibromatosis type 1, or von Recklinghausen disease, is an autosomal dominant disorder in which one-half of cases are inherited and the other half are sporadic mutations. In the hereditary cases, the penetrance is complete; however, expression of the mutation varies greatly between individuals. Neurofibromin, the protein affected, is normally expressed in all tissues and functions as a tumor suppressor by downregulating RAS, a proto-oncogene. Mutations cause neurofibromin loss-of-function, increasing the likelihood of tumor development in a variety of tissue types.

Classically, patients with NF1 present with a constellation of signs either at birth or gradually over time. Most signs are present by age 8 years. A clinical diagnosis, as defined by the NIH criteria, includes at least 2 of the following: (1) 6 or more café-au-lait macules larger than 5 mm in diameter in individuals before puberty and larger than 15 mm in diameter after puberty, (2) 2 or more neurofibromas or 1 plexiform neurofibroma, (3) axillary or inguinal freckling, (4) an optic glioma, (5) 2 or more Lisch nodules of the iris, (6) distinctive osseous lesions (such as sphenoid dysplasia or thickening of long bones), or (7) a first-degree relative who meets these criteria. If NF1 is suspected before age 8 years but the patient does not meet all the diagnostic criteria, diagnosis may require genetic testing of the neurofibromin gene. Although congenital unilateral glaucoma is not included in this list, its concurrence with NF1 has been well documented in many case reports. Thus, when congenital glaucoma is diagnosed, a complete physical examination and a detailed family history are warranted to screen for well-known systemic abnormalities associated various phakomatoses.

Individuals diagnosed as having NF1 must receive genetic counseling and should be followed closely by a physician equipped to address the sequelae of the disease, including learning disabilities, seizures, hypertension, peripheral neuropathy, macrocephaly, and tumor growth. Prognosis depends on disease severity. On average, life expectancy is shortened due to increased risk of neoplastic tumor growth.

Diagnosis

A thorough history should be taken from the patient and family members. Family members should be examined for classical signs of NF1. Physical examination should include close examination of the skin, and a complete eye examination by an ophthalmologist if an optic glioma or neurofibroma is suspected. Imaging can greatly assist in the diagnosis, particularly in helping identify optic gliomas and distinctive osseous lesions. The differential diagnosis for NF1 is wide and revolves heavily around the presenting signs and symptoms. For children with café-au-lait spots, Legius syndrome, McCune-Albright syndrome, tuberous sclerosis, and Fanconi anemia should also be considered. Suspicion of central nervous system lesions should be evaluated with imaging and proper consultation.

Our patient met the NIH diagnostic criteria for NF1 after MRI revealed both sphenoid dysplasia/asymmetry and a large, plexiform neurofibroma encasing the spine. After further inquiries regarding familial signs and symptoms of NF1, a positive family history was confirmed. In fact, the patient's grandmother had many peripheral neurofibromas on her face and the patient's mother had multiple café-au-lait spots and a history of a learning disability. This varied presentation across 3 generations reveals the wide variability in the expression of this disease. At hospital discharge, our patient exhibited 3 of the 7 criteria established by the NIH.

Management

Patients with NF1 should be followed regularly to screen for new disease manifestations and for management of disease sequelae. Annual screening should include skin examinations, blood pressure checks, and growth curve evaluation. Tanner stages should also be recorded because precocious puberty can develop if the pituitary gland becomes involved. Those with diagnosed or suspected neurofibromas should be questioned about the presence or change of neuropathic pain or weakness. Physicians should also inquire about the patient's school performance to ensure proper education for the patient.

Our patient is seen regularly by multiple health-care teams—pediatrics, genetics, ophthalmology, occupational therapy, and physical therapy. Shortly after discharge, her swallowing issues worsened, and she was placed on nasogastric tube feedings, which she tolerated well. Recently, a gastrostomy button was placed because her swallowing issues are not expected to resolve or improve at this point. We suspect that her failure to thrive is multifactorial in etiology, initially due to malnutrition in the setting of decreased stamina and poor feeding and later due to her hypotonia secondary to the large spinal neurofibroma. She also underwent the placement of an Ahmed valve to more effectively lower her IOP. She continues to struggle in meeting developmental milestones. The manifestations of her condition will be better understood as she ages.

Lessons for the Clinician

- In addition to the National Institutes of Health criteria, the presence of congenital unilateral glaucoma should raise suspicion and initiate further evaluation for the other features of neurofibromatosis type 1 (NF1).
- Classic signs of NF1 may not be evident in infancy and may develop later in childhood. Ongoing monitoring is needed.
- If the condition is suspected, a 3-generation family history should be documented, and family members should be individually evaluated for signs and symptoms of NF1.

Suggested Readings

Hirbe AC, Gutmann DH. Neurofibromatosis type 1: a multidisciplinary approach to care. *Lancet Neurol.* 2014;13(8):834–843

Payne MS, Nadell JM, Lacassie Y, Tilton AH. Congenital glaucoma and neurofibromatosis in a monozygotic twin: case report and review of the literature. *J Child Neurol.* 2003;18(7):504–508

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