A 3-month-old Girl with Failure to Thrive
Robert Listernick, MD

This 3-month-old girl was evaluated for failure to thrive and jaundice. She was the 2,685-gram product of a full-term, uncomplicated pregnancy, labor, and delivery to a 21-year-old gravida 2 para 2 (G2P2) woman.

Shortly after birth, it became clear the child had significant failure to thrive and jaundice despite multiple manipulations of formula. She had an extensive evaluation after being found to have cholestatic jaundice. Two liver biopsies were performed at an outside hospital, which showed paucity of bile ducts. She had a normal echocardiogram and normal ophthalmologic examination.

She was drinking only 15 oz a day of a cow’s milk-based formula, requiring 20 minutes to drink between 1 to 3 oz. There was no history of vomiting, coughing, or choking, but she had intermittent acholic stools. Family history was unremarkable.

On exam, she was a scrawny, malnourished-appearing girl. Her weight, length, and head circumference were all well below the 5th percentile, although they had been in the 25th percentile at birth. She had two patches of hyperpigmentation on her back and trunk. She had extremely prominent cheeks but was not dysmorphic otherwise. She was normocephalic.

Pupils were equal, round, and reactive to light. Pupils were equal, round, and reactive to light. Extraocular movements were intact. Red reflexes were normal. Palate was normal. Lungs were clear. Heart exam was normal. Her abdomen was mildly distended. Liver was palpable 4 cm below the right costal margin. There was no splenomegaly. Genitalia were normal. She had moderate truncal hypotonia and decreased head control. Deep tendon reflexes were present.

Representative laboratory findings included normal albumin; total bilirubin 4.4 mg/dL; direct bilirubin 2.6 mg/dL; GGT 1,600 IU/L; ALT 586 IU/L; AST 192 IU/L; prothrombin time 16 seconds. CBC with differential was normal.

Robert Listernick, MD, moderator: When evaluating an infant who has cholestasis, are there clues in the history, physical examination, or laboratory findings that might point the physician in one direction or another?

Udeme Ekong, MD, pediatric hepatologist: One huge laboratory clue would be a normal GGT, which would strongly point to either progressive familial intrahepatic cholestasis (PFIC) type 1 and 2 or an inborn error of bile salt metabolism. In most other cases of cholestasis, the GGT will be elevated. Extreme elevation of the GGT, perhaps greater than 1,500 IU/L, suggests the possibility of neonatal sclerosing cholangitis, a disease that gets confused clinically and pathologically with biliary atresia.

Dr. Listernick: What about the presence of poor weight gain? Is that a clue?

Dr. Ekong: Infants with alpha-1 antitrypsin deficiency and neonatal hepatitis may have failure to thrive.

Dr. Listernick: Does every infant undergo liver biopsy?

Dr. Ekong: In general, we perform biopsies on most babies to aid with diagnosis, as well as to evaluate the extent of liver disease.

Dr. Listernick: May we look at the liver biopsy?

Elaine Cham, MD, pediatric pathologist: On low power, we...
see multiple bile plugs all around the central vein. On higher power, the hepatocytes are edematous around these bile plugs, and there are pseudoxanthomatous changes seen in with chronic cholestasis. The major diagnosis to consider would be Alagille syndrome, a syndrome characterized histologically by paucity of bile ducts.

**Dr. Listerick:** Tell us about Alagille syndrome.

**Dr. Ekong:** Alagille syndrome is an autosomal dominant disorder that causes cholestatic liver disease in infants and may involve the eyes (presence of posterior embryotoxon); heart (peripheral pulmonic stenosis, septal defects, tetralogy of Fallot); skeletal system (butterfly hemivertebrae bodies); cholestasis, and characteristic dysmorphic facial features (elongated nose with bulbous tip, broad forehead). The dysmorphic features may be subtle in infancy and become more apparent with age.

**Dr. Listerick:** How do you confirm the diagnosis?

**Dr. Ekong:** Alagille syndrome is a clinical diagnosis made by the presence of bile duct paucity and three of the above five features. Mutations in the JAG1 gene, which is a ligand for the notch-1 receptor, are seen in approximately 75% of patients in whom one makes the clinical diagnosis.

---

**Alagille syndrome is a clinical diagnosis made by the presence of bile duct paucity...**

---

**Dr. Listerick:** I noticed that a “jaundice chip/cholestasis panel” was sent.

**Dr. Ekong:** This is a relatively new way of diagnosing inherited diseases of cholestasis. We can look for mutations in one of five genes associated with neonatal cholestasis simultaneously: alpha-1 antitrypsin deficiency, PFIC type 1, PFIC type 2, PFIC type 3, and Alagille syndrome.

**Dr. Listerick:** What happens to these patients?

**Dr. Ekong:** Approximately 20% ultimately develop cirrhosis. However, the majority have issues related to growth and significant pruritus, which can be quite disabling.

**Dr. Listerick:** Moving on, although her large areas of hyperpigmentation were diagnosed initially as “bathing trunk nevi,” they were actually large café-au-lait spots (CALS). These CALS were large and had quite irregular borders. They appeared quite distinct from the CALS seen in neurofibromatosis type 1. Other conditions in which one sees multiple CALS include tuberous sclerosis; neurofibromatosis type 2; Fanconi anemia; Bloom syndrome; Russell-Silver syndrome; and DNA mismatch repair syndrome, to name a few. Given the entire clinical picture, these CALS most resemble those seen in McCune-Albright syndrome (MCAS) and polyostotic fibrous dysplasia.

**Don Zimmerman, MD, pediatric endocrinologist:** MCAS is characterized by the triad of polyostotic fibrous dysplasia, autonomous endocrine hyperfunction, and the presence of areas of hyperpigmentation, as you’ve described. These manifestations develop over time and may not all be apparent at any one particular point in time.
**Key Learning Points**

1. In infants who have cholestatic liver disease, normal GGT strongly points to either progressive familial intrahepatic cholestasis (PFIC) type 1 and 2 or an inborn error of bile salt metabolism.

2. Alagille syndrome is an autosomal dominant disorder that causes cholestatic liver disease in infants and may involve the eyes (persistence of posterior embryotoxon); heart (peripheral pulmonic stenosis, septal defects, tetralogy of Fallot); skeletal system (butterfly hemivertebrae bodies); blood vessels (renal artery stenosis, cerebral aneurysms, moyamoya disease); and characteristic dysmorphic facial features (elongated nose with bulbous tip, broad forehead).

3. McCune-Albright syndrome (MCAS) is characterized by the triad of polyostotic fibrous dysplasia, autonomous endocrine hyperfunction, and the presence of areas of hyperpigmentation.

4. The most common endocrinopathy seen in MCAS is precocious puberty as a result of autonomous testicular or ovarian hyperfunctioning. Hyperthyroidism often occurs later in childhood and growth hormone excess can occur at any age.

5. The most common endocrine dysfunction in infants with MCAS is ACTH-independent Cushing’s syndrome.

---

**Dr. Listernick:** Let’s take each characteristic individually. We’ve discussed the CALS. What are the endocrine manifestations?

**Dr. Zimmerman:** Virtually any endocrine gland may undergo autonomous hyperfunctioning. The most common endocrinopathy is precocious puberty as a result of autonomous testicular or ovarian hyperfunctioning. Hyperthyroidism often occurs later in childhood and growth hormone excess can occur at any age. However, the most common endocrine dysfunction in infants is ACTH-independent Cushing’s syndrome.

**Dr. Listernick:** What about the polyostotic fibrous dysplasia?

**Dr. Zimmerman:** These lesions may be asymptomatic or quite disfiguring if in the skull, due to bony overgrowth. They may develop over time in virtually any bone. Bony overgrowth in the orbits or the auditory canals may lead to visual abnormalities or deafness.

**Dr. Listernick:** What’s the cause of MCAS?

**Dr. Zimmerman:** MCAS is due to a postconceptional somatic mutation in the alpha subunit of the stimulatory G protein in each of these organs. As such, the manifestations among individuals with MCAS are quite varied depending upon which organs have the abnormal gene. These children are mosaics for the mutated stimulatory G protein. The stimulatory G protein is constitutively active in the various endocrine glands involved, but once activated, individuals who have the MCAS mutation are unable to turn off the G protein and the gland. This leads to an unrestrained signal to produce whatever protein the cell makes.

**Dr. Listernick:** So let’s get back to our patient.

**Dr. Zimmerman:** This child has very prominent cheeks and vellus hair on the forehead that virtually comes down to the eyebrows. This is very commonly seen in glucocorticoid excess. It’s virtually a slam-dunk that this child has MCAS and Cushing’s syndrome.

**Dr. Listernick:** How do we confirm the diagnosis of hypercortisolism?

**Dr. Zimmerman:** To establish the diagnosis in a hospitalized patient, we try to suppress cortisol by administering dexamethasone. If a person has normal function of the hypothalamic-pituitary-adrenal axis, administered dexamethasone will signal the pituitary to stop stimulating the adrenal gland and the adrenal gland will stop producing cortisol.

**Dr. Listernick:** Hypercortisolism was confirmed in the child. Before we talk about treatment, we haven’t explained the cholestatic liver disease, the “chief complaint.”

**Dr. Ekong:** As it turns out, neonatal cholestatic liver disease is a rare but well-described complication of MCAS. However, the previously described pathology in all the patients was “neonatal hepatitis” with giant cell transformation of the hepatocytes, a nonspecific finding that is the response of neonatal hepatocytes to injury; bile duct paucity was not seen. This case is quite unusual.

**Dr. Zimmerman:** This child was also hypophosphatemic, probably as a result of overproduction of fibroblast growth factor-23 (FGF-23) by fibrous dysplasia tissue, which leads to phosphaturia.
Dr. Listernick: Interestingly, this child also had nephrocalcinosis seen on renal ultrasound, probably as a result of the FGF-23. This is well-described in MCAS. So now what?

Marleta Reynolds, MD, pediatric surgeon: She needs bilateral adrenalectomies. However, the key to a successful operation will be the preoperative preparation. In order to have a safe anesthetic experience, her hypertension will have to be meticulously controlled beforehand. In addition, the anesthesiologists need to be prepared for an operation similar to one we perform for pheochromocytomas. In those situations, manipulating the tumor may lead to the release of catecholamines, leading to wide fluctuations in blood pressure.

Dr. Listernick: What did the glands look like?

Dr. Reynolds: Normally, the glands are thin, triangular structures overlying the kidneys. These glands were large and a bit lumpy, remarkably abnormal in appearance.

Dr. Cham: The adrenal glands are quite enlarged and have a diffuse nodularity. Histologically, the adrenal cortex is markedly expanded with cells that have abundant cytoplasm and resemble fetal adrenal cortex. This is somewhat different from the typical nodular cortical hyperplasia seen in MCAS.

Dr. Listernick: Despite the non-classic appearance of the adrenal glands, this child has MCAS. Do we need to confirm the diagnosis genetically?

Dr. Zimmerman: There’s no question that this child has MCAS and Cushing’s disease. MCAS testing is somewhat problematic; in only 30% of cases can the diagnosis be made by testing circulating white blood cells. The yield is much higher if involved tissue can be tested. In this case, we were fortunate because the child had a liver biopsy and testing confirmed a mutation in exon 8 of the GNAS1 gene.

Dr. Listernick: How will you follow her?

Dr. Zimmerman: Obviously, she needs daily glucocorticoid and mineralocorticoid replacement. She’ll need to be monitored closely for the development of other hyperfunctioning endocrinopathies, most notably hypothyroidism and precocious puberty, as well as for the development of disabling or disfiguring bone disease.

Dr. Listernick: Thank you, everyone.