A 13-year-old Girl with ‘Fatty Liver Disease’

Robert Listernick, MD

This 13-year-old girl was first seen at this hospital at 12 years for evaluation of “fatty liver disease.” At 11 years, she started complaining of epigastric abdominal pain and was found to have hepatosplenomegaly. Liver biopsy was consistent with non-alcoholic steatohepatitis (NASH). At that time, her weight was 97 kg, markedly greater than the 95th percentile, and her height was in the 75th percentile. Her prothrombin time was 23 seconds, PTT 43 seconds, hemoglobin 14.6 g/dL, white blood cell count 3,300/mm³, platelets 45,000/mm³, albumin 3.1 g/dL, AST 78 IU/mL, ALT 96 IU/mL, and total bilirubin 2.2 mg/dL.

Past medical history was remarkable for hypothyroidism. She had longstanding obesity and had been diagnosed as having type 2 diabetes 2 years earlier and was treated with metformin. Hypertension was being treated with lisinopril.

On exam at 12 years, her liver span was approximately 10 cm, and her spleen was 8 cm below the left costal margin. There were multiple spider angioma on her face and chest. There was acanthosis nigricans on her neck.

Robert Listernick, MD, moderator: Comments?

Don Zimmerman, MD, pediatric endocrinologist: She certainly has metabolic syndrome. This is a combination of risk factors that include central obesity, hypertension, dyslipidemia, and insulin resistance. The presence of acanthosis suggests that insulin resistance has become established in our patient. Although patients with metabolic syndrome are resistant to the hypoglycemic effects of insulin, they remain sensitive to its anabolic effects. In the case of the skin, insulin stimulates the layer of skin that has melanocytes, leading to acanthosis.

Dr. Listernick: Why does NASH develop?

Estella Alonso, MD, pediatric gastroenterologist: She has NASH. NASH will be a public health problem as obesity becomes increasingly prevalent. With that said, despite her evident obesity, she looked chronically ill and “different” in an indescribable way when compared with all the obese children whom we see.

Dr. Listernick: Why did she develop liver failure?

Dr. Alonso: That’s the $64,000 question. As best as we can determine, fat is an irritant to the hepatocytes, generating free radicals that cause oxidant injury and subsequent fibrosis. Some patients tolerate the fat in the liver without creating an inflammatory reaction, non-alcoholic fatty liver disease. Patients with NASH are the ones who develop cirrhosis.

Dr. Listernick: Should obese adolescents be screened for NASH?

Dr. Alonso: It’s recommended that liver function testing be performed once the diagnosis of

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metabolic syndrome or type 2 diabetes has been established and then yearly thereafter. There’s evidence to suggest that as many as 15% to 25% of children who have a body mass index (BMI) greater than the 95th percentile have abnormal liver enzymes.

Dr. Listernick: Is there any effective treatment for NASH?

Dr. Alonso: First, you need to be sure of the diagnosis and that the child doesn’t have an alternate diagnosis. If an ultrasound shows a fatty liver and the history is consistent with NASH, a liver biopsy isn’t absolutely necessary. However, that is a heatedly debated point among hepatologists. If a liver biopsy isn’t performed, noninvasive tests for alternate diagnoses (eg, alpha-1 antitrypsin disease, Wilson’s disease, autoimmune hepatitis) should probably be done.

Once you’re sure of the diagnosis, weight loss is the only proven treatment. There’s one article that suggests metformin can be useful in children; this study has not been replicated in adults. Vitamin E and ursodeoxycholic acid therapies have been tried unsuccessfully.

Dr. Listernick: How young are your patients with NASH?

Dr. Alonso: We’re seeing it with increasing frequency in 3-year-olds and 4-year-olds.

Dr. Listernick: Is there a role for bariatric surgery in these very young patients?

Dr. Alonso: That’s a highly charged question, also. We’re involved in a multicenter epidemiologic and treatment study of NASH that will attempt to discern at which point standard dietary therapy and lifestyle changes are ineffective and more radical treatment is necessary.

Dr. Listernick: Can you give us a sense of this girl’s clinical status when you first saw her?

Dr. Alonso: She had life-threatening complications of portal hypertension. She was obviously headed to transplantation and was a huge operative risk because of her obesity. In addition, she was developing pulmonary symptoms complicating the likelihood of an effective exercise program.

Dr. Listernick: Is lack of compliance with a dietary regimen a contraindication to transplantation?

Dr. Alonso: No. Unlike the absolute necessity for sobriety in alcoholics facing transplantation, weight loss isn’t a prerequisite. The hope is that the “sobering experience” of transplantation will ensure dietary compliance.

Dr. Listernick: Eight months after her transplant evaluation, she was hospitalized at an outside hospital for treatment of pneumonia, following which she was discharged on supplemental home oxygen therapy. Over the ensuing several months, her oxygen saturations continued to decrease. Echo-cardiogram was consistent with the diagnosis of “hepatopulmonary syndrome” with moderate dilatation of the left ventricle and elevated pulmonary artery pressures.

Over the next several months, her exercise tolerance decreased remarkably. Her oxygen saturation began dropping to 40% when she was walking and 75% at rest. She required 5 L of oxygen by nasal cannula at night and continuous positive airway pressure at night.

On admission to the intensive care unit, she had lost 30 kg from the start of her illness. HEENT exam was unremarkable. Lungs and heart were difficult to assess because of her body habitus. She had caput medusae. Liver was palpable 5 cm below the right costal margin, and spleen was palpable 4 cm below the left costal margin. Neurologic exam was unremarkable.

Dr. Listernick: What is hepatopulmonary syndrome (HPS)?

Dr. Alonso: HPS is the triad of liver disease, hypoxemia, and intrapulmonary vascular dilatation. HPS is a result of abnormal pulmonary vasodilatation, leading to poor arterial oxygenation. Although the exact pathophysiology has not been established, it seems clear that splanchnic blood must pass through the liver in order to prevent pulmonary vascular dilatation.

Wayne Franklin, MD, pediatric cardiologist: Cardiologists have observed the same phenomenon in patients who’ve undergone a Glenn shunt procedure in which the superior vena cava has been hooked up directly to the pulmonary artery. Blood flow is inadvertently diverted from the lung into the liver, and we see the development of pulmonary arteriovenous malformations and the same physiology as HPS in the absence of liver disease. Presumably, blood is
diverted from the portal circulation and, as yet, unidentified factors or cytokines are not detoxified by the liver resulting in pulmonary vasodilatation. One of the potential mediators is vascular endothelial growth factor (VEGF).

Kim Watts, MD, pediatric pulmonologist: A sensitive measure of the magnitude of hypoxia in HPS is the alveolar-arterial oxygen gradient, which may increase substantially before the measured pO2 falls.

Dr. Lister nick: What are the symptoms of HPS?

Dr. Watts: Just what she had, dyspnea on exertion or rest, orthopnea, and progressive hypoxemia. The worsening of her symptoms at night might be related to hypventilation or obstructive sleep apnea related to her obesity. Other classic symptoms of HPS that she did not have are platypnea, shortness of breath that is relieved when lying down, and orthodeoxia, which is a decrease in pO2 when standing. The latter occurs as a result of blood pooling in the pulmonary shunts, leading to increased V/Q mismatch. She can’t get from the bed to the bathroom without experiencing significant decline in her oxygen saturation.

Dr. Franklin: The diagnosis of HPS can be confirmed by performing a “bubble study,” which is contrast-enhanced echocardiography. The “contrast” is saline that’s been agitated to create microbubbles. If there’s a right-to-left shunt at the level of the atrium, you’ll see bubbles on the left side of the heart, usually within three heartbeats. When necessary, pulmonary angiography can confirm these findings, document the dilated pulmonary vasculature, and identify large arteriovenous connections that may be embolized.

Dr. Lister nick: Is there any specific therapy for HPS?

Dr. Alonso: There’s no accepted treatment except supportive care. Some centers have tried creating transjugular intrahepatic portosystemic shunts (TIPS) in order to decrease portal hypertension and, consequently, pulmonary vasodilatation. There are anecdotal reports of its efficacy, but it’s rarely used in these circumstances. Other unproven therapies that have been tried include nitric oxide inhibitors, cyclooxygenase inhibitors, glucocorticoids, and somatostatin.

Dr. Lister nick: Moving ahead, as Dr. Alonso mentioned earlier, her caretakers always thought she looked somewhat unusual. X-rays of her hands revealed shortened fourth and fifth metacarpals, as well as an extremely short distal phalanx of the thumbs. In the context of this patient’s phenotype, she has pseudohypparathyroidism. Although this actually refers to a group of disorders, the most well-described variant is pseudohypparathyroidism type 1a. This is caused by an inactivating mutation in GNAS1, which codes for the alpha subunit of the GTP stimulatory protein. This is in contrast to activating mutations in the GTP stimulatory protein that lead to McCune-Albright syndrome.

Dr. Lister nick: What are the clinical manifestations of pseudohypparathyroidism?

Dr. Zimmerman: The characteristic phenotype includes short stature, obesity, round face, mild mental retardation, soft tissue ossification, and the skeletal abnormalities that I previously described.

Dr. Lister nick: What are the endocrine manifestations?
Dr. Zimmerman: In type Ia, patients generally develop hypothyroidism and hypocalcemia with elevated levels of parathyroid hormone. Because this particular protein is necessary for proper functioning of other hormones, including gonadotropins, adrenocorticotropic, and growth hormone releasing hormone, abnormalities in these systems should be considered.

Dr. Listernick: What are the genetics of this condition?

Dr. Zimmerman: They’re quite interesting. Although it is inherited in an autosomal dominant fashion, it displays genetic imprinting. The hormonal abnormalities only appear if the abnormal gene is inherited from the mother; if the gene is inherited from the father, the child develops the skeletal abnormalities without the endocrine manifestations.

Dr. Listernick: She was determined to have a mutation in the GNAS1 gene. She’s currently still in the intensive care unit awaiting liver transplantation. Thank you, everybody.