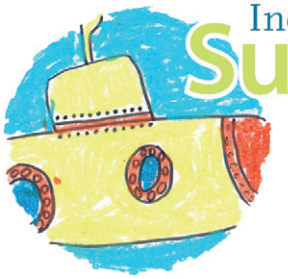

Index of Suspicion

1 Hepatomegaly and Growth Failure in an 11-year-old Girl With Type 1 Diabetes

Jennifer Myaeng, DO,* Bruce Ong, MD,* Jordan E. Pinsker, MD†

*Tripler Army Medical Center, Pediatrics, Honolulu, HI.
†William Sansum Diabetes Center, Pediatrics, Santa Barbara, CA.

EDITOR'S NOTE

We invite readers to contribute case presentations and discussions. Please use the Submit and Track My Manuscript link on the Pediatrics in Review homepage: http://pedsinreview.aappublications.org.

AUTHOR DISCLOSURE Drs Myaeng and Ong have disclosed no financial relationships relevant to this article. Dr Pinsker has disclosed that he has received prior grant funding for diabetes technology research from the US Army Public Health Command's Health Promotion and Prevention Initiatives (HPPI) program as well as from the US Army Medical Department's Advanced Medical Technology Initiative (AAMTI) through the Telemedicine and Advanced Technology Research Center (TATRC). He also disclosed the William Sansum Diabetes Center has received material support from Roche Diabetes Care, Lifescan, Inc, and Animas Corp. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 11-year-old girl with a 5-year history of type 1 diabetes mellitus presents for evaluation of poor growth. She has had with no linear growth for 6 months. Although she is taking a multiple-daily injection insulin regimen, she has had inconsistent follow-up, and her hemoglobin A1c (HbA1c) has been greater than 9.5% for the last few years.

Her only other recent medical history is a mildly positive purified protein derivative (PPD) of 5-mm induration with a negative chest radiograph, for which she has been taking isoniazid for 4 days.

Vital signs are within normal ranges, but her height is below the 1st percentile, with weight at the 10th percentile. The only findings of note on physical examination are lipohypertrophy at frequent insulin injection sites on her left arm and abdomen and hepatomegaly, as evidenced by percussion to 4 cm below the costal margin. No stigmata of chronic liver disease are found. Genitourinary examination reveals sexual maturity rating of stage 1.

Initial laboratory results are as follows:

- Thyrotropin 1.1 mIU/L (normal, 0.45–4.5 mIU/L)
- Free thyroxine 1.12 ng/dL (14.4 pmol/L) (normal, 0.93–1.6 ng/dL [12.0–20.6 pmol/L])
- Insulinlike growth factor-1 (IGF-1) 45 ng/mL (5.9 nmol/L) (normal 132–376 ng/mL [17.3–49.3 nmol/L])
- Sodium 136 mEq/L (136 mmol/L)
- Potassium 4.6 mEq/L (4.6 mmol/L)
- Chloride 98 mEq/L (98 mmol/L)
- Bicarbonate 26 mEq/L (26 mmol/L)
- Blood urea nitrogen 10 mg/dL (3.6 mmol/L)
- Creatinine 0.45 mg/dL (39.8 μmol/L)
- Glucose 169 mg/dL (9.4 mmol/L)
- Total bilirubin 0.5 mg/dL (8.6 μmol/L)
- Tissue transglutaminase (IgA) less than 3 U/mL with a normal total IgA concentration
- Aspartate aminotransferase (AST) 376 U/L (6.3 μkat/L)
- Alanine aminotransferase (ALT) 396 U/L (6.6 μkat/L)
- Gamma-glutamyltransferase (GGT) 94 U/L (1.6 μkat/L)

Her karyotype is 46,XX.

Additional studies confirm the suspected cause of her hepatomegaly and elevated liver enzyme values.

DISCUSSION

Her QuantiFERON-TB test results were negative and it was believed that her PPD result was not true-positive. In addition, specialists advised that hepatotoxicity from isoniazid rarely results in transaminase levels greater than five times normal and does not normally lead to elevation of GGT. After discontinuing isoniazid, the AST, ALT, and GGT values remained elevated. Further laboratory evaluation by a pediatric gastroenterologist revealed a negative hepatitis A through E panel, negative Epstein-Barr virus and cytomegalovirus titers, negative autoimmune hepatitis antibody panel, and normal copper and ceruloplasmin levels.

Liver ultrasonography revealed nonspecific liver enlargement without fat deposition. Based on the clinical history of poorly controlled type 1 diabetes, elevated liver enzymes, hepatomegaly without another underlying cause, poor linear growth, and delayed puberty, the patient was diagnosed with Mauriac syndrome (MS). With extensive education and support from the diabetes team, the girl achieved improved blood glucose concentrations. Her HbA1c decreased from 13.2% to 8.0%, and within 5 months, her liver function normalized. Follow-up GGT was 38 U/L (0.6 μkat/L), ALT 41 U/L (0.7 μkat/L), and AST 47 U/L (0.8 μkat/L). Her linear growth improved and hepatomegaly resolved.

The Condition

MS was first described in 1930 by Dr. Pierre Mauriac. His description included growth failure, delayed puberty, hepatomegaly, abdominal distension, and cushingoid features in children with poorly controlled type 1 diabetes mellitus. When insulin initially was available only in the short-acting form, wide fluctuations in glucose were common, with frequent patterns of over- and underinsulinization. Prolonged periods of hyperglycemia lead to glucose accumulation in the liver. Subsequent administration of insulin results in conversion of glucose to glycogen in the hepatocytes, leading to hepatomegaly and abnormal liver function. Thus, the liver disease in MS is often referred to as "glycogenic hepatopathy."

Secondary hyperadrenalism can occur during episodes of ketosis and hypoglycemia, leading to the development of cushingoid features. Subcutaneous deposition of glycogen may give rise to the round, moonlike facies seen in these patients.

Although the incidence of MS had decreased significantly with the introduction of long-acting insulin, this syndrome recently has re-emerged. MS has now been reported in children without cushingoid features or central obesity, suggesting chronic hyperglycemia due to omission of insulin doses as the primary cause, similar to this patient's presentation.

MS more commonly occurs in children with type 1 diabetes receiving premixed insulin and during adolescence. It is still not clear why some children with prolonged elevated blood glucose, as evidenced by elevated HbA1c, develop MS, while others do not. Poor growth may be related to decreased circulating IGF-1 concentrations or a relative growth hormone-resistant state. MS also has been reported in children as young as age 3 years.

If liver biopsy is performed in a child with MS, liver inflammation and fibrosis are often present. It is important to note that children with obesity and insulin resistance can develop fatty liver infiltration or nonalcoholic steatohepatitis (NASH). Steatosis (fat deposition) in the liver can be seen in MS as well, making these two forms of liver disease more difficult to differentiate in overweight children with all forms of diabetes. Liver fibrosis can occur in both NASH and MS. Although the long-term consequences of abnormal liver function in patients with MS have not been well studied, without improvement in blood glucose control, significant liver disease could potentially occur into adulthood.

Management

Growth failure, delayed puberty, abnormal liver function, and hepatomegaly in MS improve with glycemic control, as occurred with this patient. Although IGF-1 values may improve with insulin treatment, catch-up growth may be incomplete. In published series of children with hepatopathy from MS, transaminases followed the course of the child's HbA1c, improving as glucose levels decreased to the target range. The clear conclusion is that extensive diagnostic evaluation is often not needed. Rather, the diabetes management team must coordinate efforts to effectively change key self-care behaviors to improve glycemic control. This is often time-consuming and complex and requires multidisciplinary expertise, but it affords the best outcomes.

Clinicians must also be aware that aggressive insulin replacement has been reported to lead to rapid development and progression of retinopathy in children with MS. Therefore, in patients with chronically poor glucose control, gradual increases in insulin doses over time are advised.

Lessons for the Clinician

- Mauriac syndrome (MS) is characterized by growth failure, delayed puberty, hepatomegaly, abnormal liver function, and sometimes cushingoid features with a protuberant abdomen in children with poorly controlled type 1 diabetes mellitus.

- Long-term improvement in glucose control is the only treatment that affects the findings seen in MS, with improvements in liver function, growth, and pubertal development following the course of the child's hemoglobin A1c.
- Regular abdominal examinations should be performed in children with persistently poorly controlled diabetes to allow for early detection of these complications and intensified interventions to improve glycemic control.
- Gradual increases in insulin doses over time are recommended for children with chronically elevated blood glucose because these may prevent rapid development and progression of retinopathy that can occur when blood glucose is rapidly normalized with high doses of insulin.

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

References for this article are at http://pedsinreview.aappublications.org/content/36/10/459.full.

Parent Resources from the AAP at HealthyChildren.org

- https://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Diabetes-Mellitus-Type-1-Diabetes.aspx

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