Clinical Case Report

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Nonalcoholic fatty liver disease with prolactin-secreting pituitary adenoma in an adolescent

A case report

Yugo Takaki, MD, Tatsuki Mizuochi, MD, PhD*, Junko Nishioka, MD, PhD, Keisuke Eda, MD, Shuichi Yatsuga, MD, PhD, Yushiro Yamashita, MD, PhD

Abstract

Rationale: Nonalcoholic fatty liver disease (NAFLD), among the commonest chronic liver disorders in children and adolescents, is considered a reflection of the current obesity epidemic in children and adults. This liver disease has been linked with various metabolic disorders, but not with prolactinoma (PRLoma).

Patient concerns: A 13-year-old Japanese girl manifested obesity, serum transaminase and γ-glutamyltransferase elevations, and amenorrhea. Abdominal ultrasonography showed fatty liver. Her serum prolactin concentration was elevated, and cranial magnetic resonance imaging showed a pituitary mass consistent with macroadenoma.

Diagnoses: NAFLD and PRLoma.

Interventions and outcomes: After the patient's NAFLD failed to respond to diet and exercise, cabergoline treatment of the PRLoma decreased body weight, serum transaminase and γ-glutamyltransferase elevations, and ultrasonographic fatty liver grade as the tumor became smaller.

Lessons: Physicians should consider the possibility of PRLoma when diet and exercise fail to improve fatty liver disease in a patient with endocrine symptoms such as amenorrhea.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyltransferase, MRI = magnetic resonance imaging, NAFLD = alcoholic fatty liver disease, PRLoma = prolactinoma.

Keywords: amenorrhea, cabergoline, children, nonalcoholic fatty liver disease, prolactinoma

1. Introduction

Nonalcoholic fatty liver disease (NAFLD), an important chronic liver disorder in many countries,[1,2] ranges from benign nonalcoholic fatty liver to nonalcoholic steatohepatitis. The latter condition includes progressive fibrosis, which is associated with high overall and disease-specific mortality.[3] NAFLD has become one of the most common chronic liver diseases in children, as they are affected by the rising obesity epidemic. Association of NAFLD with metabolic disorders including obesity, hypertension, dyslipidemia, insulin resistance, and type 2 diabetes has been reported.[4,5]

In girls, prolactinoma (PRLoma), the most common secretory pituitary adenoma, can cause delayed puberty, menstrual disorder, galactorrhea, and headache.[6] We know of no reports associating NAFLD with PRLoma, although PRLoma may increase body weight.[7]

Here we report a 13-year-old Japanese girl with NAFLD and PRLoma, both of which improved with cabergoline.

2. Case presentation

A 13-year-old Japanese girl with obesity, but no symptoms of chronic liver disease, was referred to our hospital because of unexplained transaminase elevations. She was born after an uncomplicated pregnancy and delivery to healthy parents having no consanguinity. She had no history of drug or alcohol intake. She had no physical findings suggesting a liver disorder, such as hepatosplenomegaly or jaundice. Vital signs and neurologic findings were normal. Height, body weight, and body mass index, respectively, were 158 cm (+0.4 SD), 67.4 kg (+2.2 SD), and 27 kg/m^2 (normal range, 18.5–24.9).

Initial laboratory results included serum aspartate aminotransferase (AST), 160 U/L (normal range, <33); alanine aminotransferase (ALT), 338 U/L (<30); γ-glutamyltransferase (GGT), 99 U/L (<47); total/direct bilirubin, 0.96/0.09 mg/dL (<1.2/<0.6); albumin, 4.6 g/dL (4.0–5.0); total bile acids, 2.7 μmol/L (<10); type IV collagen, 133.0 ng/mL (<140); low-density lipoprotein cholesterol, 132 mg/dL (<139); high-density lipoprotein cholesterol 48 mg/dL (>40); fasting plasma glucose 95 mg/dL (<109); HbA1c

Editor: N/A.

The authors have no funding and conflicts of interest to disclose.

Department of Pediatrics and Child Health, Kurume University School of Medicine, Kurume, Japan.

* Correspondence: Tatsuki Mizuochi, Department of Pediatrics and Child Health, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan (e-mail: mizuochi_tatsuki@kurume-u.ac.jp)

Medicine (2018) 97:42(e12879)

Received: 22 June 2018 / Accepted: 25 September 2018

http://dx.doi.org/10.1097/MD.0000000000012879

Table 1

Clinical, laboratory, and ultrasonographic findings before and during cabergoline treatment.

Months after initiation of cabergoline treatment	Before	1	3	7	14	17
Body weight, kg	67.4	67.9	66.2	64.7	65.8	64.5
Serum prolactin, ng/mL [normal range, 4.1–28.9]	485.6	148.7	80.3	61.4	38.4	38.9
Serum aspartate aminotransferase, U/L [<33]	160	168	78	42	51	40
Serum alanine aminotransferase, U/L [<30]	338	382	153	66	92	68
Serum γ-glutamyltransferase, U/L [<47]	99	110	47	32	36	31
Ultrasonographic grade of fatty liver disease*	3			1		1
Cabergoline treatment, mg/wk		0.25	0.5	1	2	3.5

* Grade 3: marked increase in fine echoes with poor or nonvisualization of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver; grade 2: moderate, diffuse increase in fine echoes with slightly impaired visualization of intrahepatic vessels and diaphragm; grade 1: slight, diffuse increase in fine echoes in liver parenchyma with normal visualization of diaphragm and intrahepatic vessel borders; grade 0: normal echogenicity[8].

5.5% (4.9–6.0); and prothrombin time–international normalized ratio, 0.89 (0.87–1.25). The complete blood cell count was normal. Various causes of chronic liver disease such as autoimmune hepatitis, viral hepatitis, and other metabolic conditions were excluded by appropriate laboratory tests. Abdominal ultrasonography showed fatty liver (ultrasonographic grade 3), with a marked increase in fine echoes and little or no visualization of intrahepatic vessel outlines, the diaphragm, and the posterior right lobe of the liver (Table 1).[8] Liver biopsy was not performed because signs of steatohepatitis with fibrosis such as thrombocytopenia, coagulopathy, cholestasis, and elevation of serum type IV collagen all were absent.

We clinically diagnosed the patient with NAFLD and obesity, to be treated with diet and exercise. However, body weight increased. As breast enlargement at 11 years and pubic hair growth at 12 years were neither accompanied nor followed by menstruation, endocrine functions were assessed. Luteinizing hormone was <0.2 mIU/mL (0.05–2.44); follicle-stimulating hormone, 1.9 mIU/mL (0.92–3.29); free thyroxine, 0.98 ng/dL (0.93–1.70); thyroid-stimulating hormone, 0.94 μIU/mL (0.50–5.00); estradiol, <25 pg/mL (<42.8); and prolactin, 485.6 ng/mL (4.1–28.9). Cranial magnetic resonance imaging (MRI) including contrast administration showed a pituitary mass consistent with macroadenoma (Fig. 1A). We diagnosed the patient with PRLoma and treated her with cabergoline, a dopamine agonist, at a dose of 0.25 to 3.5 mg/wk (Table 1). In addition to tumor shrinkage demonstrated by MRI (Fig. 1B), her weight and serum AST/ALT and GGT decreased, as did the ultrasonographic grade of fatty liver disease (Table 1). Menarche occurred 21 months after initiation of cabergoline, when serum prolactin was 32.8 ng/mL.

Currently, 2 years after initiation of cabergoline, the patient is receiving cabergoline at a dose of 3.5 mg/wk.

3. Discussion

We present a 13-year-old girl with NAFLD and PRLoma. Cabergoline treatment for PRLoma improved not only tumor size, serum prolactin, and amenorrhea, but also obesity and NAFLD.

NAFLD is the most common cause of chronic liver disease in children.[9] Our patient satisfied both criteria for NAFLD: evidence of hepatic steatosis by either imaging or histopathology, and absence of causes for secondary hepatic fat accumulation such as significant alcohol consumption, steatogenic medication, or certain hereditary disorders.[10] Patients with NAFLD tend to

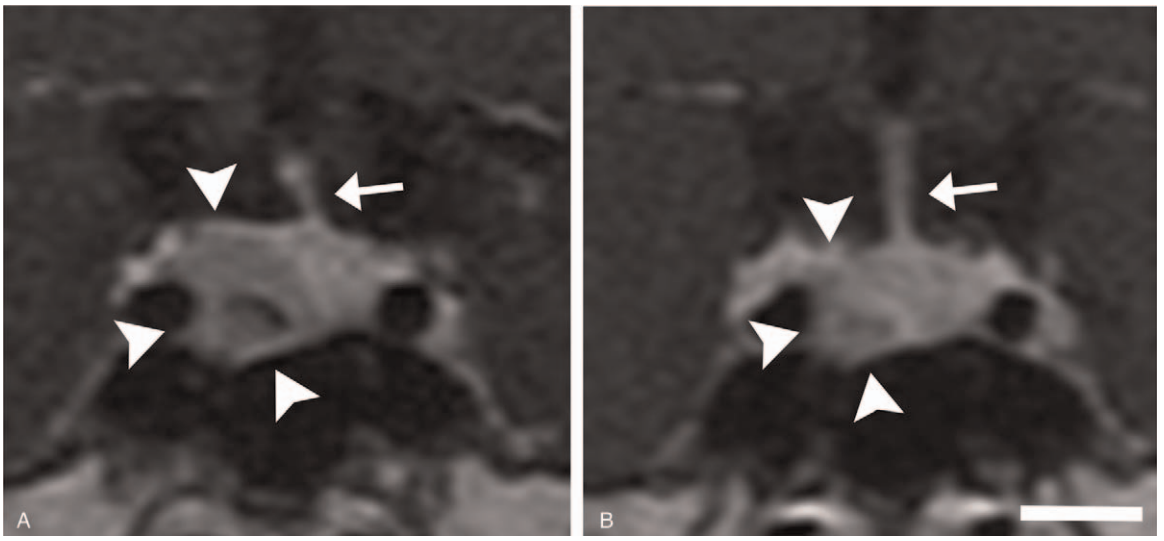

Figure 1. Magnetic resonance imaging of the prolactinoma before and after initiation of cabergoline treatment. T2-weighted coronal cranial magnetic resonance imaging before cabergoline (A) disclosed a 13 × 11-mm macroadenoma involving the right side of the anterior pituitary (arrowheads) and displacing the pituitary stalk (arrow) to the left. Follow-up MRI 17 months after initiation of cabergoline treatment (B) showed shrinkage of the tumor to 9 × 6 mm (arrowheads) and return of the pituitary stalk (arrow) to a normal position. Bar, 10 mm.

be obese, with consequent insulin resistance and/or type 2 diabetes, dyslipidemia, and hypertension—all risk factors for cardiovascular diseases in adulthood.[11] The American Association for the Study of Liver Disease, American College of Gastroenterology, and American Gastroenterological Association guidelines for NAFLD recommend weight loss as a way to reduce hepatic steatosis, achieved by low-calorie diet alone or in conjunction with increased physical activity. Loss of at least 3% to 5% of body weight appeared necessary to improve steatosis. In adults with NAFLD, exercise alone sometimes may reduce hepatic steatosis. Ordinarily, management of patients with NAFLD consists of treating liver disease by these methods as well as treatment of associated metabolic comorbidities.[10] However, diet and exercise failed in our patient.

PRLoma, a prolactin-secreting tumor, is the most common functioning neoplasm of the pituitary. By baseline tumor diameter, these tumors are characterized as microprolactinomas (<10 mm) or macroprolactinomas (≥10 mm).[12] PRLomas are relatively rare in childhood; in children and adolescents, estimated incidence is 0.1 per 1 million, accounting for <2% of all childhood intracranial tumors but up to 50% of hypophyseal adenomas. Patients with PRLoma typically present with clinical features of hyperprolactinemia, including gonadal dysfunction, amenorrhea, and galactorrhea. Patients with large tumors may also have headaches and visual field defects.[6] Our patient had amenorrhea, but no headache or galactorrhea. As noted earlier, she had normal anterior pituitary functions except for elevated prolactin.

The long-acting dopamine agonist cabergoline is first-line treatment for PRLoma because of its effectiveness in decreasing serum prolactin and tumor size.[6] Cabergoline has high affinity for dopamine D2 receptors but low affinity for dopamine D1 receptors, α1- and α2-adrenergic receptors, and 5-hydroxytryptamine 1- and 5-hydroxytryptamine 2-serotonin receptors. Dopamine agonists are effective in suppressing prolactin hypersecretion, reducing tumor size, and restoring normal gonadal function.[13]

Hyperprolactinemia may be associated with obesity, whereas patients with PRLoma s treated with another D2 receptor agonist, bromocriptine, have been reported to lose weight.[7] Korner et al reported that 13 of 16 patients treated with cabergoline for hyperprolactinemia lost weight, suggesting that cabergoline may be an effective weight reduction therapy in such patients.[14] Our patient's improved liver function test results and ultrasonographic grade may well reflect weight loss facilitated by cabergoline.

Various conditions can be associated with NAFLD. We believe that NAFLD in our patient most likely resulted from hyperprolactinemia-associated obesity, whereas cabergoline treatment improved not only serum prolactin and tumor size but also obesity and fatty liver. To our knowledge, this is the first report of a patient with PRLoma and possibly consequent NAFLD.

Limitations of this study include its focus on only one NAFLD patient with PRLoma. A large population, prospective, multicenter study is needed to establish the extent to which cabergoline is effective in NAFLD patients with PRLoma.

4. Conclusion

We report an adolescent patient with NAFLD and PRLoma, both responding to cabergoline. Physicians should consider the possibility of PRLoma when they treat patients with NAFLD resistant to diet and exercise, especially in the presence of endocrine symptoms such as amenorrhea.

Acknowledgments

The authors thank the patient and the parents for their cooperation.

Author contributions

TM contributed to the concept and design of the study. YT, TM, JN, KE, SY, and YY analyzed and interpreted the data. YT and TM wrote the manuscript, whereas JN and SY edited it. YY supervised the study and reviewed the manuscript. Thus, all authors contributed to the study.

Conceptualization: Tatsuki Mizuochi.
Data curation: Yugo Takaki, Tatsuki Mizuochi, Junko Nishioka, Keisuke Eda, Shuichi Yatsuga.
Formal analysis: Yugo Takaki, Tatsuki Mizuochi.
Investigation: Yugo Takaki, Tatsuki Mizuochi, Junko Nishioka, Keisuke Eda, Shuichi Yatsuga, Yushiro Yamashita.
Methodology: Tatsuki Mizuochi.
Project administration: Yushiro Yamashita.
Supervision: Yushiro Yamashita.
Validation: Tatsuki Mizuochi.
Writing – original draft: Yugo Takaki, Tatsuki Mizuochi.
Writing – review & editing: Junko Nishioka, Shuichi Yatsuga, Yushiro Yamashita.

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