Case report

Pediatric nonalcoholic steatohepatitis associated with hypopituitarism

Kenichiro Nakajima¹, Etsuko Hashimoto¹, Hiroyuki Kaneda¹, Katsutoshi Tokushige¹, Keiko Shiratori¹, Naomi Hizuka², and Kazue Takano²

¹Department of Internal Medicine and Gastroenterology, Tokyo Women’s Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
²Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women’s Medical University, Tokyo, Japan

We experienced two cases of pediatric nonalcoholic steatohepatitis (NASH) associated with hypopituitarism. The first patient was diagnosed with a craniopharyngioma at 5 years of age. After an operation to treat the condition, the patient gradually became obese, and an elevation of transaminases was observed. At 16 years of age, the patient was diagnosed as having NASH with liver cirrhosis. He was started on hormone replacement therapy; however, his insulin resistance and liver fibrosis, as evaluated by hyaluronic acid and platelet count, progressed. In addition, his hyperleptinemia continued. The second patient was diagnosed, at 10 years of age, as having pituitary dysfunction due to fetal asphyxia, and he was started on hormone replacement therapy. This patient was noted to have been obese throughout his life. He was diagnosed as having NASH with advanced fibrosis at 18 years of age. It is important for both hepatologists and endocrinologists to be aware of the association between pituitary dysfunction and NASH.

Key words: NASH, cirrhosis, pediatric NASH, hypopituitarism, leptin

Introduction

Nonalcoholic steatohepatitis (NASH) is a liver disease characterized by the histological features of steatohepatitis in the absence of significant alcohol consumption. NASH is associated with obesity, type 2 diabetes, and dyslipidemia, the so-called metabolic syndrome. Insulin resistance, which is the main feature of the metabolic syndrome, is regarded as a hallmark and causal factor of NASH. NASH should no longer be considered as a primary liver disease, but, rather, as part of the metabolic syndrome.¹⁻² Changes in human behavior and lifestyle over the past century have resulted in a dramatic increase in the incidence of metabolic syndrome worldwide.³

Recently, it has been reported that patients with hypothalamic disorders and/or hypopituitarism, who are at risk of excessive weight gain, impaired glucose tolerance, and dyslipidemia, may also have NASH.⁴ Within this group, NASH in pediatric patients is particularly severe, and this places them at risk of liver-related death. To our knowledge, ten pediatric NASH patients with hypothalamic and pituitary dysfunction have been reported to date.⁴⁻⁷

Here, we report our experience with two such patients to illustrate the clinical course of pediatric NASH with hypopituitarism. We also evaluated the role that insulin resistance and adipocyte hormones play in this condition.

Case reports

Case 1

A 16-year-old obese male was referred to our hospital for the evaluation of elevated liver enzymes. He had undergone neurosurgical treatment for suprasellar craniopharyngioma at the age of 5 years. After the operation, he received adequate substitution therapy of antidiuretic hormone, though he gained weight every year, due to hyperphagia. His serum transaminase level was found to have gradually increased (Fig. 1). During follow up, blood glucose and lipid status were not evaluated. He had no history of blood transfusion, drug abuse, or hypertension. The physician and family members who were in close contact with the patient confirmed that he had no alcohol intake. On physical examination, the patient’s body weight was 69.5 kg,
height was 156 cm, and body mass index (BMI) was 28.6 kg/m².

Laboratory data revealed the following: aspartate aminotransferase (AST), 125 U/l (normal range, <31 U/l); alanine aminotransferase (ALT), 67 U/l (normal range, <31 U/l); gamma-glutamyl transpeptidase (γ-GTP), 180 U/l (normal range, 7–28 U/l); alkaline phosphatase (ALP), 283 U/l (normal range, 79–205 U/l); total bilirubin, 0.6 mg/dl; albumin, 4.6 g/dl; total cholesterol, 193 mg/dl; triglycerides, 345 mg/dl; fasting blood sugar, 80 mg/dl; hemoglobin, 13.8 g/dl; platelet count, 26.3 × 10⁹/µl; and prothrombin time, 67.9%. Results of serological tests for viral hepatitis (hepatitis B surface antigen, hepatitis B core antigen, hepatitis B surface antibody, hepatitis C antibody, and hepatitis C virus-RNA) were all negative. Antinuclear antibody, hepatitis C virus antibody, and hepatitis C virus antigen were not detected. The antithyroid peroxidase antibody, antithyroglobulin antibody, and thyroid-stimulating hormone (TSH) were also negative. Viral hepatitis, autoimmune liver disease, alcoholic liver disease, non-alcoholic fatty liver disease, Wilson disease, and metabolic liver disorders (Wilson disease, etc) were all excluded. Other laboratory results included: thyroid-stimulating hormone (TSH), 2.37 mIU/ml (normal range, 0.53–4.43 mIU/ml); growth hormone (GH), <0.1 ng/ml (normal range, <0.5 ng/ml); insulinlike growth factor, <10 ng/ml (normal range, 106–398 ng/ml); prolactin (PRL), <0.6 ng/ml (normal range, <15 ng/ml); cortisol, <1.0 µg/dl (normal range, 2.7–15.5 µg/dl); luteinizing hormone (LH), <0.5 mIU/ml (normal range, 1.6–9.5 mIU/ml); and follicle-stimulating hormone (FSH), <0.2 mIU/ml (normal range, 1.2–8.2 mIU/ml). We performed a hormone stimulation test, with thyrotropin-releasing hormone, LH-releasing hormone, and corticotrophin-releasing hormone, which showed that all the hormone responses, including GH, TSH, PRL, LH, FSH, and adrenocorticotropic hormone β endorphin were low; we, therefore, diagnosed the patient as having hypopituitarism. Serum leptin levels were elevated, and serum adiponectin levels were slightly decreased. Ultrasonography (US) and computed tomography (CT) revealed hepatomegaly with fat deposition and splenomegaly. A liver biopsy was performed. Liver histology revealed severe steatosis, inflammation, ballooning degeneration, and regenerative nodules (Fig. 2a,b). Thus, the patient was diagnosed as having NASH with cirrhosis.

We started the patient on hormone replacement therapy (GH, cortisol, and thyroid hormone). However, his obesity and HOMA-IR did not improve. Though the serum transaminase level decreased, the platelet count decreased and the hyaluronic acid level increased, suggesting that his liver fibrosis was progressing. Serum leptin levels and adiponectin levels were not affected by the hormone replacement therapy.

Case 2

A 14-year-old boy was referred to our hospital for the evaluation of elevated transaminase levels. At the time of his birth, in 1979, he had suffered from fetal asphyxia. He had been obese all his life. At 10 years of age, he saw a doctor because of his short stature, and he was diagnosed as having pituitary dysfunction. Hormone replacement therapy was started (thyroid hormone, cortisol, and GH). Around that time, slight serum transaminase elevation was observed. Subsequently, the serum transaminase level increased gradually. He gained weight every year, due to hyperphagia. At the age of 14 years, the serum transaminase level was over 100 U/l. He was again referred to our hospital at age 18, because the liver function test results continued to be abnormal. On physical examination, his height was 179 cm; weight, 86.5 kg; and BMI was 27 kg/m². He had no history of metabolic syndrome. His physician and family members who were in close contact with the patient confirmed that he had no alcohol intake. Laboratory data revealed the following: AST, 329 U/l; ALT, 740 U/l; γ-GTP, 239 U/l; ALP, 379 U/l; total bilirubin, 0.7 mg/dl; albumin, 4.6 g/dl; total cholesterol, 280 mg/dl; triglycerides, 239 mg/dl; fasting blood sugar, 89 mg/dl; hemoglobin, 11.2 g/dl; platelet count, 14.7 × 10⁹/µl; and prothrombin time, 67.9%. Results of serological tests for viral hepatitis (hepatitis B surface antigen, hepatitis B core antigen, and hepatitis C virus-RNA) were all negative. Antinuclear antibody, hepatitis C virus antibody, and hepatitis C virus antigen were not detected. The antithyroid peroxidase antibody, antithyroglobulin antibody, and thyroid-stimulating hormone (TSH) were also negative. Viral hepatitis, autoimmune liver disease, alcoholic liver disease, non-alcoholic fatty liver disease, Wilson disease, etc were all excluded. Other laboratory results included: thyroid-stimulating hormone (TSH), 8.2 mIU/ml; growth hormone (GH), <0.1 ng/ml (normal range, <0.5 ng/ml); insulinlike growth factor, <10 ng/ml (normal range, 106–398 ng/ml); prolactin (PRL), <0.6 ng/ml (normal range, <15 ng/ml); cortisol, <1.0 µg/dl (normal range, 2.7–15.5 µg/dl); luteinizing hormone (LH), <0.5 mIU/ml (normal range, 1.6–9.5 mIU/ml); and follicle-stimulating hormone (FSH), <0.2 mIU/ml (normal range, 1.2–8.2 mIU/ml). We performed a hormone stimulation test, with thyrotropin-releasing hormone, LH-releasing hormone, and corticotrophin-releasing hormone, which showed that all the hormone responses, including GH, TSH, PRL, LH, FSH, and adrenocorticotropic hormone β endorphin were low; we, therefore, diagnosed the patient as having hypopituitarism. Serum leptin levels were elevated, and serum adiponectin levels were slightly decreased. Ultrasonography (US) and computed tomography (CT) revealed hepatomegaly with fat deposition and splenomegaly. A liver biopsy was performed. Liver histology revealed severe steatosis, inflammation, ballooning degeneration, and regenerative nodules (Fig. 2a,b). Thus, the patient was diagnosed as having NASH with cirrhosis.

We started the patient on hormone replacement therapy (GH, cortisol, and thyroid hormone). However, his obesity and HOMA-IR did not improve. Though the serum transaminase level decreased, the platelet count decreased and the hyaluronic acid level increased, suggesting that his liver fibrosis was progressing. Serum leptin levels and adiponectin levels were not affected by the hormone replacement therapy.