

[CASE REPORT]

Bardet-Biedl Syndrome Caused by Skipping of *SCLT1* Complicated by Microvesicular Steatohepatitis

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Abstract:

We treated the case of a 22-year-old male patient with liver dysfunction. At 1 year of age, hepatic fibrosis was suspected. In addition, due to the presence of retinitis pigmentosa, renal failure, obesity, mental retardation, and hypogonadism, he was diagnosed with Bardet-Biedl syndrome (BBS). Skipping of exons 14 and 17 in the *sodium channel and clathrin linker 1 (SCLT1)* gene was observed. At 22 years of age, the liver enzyme levels were further elevated and a diagnosis of microvesicular steatohepatitis was made. Insulin resistance, a reduction of muscle mass, an impairment of the fatty acid metabolism, and hyperleptinemia in this syndrome may cause steatohepatitis.

Key words: Bardet-Biedl syndrome, hepatic fibrosis, microvesicular steatohepatitis, *sodium channel and clathrin linker 1 (SCLT1)*, hyperleptinemia

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Introduction

Bardet-Biedl Syndrome (BBS) is a rare human hereditary autosomal recessive disorder that typically manifests with obesity, retinopathy, renal defects, polydactyly, learning disabilities, and hypogonadism (1-3). The ductal plate malformation is a developmental abnormality of the portobiliary system (4, 5). A lack of primary villi results in malformations in the brain, retina, kidney, and limbs; these are known as ciliopathies (6, 7). Other ciliopathies cause the liver diseases hepatic fibrosis, Caroli syndrome, and polycystic liver disease. BBS has an estimated prevalence of 1/125,000-1/160,000 in Europe (8, 9). There have been limited reports in Japan, however, and the first nationwide survey revealed only seven patients with clinically definitive BBS (10). A number of complications of BBS have been reported, including red-cone dystrophy in 93% of cases, polydactyly in 63-81%, genital anomalies in 59-98%, renal anomalies in

53%, and learning difficulties in 61% (6). Moreover, 72-92% of such patients show obesity beginning in early childhood, with the rate increasing with age (11).

In summary, we experienced a case of BBS with hepatic fibrosis and steatohepatitis that exhibited a prolonged elevation of the liver enzymes. This study was conducted in accordance with the principles of the Declaration of Helsinki and the ethical principles of Tokyo Women's Medical University Hospital (Tokyo, Japan).

Case Report

We experienced the case of a 22-year-old male patient who was admitted to our hospital with liver dysfunction. He had no relevant family history. He was born at 41 weeks of gestation with a body weight of 3,442 g. He had neonatal asphyxia and meconium aspiration syndrome and was treated in the intensive care unit. At 1 year of age, his transaminase levels continued to be elevated, and a liver biopsy

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revealed hepatic fibrosis. Retinitis pigmentosa was noted at 2 years of age, and due to obesity, mental retardation, and hypogonadism, he was diagnosed with BBS. At 10 years of age, the patient was referred to our hospital for peritoneal dialysis due to renal dysfunction. At 12 years of age, he underwent living-donor kidney transplantation with his father as the donor. No significant abnormalities were detected on brain computed tomography (CT).

At 19 years of age, he was referred to our department due to liver dysfunction. At that time, his body weight was 57 kg and his height was 142 cm [body mass index (BMI) 28.7 kg/m²]. He had elevated liver enzyme levels: aspartate aminotransferase (AST), 30-50 U/L; alanine aminotransferase (ALT), 50-100 U/L; and gamma-glutamyl transferase (γ -GTP), 100 U/L. The serum levels of prolactin, adrenocor-

ticotropic hormone, and cortisol were also slightly elevated to 17.2 ng/mL, 67.4 pg/mL, and 19.2 μ g/dL, respectively (Table 1). The patient's testosterone level was 401.6 ng/dL and that of aldosterone was 249 pg/mL. The levels of other androgens and gonadotropins were within the normal range. His growth hormone level was low (<0.03 ng/mL), but that of insulin-like growth factor-1 (219 ng/mL) was within the normal range. He was started on a fat- and sugar-restricted diet (1,000 kcal/day). However, his transaminase levels increased further: AST, 155 U/L; ALT, 422 U/L; and γ -GTP, 235 U/L. His diet was changed to 1,400 kcal/day, after which his transaminase levels improved: AST, 41 U/L; ALT, 119 U/L; and γ -GTP, 216 U/L. The serum levels of total cholesterol and triglyceride had increased to 696 and 483 mg/dL, respectively. The administration of ezetimibe was started at 21 years of age. After 3 months of treatment, his transaminase levels had increased: AST, 90 U/L; ALT, 211 U/L; and γ -GTP, 339 U/L. Due to a suspicion of drug-induced liver injury (DILI) caused by ezetimibe, treatment with that drug was stopped. At 22 years of age, bezafibrate was started and his transaminase levels improved after 2 weeks of treatment (Fig. 1). However, the serum level of creatinine increased from 1.71 to 1.96 mg/dL, so bezafibrate was stopped. After 3 months, his serum creatinine level improved and a half dose of bezafibrate was restarted. After 2 weeks of treatment, the transaminase and creatinine levels were again elevated (creatinine, 1.93 mg/dL; AST, 129 U/L; ALT, 230 U/L; and γ -GTP, 247 U/L), which continued after the discontinuation of treatment.

The patient was admitted to our hospital for an evaluation of liver dysfunction. At that time, the patient was 156.5 cm in height, 84.5 kg in body weight (BMI 34.5 kg/m²), and 110.8 cm in waist circumference. The results of biochemical

Table 1. Levels of Pituitary and Adrenal Hormones at 19 Years of Age.

	Range	Value
Prolactin	<15.0	17.2 ng/mL
Adrenocorticotrophic hormone	7.2–63.3	67.4 pg/mL
LH	1.7–11.2	4.3 mIU/mL
FSH	2.1–18.6	1.8 mIU/mL
Growth hormone	<2.47	<0.03 ng/mL
Insulin-like growth factor-1	143-501	219 ng/mL
TSH	0.500-5.00	0.940 μ IU/mL
Cortisol	4.0-18.3	19.2 μ g/dL
Aldosterone	35.7–240	249 ng/mL
DHEA-S	24–537	357 μ g/dL
11-OHCS	7.0-23.0	18.7 μ g/dL
Testosterone	284–799	401.6 ng/dL

TSH: thyroid-stimulating hormone, DHEA-S: dehydroepiandrosterone sulfate (CLEIA method), 11-OHCS: 11-hydroxycorticosteroid

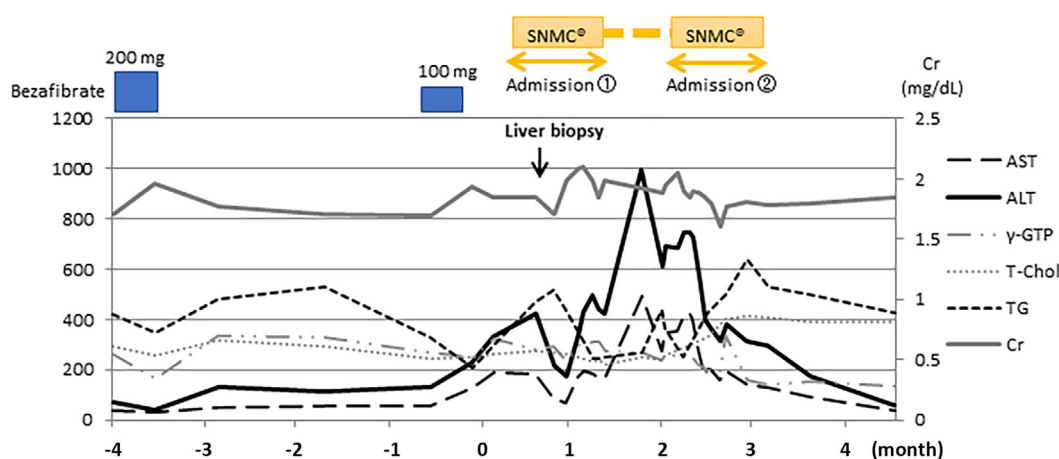


Figure 1. Clinical course. The AST level was increased to 30-50 U/L, ALT to 50-100 U/L, and γ -GTP to 100 U/L until 21 years of age (201X-1 year). After the administration of bezafibrate at 22 years of age (201X year), the transaminase levels increased (AST, 86 U/L; ALT, 219 U/L; and γ -GTP, 399 U/L) and the patient was admitted to our hospital. Treatment with ursodeoxycholic acid and Stronger Neo-Minophagen[®] C (SNMC[®]) was started and the transaminase levels decreased. However, the transaminase levels again became elevated after tapering SNMC[®] treatment and the patient required hospitalization on two occasions.

Table 2. Laboratory Data at the Time of Admission to Our Hospital.

Hematology		Coagulation	
WBC	6,130 / μ L	PT-INR	0.90
RBC	3.87 $\times 10^6$ / μ L	PT%	>100.0 %
Hb	11.5 g/dL		
Ht	35.4 %	Hormone	
PLT	29.7 $\times 10^4$ / μ L	Leptin	197 ng/mL
Biochemistry		Serology	
TP	7.5 g/dL	IgG	898 mg/dL
ALB	4.6 g/dL	IgM	125 mg/dL
T-BIL	0.8 mg/dL	ANA	<40
D-BIL	0.2 mg/dL	AMA	(-)
D/T ratio	0.38		
AST	86 U/L	Hepatitis virus	
ALT	219 U/L	HBs antigen	(-)<0.02 IU/mL
ALP	399 U/L	HCV antibody	(-) COI
γ -GTP	290 U/L		
LDH	357 U/L	Drug Monitoring	
BUN	29.0 mg/dL	Cyclosporine	145 ng/mL
Cr	1.71 mg/dL		
eGFR	44.4 mL/min/1.73 m ²	Functional test	
Na	139 mEq/L	75-g OGTT	
K	4.0 mEq/L	BS pre	81 mg/dL
Cl	105 mEq/L	BS 30 min	145 mg/dL
FBS	111 mg/dL	BS 60 min	131 mg/dL
Hb _{A1c} (NGSP)	5.7 %	BS 120 min	142 mg/dL
Fe	172 μ g/mL	Insulin pre	30.2 μ IU/mL
Ferritin	483 ng/dL	Insulin 30 min	257.9 μ IU/mL
TC	268	Insulin 60 min	175.1 μ IU/mL
LDL-C	146	Insulin 120 min	395.7 μ IU/mL
TG	515		
CRP	0.02 mg/dL	ICG R15	2 %

ALB: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AMA: anti-mitochondrial antibody, ANA: antinuclear antigen, AST: aspartate aminotransferase, BS: blood sugar, BUN: blood urea nitrogen, ChE: cholinesterase, Cl: chloride, Cr: creatinine, CRP: C-reactive protein, D-BIL: direct bilirubin, FBS: fasting blood sugar, Fe: iron, Hb: hemoglobin, HBs antigen: hepatitis B surface antigen, HCV: hepatitis C virus, Ht: hematocrit, ICG R15: indocyanine green retention rate at 15 minutes., IgG: immunoglobulin G, IgM: immunoglobulin M, K: potassium, LDH: lactate dehydrogenase, LDL-C: low-density lipoprotein cholesterol, Na: sodium, NGSP: National Glycohemoglobin Standardization Program, OGTT: oral glucose tolerance test, PLT: platelet, PT-INR: international normalized ratio of prothrombin time, PT: prothrombin time, RBC: red blood cells, T-BIL: total bilirubin, TC: total cholesterol, TG: triglycerides, TP: total protein, WBC: white blood cells, γ -GTP: gamma-glutamyl transferase

tests were as follows: albumin 4.6 g/dL, total bilirubin 0.8 mg/dL, direct bilirubin 0.2 mg/dL, AST 86 U/L, ALT 219 U/L, alkaline phosphatase 399 U/L, γ -GTP 290 U/L, and prothrombin time >100% (Table 2). The patient was negative for hepatitis viruses and autoantibodies. He showed dyslipidemia (total cholesterol 268 mg/dL and triglyceride 515 mg/dL). A fasting glucose level of 111 mg/dL and a hemoglobin_{A1c} of 5.7%. He also showed insulin resistance, as indicated by a homeostasis model assessment as an index of insulin resistance (HOMA IR) score of 6.07. His indocyanine green clearance was 2% at 15 minutes. The serum level of leptin was extremely high, at 197 mg/mL (normal

range for males, 0.79-10.31 ng/mL). The ultrasound and CT findings showed fibrosis of the liver, but there was no evidence of fatty liver (Fig. 2a, b). The visceral fat area estimated by CT was 166.55 cm², and the patient showed visceral obesity (Fig. 2c). The liver-to-spleen attenuation ratio was 1.18. An analysis of his body composition by bioelectrical impedance showed a skeletal muscle mass of 22.6 kg and a body fat mass of 42.9 kg (50.8%, Table 3). Liver biopsy revealed mild microvesicular steatosis with severe hydropic changes of hepatocytes (Fig. 3). Inflammation and fibrosis were both mild. Based on the above, disturbance of beta-oxidation in mitochondria was suspected. The results of

a fatty acid fractionation analysis indicated an increased serum level of oleic acid.

Treatment with ursodeoxycholic acid, an injectable preparation of glycyrrhizin (an extract of the saponin component of the roots of the licorice *Glycyrrhiza inflata* comprised of dried roots and stolons), and Stronger Neo-Minophagen[®] C (SNMC[®]) were started. The patient's aminotransferase levels were still high (AST, 172 U/L; ALT, 425 U/L; and γ -GTP, 275 U/L). The SNMC[®] treatment was tapered after discharge, resulting in increased aminotransferase levels (AST, 490 U/L; ALT, 996 U/L; and γ -GTP 266 U/L), and the patient was re-admitted to the hospital. Daily treatment with

SNMC[®] was continued, and after 1 month his aminotransferase levels had decreased (AST, 193 U/L; ALT, 379 U/L; and γ -GTP 193 U/L). Two months later, his aminotransferase levels had further decreased (AST, 34 U/L; ALT, 60 U/L; and γ -GTP, 131 U/L), but his body weight remained steady. A genetic analysis was performed at the Department of Pediatrics, Kobe University Graduate School of Medicine, and the skipping of exons 14 and 17 in the *sodium channel and clathrin linker 1 (SCLT1)* gene was identified (12).

Discussion

We treated a case of BBS complicated with hepatic fibrosis and microvesicular steatohepatitis caused by impaired glucose tolerance, hyperlipidemia, and hyperleptinemia. Drug administration caused more severe liver injury and the transaminase increase was prolonged. Microvesicular steatohepatitis suggested disturbed beta-oxidation in mitochondria, a rare hepatic manifestation of BBS. *SCLT1* skipping may be implicated in this instance of BBS.

BBS is an autosomal recessive ciliopathy. Genetic analyses have identified 21 causative mutations (6, 13) that are present in ~80% of cases of BBS. In our case, the skipping of exons 14 and 17 in *SCLT1* was observed, as reported previously (12). A proteomics analysis demonstrated that *SCLT1* forms the distal appendages of the centrioles and is involved in ciliogenesis (14). *SCLT1* is associated with the functioning of cilia; its deletion was reported to cause ciliopathy in mice, and it was therefore considered related to cystic kidney disease (15). Katagiri et al. reported that skipping of exons 14 and 17 resulted in obesity and a renal disturbance in a Japanese population (16). In our case, renal failure, retinitis pigmentosa, obesity, mental retardation, and hypogonadism led to a diagnosis of BBS. Therefore, *SCLT1* skipping may be involved in BBS. Although, *SCLT1* skipping may be associated with ciliopathy and cystic fibrosis of the kidney, the precise mechanism underlying the development of steatohepatitis has not yet been elucidated.

BBS is a ciliopathy (6, 7). The disruption of cilia formation involved in intraflagellar transport causes multiple phenotypes of BBS (17). In *Caenorhabditis elegans*, only sensory neurons are ciliated, and ciliary defects result in excessive secretion of hormones and altered body size (obesity), feeding, and fat accumulation (18, 19). Obesity results from

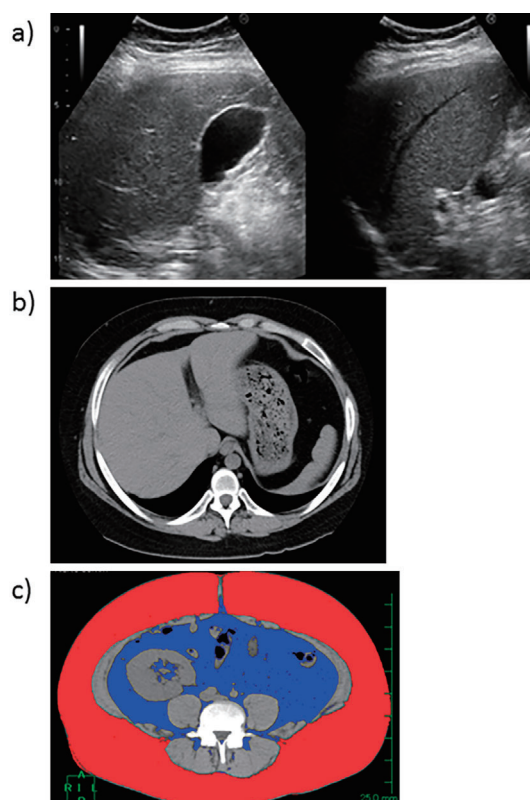


Figure 2. Abdominal ultrasound and CT findings. a) Abdominal ultrasound and b, c) CT scans. Fibrosis of the liver was indicated by abdominal ultrasound and CT, but there was no evidence of fat accumulation (a, b). The visceral fat area estimated by CT was 166.55 cm², suggesting visceral obesity (c). The liver-to-spleen attenuation ratio was 1.18. CT: computed tomography

Table 3. The Patient's Body Composition Based on a Bioelectrical Impedance Analysis.

Muscle-fat analysis		Body composition analysis	
Body weight	84.5 kg	Intracellular water	18.8 L
Height	156.5 cm	Extracellular water	11.8 L
Body mass index	34.5 kg/m ²	Protein mass	8.1 kg
Skeletal muscle mass	22.6 kg	Mineral mass	2.79 kg
		Body fat mass	42.9 kg
		Percent body fat	50.8 %
		Waist/hip ratio	1.03

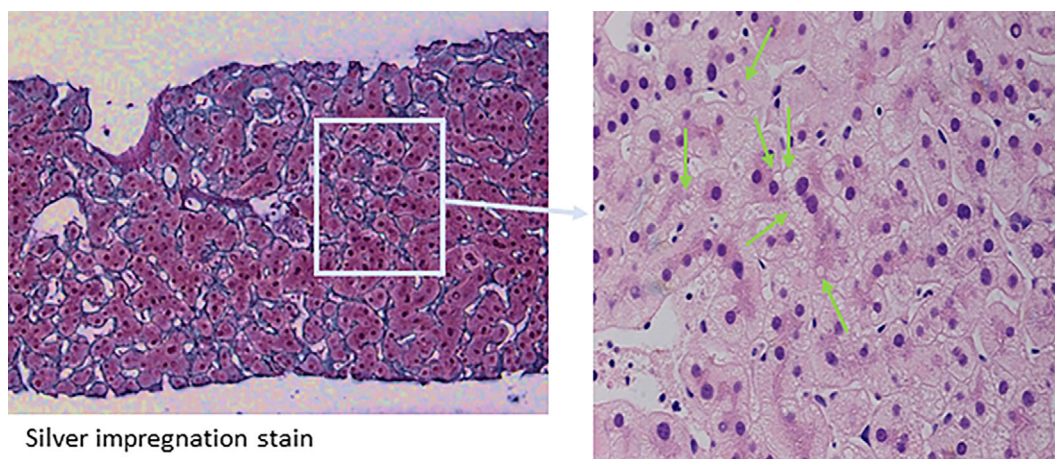


Figure 3. Pathological liver findings. Liver biopsy revealed mild microvesicular steatosis (arrow), with severe hydropic changes in the hepatocytes based on Hematoxylin and Eosin staining. Inflammation was mild. Fibrosis was mild on silver impregnation staining.

an imbalance between ingested and expended calories; BBS mice are hyperphagic with a 20-30% increase in daily food intake (20, 21). Moreover, patients with BBS undertake less physical activity, leading to obesity and greater abdominal visceral fat compared to BMI-matched control subjects (22). In the current case, the patient's daily intake of food was controlled by his parents, but his physical activity was low because he was almost blind due to retinitis pigmentosa.

A hepatic complication of BBS, hepatic fibrosis, was diagnosed at 1 year of age. The patient also showed microvesicular steatosis in the liver on liver biopsy. However, there was no evidence of fat deposition in the liver by ultrasound or CT, which ruled out fatty liver. Steatohepatitis occurs in only 18.5% of BBS cases (3, 23). In addition to non-alcoholic steatohepatitis (NASH), hypertension and hypothyroidism can develop in patients with BBS (24). Microvesicular steatosis is observed in 10% of adults and 19% of children with non-alcoholic fatty liver disease (NAFLD) (25); it is more common in patients with Reye syndrome or other forms of mitochondrial injury (26). In our case, oleic acid elevation and microvesicular steatosis indicated impaired fatty acid metabolism and caused fat accumulation in hepatocytes.

Insulin resistance and a low skeletal muscle mass may be associated with the initiation of steatosis (27-29). Grace et al. reported that patients with BBS and other obese individuals have similar absolute resting metabolic rates (RMR) (30). Another potential cause of the energy imbalance in this syndrome is the hypothalamic action of leptin (31). Leptin in the central nervous system promotes weight loss by reducing food intake and increasing energy expenditure (32, 33). BBS proteins are important mediators of leptin receptor trafficking, and loss of the encoding genes results in leptin resistance (31). Patients with BBS exhibit hyperleptinemia (21, 22). In mice with BBS, eliminating obesity and hyperleptinemia by calorie restriction does not restore leptin sensitivity, indicating that leptin resistance is

intrinsic rather than secondary to hyperleptinemia and obesity (34, 35). In our case, the serum leptin level was extremely high compared to normal subjects. A 1,000 kcal/day diet did not reduce the liver enzyme levels. However, bariatric surgery is reportedly effective against morbid obesity and NAFLD in BBS (36). In addition, in our case, the liver enzyme levels were markedly elevated after drug administration and remained elevated for a prolonged period. The administration of SNMC[®] decreased the aminotransferase levels, however, this does not represent a radical treatment for BBS patients. We speculated that the patient's renal function was impaired due to the prior kidney transplantation, which increased the drug concentration and induced liver damage. Although it was unclear whether the microvesicular steatosis was drug-induced or caused by leptin resistance, leptin resistance may well have been the main cause as ezetimibe is not commonly associated with drug-induced steatohepatitis. Although it has been reported that BBS is related to obesity because of hyperleptinemia (caused by a defect in leptin signaling), dysregulation of feeding, and reduced physical activity, not all patients showed steatohepatitis. In this case report, a phenotype similar to other types of BBS, but with a different genetic background, was observed (1-3). Further studies are needed to elucidate the mechanism and determine the management of steatohepatitis in patients with BBS.

In this case, we found no evidence of steatohepatitis until obtaining the liver biopsy results. Microvesicular steatohepatitis is difficult to diagnose by radiological examinations. The inclusion of liver biopsy in clinical workup may increase the rate of identification of cases of steatohepatitis. Clinicians should be aware of the possibility of liver disease during the follow-up and treatment of patients with BBS.

In conclusion, we experienced a case of BBS complicated by hepatic fibrosis and microvesicular steatohepatitis. Insulin resistance, reduction of muscle mass, impairment of fatty acid metabolism, and high leptinemia may cause steatohepa-

titis.

The authors state that they have no Conflict of Interest (COI).

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