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Case Report

The long-term management of congenital generalized lipodystrophy (Berardinelli-Seip syndrome): the clinical manifestations of Japanese siblings for approximately 20 years

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Abstract. Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disease that is characterized by loss of subcutaneous and visceral adipose tissues, and associated with dysregulation of glycolipid metabolism. In the present study, we reported the clinical manifestations and treatments of Japanese siblings with CGL caused by *BSCL2* gene mutations with a clinical course of approximately 20 yr. Comprehensive management with metreleptin therapy, dietary control with additional medication, and psychosocial counseling in line with the patients' stages of growth and development were important in achieving long-term metabolic control of this condition.

Key words: lipodystrophy, Berardinelli-Seip syndrome, *BSCL2* gene, metreleptin

Introduction

Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disease that is characterized by loss of subcutaneous and visceral adipose tissues, and associated with dysregulation of glycolipid metabolism (1, 2). *AGPAT2, BSCL2, CAV1*, *PTRF*, *PCYT1A,* and *PPARγ* genes have been reported to be responsible for CGL with very low the prevalence (one per 1.3 million people in Japan) (3). CGL can be complicated by various glycolipid metabolic abnormalities, including severe diabetes, dyslipidemia, and fatty liver, which starts in early infancy. Lipids in the blood accumulate in non-adipose tissues such as the liver and the skeletal muscle and cause insulin resistance and hepatosteatosis (1, 2). Furthermore, insufficient excretion of adipocytokine from the adipocytes can synergistically exacerbate lipid metabolism. In particular, leptin deficiency can induce hypothalamic overreaction to aggravate metabolic abnormalities (1, 4). Patients with CGL have considerably high risks of diabetic complications and cardiovascular events from early childhood. Thus, early intervention is essential for preventing early complications (1, 2). In Japan, clinical trials on leptin and patients with CGL started in 2002, and metreleptin replacement therapy was approved in 2013 (5), before being applied worldwide (6, 7). Metreleptin

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Table 1. Physical manifestations and laboratory data for the siblings at their respective first clinical evaluations

			Case 1	Case 2
Months at evaluation (mo of age)			5	1
Physical findings	Birth weight (g)		2,520	2,314
	Birth height (cm)		46	45
	Less subcutaneous tissue		+	+
	Acanthosis nigricans		+	–
	Hepatomegaly		+	+
	Hypertrophic cardiomyopathy		+	–
Initial examination	AST	IU/l	117.6	157.5
	ALT	IU/l	164.1	75.4
	TP	g/dl	6.9	5.5
	TG	mg/dl	387	2629
	Chol	mg/dl	151.6	211.7
	Glucose	mg/dl	88	115
	IRI	μU/ml	17.8	17.7
	Leptin #	ng/ml	0.9 *	0.6 **

Reference values of median [25th–75th percentile] are 2.3 [1.5–3.8] for girls and 1.5 [1.0–2.6] for boys (13). * data at 9 mo of age. ** data at 3 mo of age.

therapy has been shown to improve markedly glycolipid metabolism in studies from the United States and Europe (8–10). The effectiveness of long-term administration of metreleptin is attenuated partially due to the presence of neutralizing anti-metreleptin antibodies (11). Consequently, comprehensive treatment consisting of diet therapy and the administration of various antidiabetic drugs with metreleptin has been recognized as important for life-long management of CGL patients (1, 8, 10, 12).

Herein, we reported the clinical manifestations and treatments of Japanese siblings with CGL with a clinical-course of approximately 20 yr. Metreleptin therapy, dietary control, medication, and psychosocial counseling in line with the patients' growth and developmental stages were important for the long-term holistic management of these patients with CGL.

Case Report

Case 1

The female patient was born to non-consanguineous Japanese parents at 38 wk of gestational age. Poor weight gain was seen during a health checkup at 3 mo of age, and her parents consulted a pediatrician. Physical examination showed a generalized reduction in the subcutaneous adipose tissue with marked hepatomegaly. Laboratory analysis revealed notable hyperinsulinemia and hypertriglyceridemia. Generalized lipoatrophy was suspected and the patient was introduced to our department, Oita University Hospital at 5 mo of age. The characteristic physical findings of CGL were detected as shown in Table 1. Cardiac ultrasonography demonstrated hypertrophic cardiomyopathy. The serum leptin concentration was markedly low (0.9 ng/mL) (13). Genetic testing revealed compound heterozygous pathogenic variants of *BSCL2* gene; the already reported variant (c.823C>T [p.Arg275Ter]) and the unreported variant (c.576C>A [p.Tyr192Ter]). She was therefore diagnosed with CGL (Berardinelli-Seip syndrome). The clinical course is shown in Fig. 1A. At 5 mo of age, dietary management was initiated for calorie and lipid restriction (calorie 90 Cal/kg/d; carbohydrate

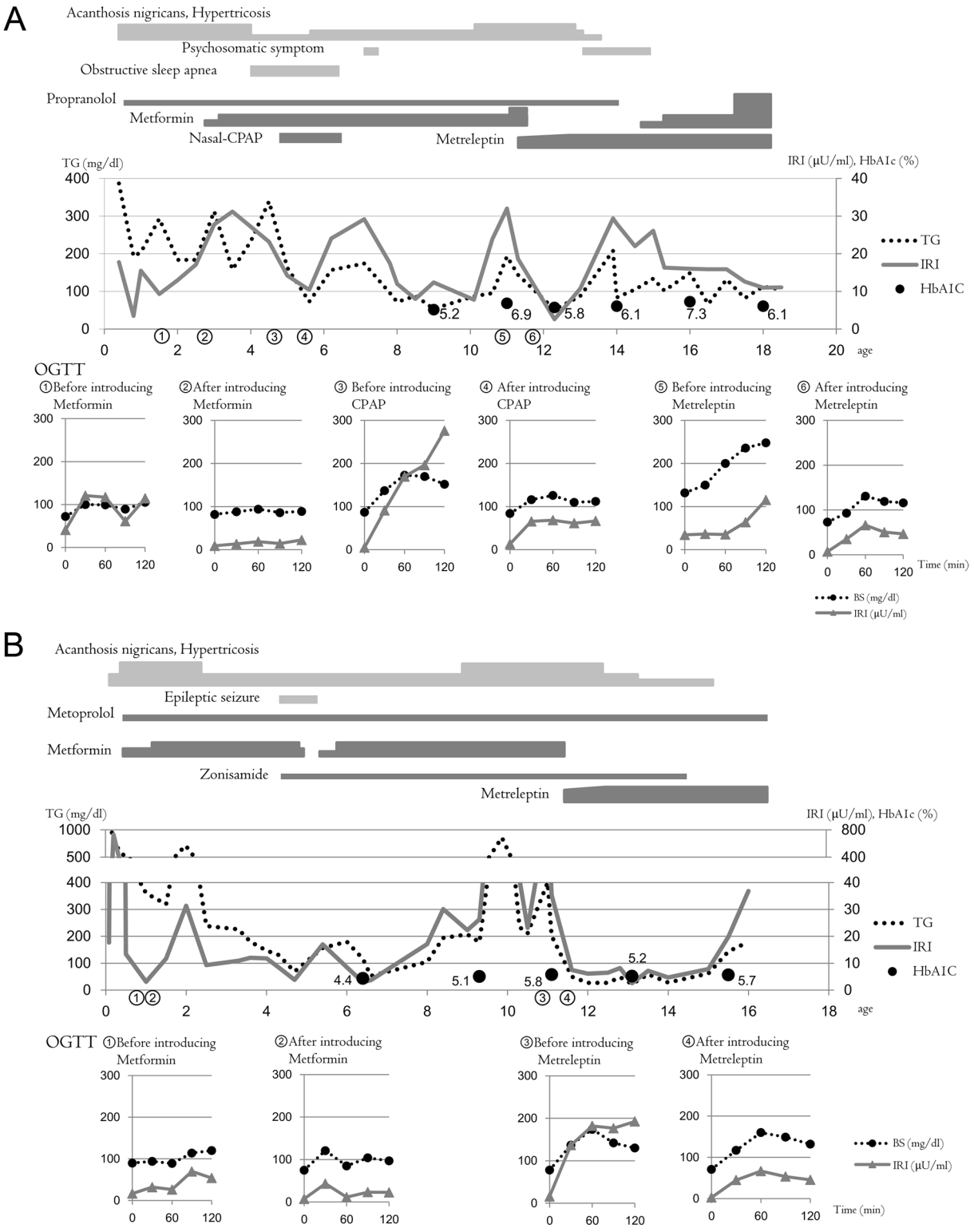

Fig. 1. Clinical courses of the siblings. (A) Case 1 and (B) Case 2. Each figure shows the serial data or parameters. The upper portions show the physical symptoms of CGL and its medical interventions. The middle portions show the serum triglyceride (TG), IRI, and HbA1c levels. The lower portions show the oral glucose tolerance test (OGTT) data.

55%, lipid 20%, protein 20%). At 2 yr and 6 mo of age, metformin treatment (500 mg/d: 30 mg/kg/d) commenced because of marked insulin resistance with hepatic dysfunction. Metformin treatment seemed effective for insulin resistance (Fig. 1A. OGTT①②). At approximately 4 yr of age, obstructive sleep apnea, which is known as a characteristic complication of CGL appeared, and insulin resistance and lipid metabolism also worsened. Artificial respiratory support for continuous positive airway pressure was introduced, which stabilized her sleeping status with stable oxygenation. Her glucose metabolism with insulin resistance then partially improved (Fig. 1A. OGTT③④). At the beginning of puberty (approximately 10 yr of age), hyperglycemia with hyperinsulinemia gradually deteriorated and the oral glucose tolerance test (OGTT) showed diabetic glucose response (Fig. 1A.OGTT⑤). At 11 yr and 5 mo of age, she was enrolled in a clinical trial of metreleptin. Metreleptin treatment was initiated at a dose of 0.06 mg/kg/d. Marked effectiveness of metreleptin appeared as early as 1 mo after the initiation, and metformin treatment was discontinued. Based on the results of the metreleptin trial, treatment with metreleptin was approved in 2013. Continuous treatment had consistent effects on patient's glucose and fat metabolism. At approximately 13 yr of age, she sometimes had insomnia, headaches, and abdominal pains, followed by aggravation of her HbA1c and triglyceride levels, due to stressful relationship with her friends. Oral administration of metformin was then resumed, and socio-psychological counseling by a child psychiatrist was initiated. Her glycolipid metabolism status fluctuated according to her psychological state that is in line with her school year, and combined management with metreleptin, metformin, dietary therapy, and socio-psychological intervention were continued. As a result, the headaches and insomnia gradually decreased, and there was also an improvement in her glycolipid metabolism. Anti-metreleptin antibodies were detected (titer: 1:25) at 14 yr and 4 mo old. At 14 yr and 8 mo of age, Kauffman therapy was initiated due to irregular menstruation. At 18 yr and 8 mo of age and 7 yr after the commencement of metreleptin therapy, she began receiving metreleptin (3.8 mg/d [0.08 mg/kg/d]), metformin (2250 mg/d), as well as dietary management to regulate the levels of calorie and lipid. Her height was 154 cm, weight 48 kg, and her HbA1c level was 6.0% in a stable state. She graduated from high school and entered the university without apparent hindrance in her daily life.

Case 2

The male patient who was born at 36 wk of gestational age was the younger (3 yr younger) brother of case 1. He also showed apparent reduction of the subcutaneous adipose tissue at 1 mo of age. At that time, he already had characteristic symptoms of CGL, including an inverted triangular face, sparse subcutaneous tissue, and hepatomegaly. Laboratory examination demonstrated extremely high triglyceride level and low leptin level (Table 1). Compound heterozygous variants of *BSCL2* gene were identified; these were identical to the gene variants found in his sister. The clinical course is shown in Fig. 1B. Serum triglyceride and insulin levels increased to more than 2000 mg/dL and 700 μU/mL, respectively, at 2 mo of age. Following this, low-fat dietary formula was introduced (calories, 350 Cal/d; fat ratio, 20%). Metformin therapy was initiated at 7 mo of age (250 mg/d [34 mg/kg/d]). At approximately 1 yr of age, when he started eating solid foods, hyperlipidemia and hyperinsulinemia resolved. Thereafter, his examination findings remained relatively stable for approximately 10 yr under management with nutritional and metformin therapies. His insulin resistance worsened and his triglyceride level increased during puberty (Fig. 1B. OGTT③). At 11 yr and 6 mo of age, metreleptin was introduced at a dose of 0.04 mg/kg/d, and there was an immediate improvement of hyperinsulinemia and hyperlipidemia

resulting in discontinuation of metformin. A few months later, hyperinsulinemia and liver dysfunction reappeared, and metformin treatment was reinitiated. An intelligence test (WISC-IV) at 12 yr of age demonstrated that his full-scale intelligence quotient was 58, indicating slightly retarded mental development with mild intellectual disability. At the time of writing this report, he was 16 yr and 4 mo of age and has received metreleptin therapy for approximately 4 yr.

Discussion

The present cases demonstrated the clinical efficacy of metreleptin in two siblings who received metreleptin for 7 yr (from 11 yr 5 mo of age) and 4 yr (from 11 yr 6 mo of age), respectively. The lipid and carbohydrate metabolisms were successfully controlled during the treatment period. No apparent side effects (e.g. changes in biochemical data, clinical parameters associated with the autonomic nervous system, blood pressure, body temperature, body weight, and height velocity) were observed. In case 1, the effect of metreleptin was attenuated during puberty at approximately 5 yr after commencement of treatment whereas the younger brother did not show such deterioration at puberty. The attenuation of the drug efficacy by neutralizing antibody has been reported previously (11, 12), but the antibody titer in case 1 was low without clinical significance.

In addition to metreleptin, dietary management in infancy before the introduction of metreleptin treatment has been reported to be important in the metabolic control of children with CGL (1, 2, 14). Low-fat milk and dietary management including calorie and lipid limitation in early childhood showed some efficacy in improving hyperlipidemia and hyperglycemia. Since the safety of long-term extensive management with medical treatment in early infancy has not been established, conventional dietary therapy is considerably important.

Metformin is safe and partially effective in improving glucose and lipid metabolisms (1, 2). Although only metformin treatment did not result in a marked metabolic improvement compared to metreleptin, it has synergistic or additional effects on metabolism in both infancy and pubertal stage. Metformin is known to improve insulin resistance in the liver and the muscle (15, 16), and its efficacy was confirmed in the present cases. In case 1, metformin treatment at maximum dose successfully dodged insulin therapy when metreleptin treatment alone was not sufficiently effective. Hence, metformin would be a good adjuvant drug for patients receiving metreleptin as oral medical therapy.

Further, psychological intervention was critically important in metabolism management and for social or school adaptation. The laboratory data and clinical symptoms of CGL patients fluctuate greatly during puberty due to socio-psychological stress, such as sleep deprivation, dietary fluctuation, and refusing going to school (17–19). The lipoatrophic facial appearance and skinny body may be very sensitive and serious issues, especially for teenage girls. Providing psychological support accordingly is important in managing glycolipid metabolism of lipodystrophy. Managing socio-psychological problems is important for children with any chronic disease, not only CGL; however, an impaired glucose tolerance and lipedema can be easily exacerbated. Therefore, we emphasize the importance of psychological support for CGL children.

Several limitations associated with the present study need to be mentioned. We are unsure why the siblings with the same genotype showed different clinical courses despite receiving nearly identical management treatment. Although there is no epidemiological evidence of gender differences in CGL patients, fat metabolism and insulin resistance are exacerbated by estrogen administration and pregnancy (1). We speculated that estrogen

might be responsible for the symptoms presented by CGL patients.

To provide long-term comprehensive medical care, a tailored approach in collaboration with neonatologists, pediatric neurologists, clinical geneticists, and child psychiatrists is important for patients with CGL.

Conclusion

Metreleptin was the main line of treatment to improve the metabolism of two siblings with CGL. It showed stable efficacy for more than 7 yr during the childhood of the older sibling. Long-term comprehensive management with various medicines, dietary management, and psychosocial care are important for children with CGL.

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