

Severe aortic stenosis during leptin replacement therapy in a patient with generalized lipodystrophy-associated progeroid syndrome due to an *LMNA* variant: A case report

Takayoshi Sasako¹ , Hiroko Kadowaki², Takayuki Fujiwara³ , Satoshi Kodera³, Issei Komuro³, Takashi Kadowaki⁴, Toshimasa Yamauchi¹*

¹Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, ²Department of Pediatrics, Sanno Hospital, Tokyo, Japan, ³Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, and ⁴Toranomon Hospital, Tokyo, Japan

Keywords

Adiponectin, Generalized lipodystrophy-associated progeroid syndrome, Leptin replacement therapy

*Correspondence

Toshimasa Yamauchi
 Tel.: +81-3-5800-8815
 Fax: +81-3-5800-9797
 E-mail address:
 tyamau@m.u-tokyo.ac.jp

J Diabetes Investig 2022; 13: 1636–1638

doi: 10.1111/jdi.13827

ABSTRACT

Leptin replacement therapy (LRT) has drastically improved the prognosis of patients with lipodystrophy, but pro-inflammatory properties of leptin could become evident in the long term. Here, we report a 30-year-old Japanese woman with generalized lipodystrophy-associated progeroid syndrome due to a heterozygous *LMNA* variant (c.29C > T; p.T10I), who was diagnosed with severe aortic stenosis (AS) after more than a decade of LRT, which required transcatheter aortic valve implantation. Given her marked hypoadiponectinemia and the *LMNA* variant, our patient might have been susceptible to progeria-associated disorders, including aortic stenosis, which could have been exaggerated by the prolonged ‘imbalanced adipokines’ caused by LRT between pro-inflammatory leptin and anti-inflammatory adiponectin. Thus, long-term LRT could be associated with AS in patients with the *LMNA* variant to cause generalized lipodystrophy-associated progeroid syndrome and hypoadiponectinemia.

INTRODUCTION

Lipodystrophy is a syndrome characterized by the loss of adipose tissue, which leads to severe metabolic disorders, such as diabetes mellitus, hypertriglyceridemia and hepatic steatosis, partly due to adipokine insufficiency. Leptin is one of the major adipokines to regulate glucose and lipid metabolism, and leptin replacement therapy (LRT) during the past two decades have drastically improved the prognosis of patients with lipodystrophy^{1,2}. In addition to the benefits on metabolism, leptin is also known to have pro-inflammatory properties, in contrast to an anti-inflammatory adipokine, adiponectin³, which could become evident in long-term LRT. Here, we show a case to suggest the potential association between long-term LRT and aortic stenosis (AS).

CASE REPORT

A 30-year-old Japanese woman was aware of systemic fat loss at the age of 10 years, and was diagnosed with generalized lipodystrophy at the age of 13 years. Three-time acute pancreatitis due to marked hypertriglyceridemia (triglyceride at maximum >10,000 mg/dL) and poor glycemic control (glycated hemoglobin >8%) led her to start receiving LRT (metreleptin 0.08 mg/kg bodyweight) at the age of 16 years².

Although hypertriglyceridemia and hyperglycemia improved, and pancreatitis did not recur thereafter, she was diagnosed with mild AS with tricuspid aortic valve at the age of 23 years. AS gradually deteriorated, after remaining asymptomatic for 6 years with optimal medical therapy, and stable control of hypertriglyceridemia and diabetes (triglyceride 130–1,200 mg/dL; glycated hemoglobin 5–6%), she was subsequently diagnosed with congestive heart failure (CHF) when she presented

Received 8 December 2021; revised 28 March 2022; accepted 1 May 2022

with nocturnal dyspnea, and required hospitalization for worsening of CHF triggered by infection. Despite the absence of severe cardiomyopathy frequently associated with lipodystrophy, her symptoms persisted due to AS (Figure 1), and she was scheduled for hospitalization to undergo transcatheter aortic valve implantation (TAVI).

The patient's medical history included fatty liver disease, hypertension and refractory foot ulcer at the ages of 15, 24 and 25, respectively. Genetic analysis showed a non-inherited heterozygous *LMNA* variant (c.29C > T; p.T10I)⁴. She had no family history of lipodystrophy or heart disease, although her brother was diagnosed with hepatoblastoma.

On admission, her height was 157.5 cm, her bodyweight was 31.3 kg and her body mass index was 12.6 kg/m². A physical examination showed systolic murmur (Levine IV), but no edema in the lower extremities. Laboratory data showed dyslipidemia (high-density lipoprotein cholesterol 20 mg/dL; low-density lipoprotein cholesterol 71 mg/dL; and triglycerides 1,056 mg/dL), good control of diabetes (glycated hemoglobin 5.8%) and CHF (brain natriuretic peptide 107 pg/mL). They also showed marked hypo adiponectinemia (total adiponectin 0.59 µg/mL; and high-molecular-weight adiponectin 0.01 µg/

mL) and hyperleptinemia (leptin 52.6 ng/mL) 3 h after administration of metreleptin. Her medication included candesartan, bisoprolol, furosemide, bezafibrate and metreleptin at the dose stated above.

Chest X-ray examination showed cardiomegaly (cardiothoracic ratio 60%). Transthoracic echocardiography showed severe AS (aortic valve peak velocity 6.6 m/s; mean pressure gradient 82 mmHg; and aortic valve area 0.4 mm²), moderate mitral stenosis, moderate left ventricular hypertrophy (left ventricular mass index 207 g/m²) and right ventricular overloading (right ventricular systolic pressure 67 mmHg), despite normal left ventricular systolic function (ejection fraction 63%) with no asynergy. Coronary angiography showed diffuse coronary artery calcification without significant stenosis.

On day 7 of hospitalization, TAVI was successfully carried out, with marked improvement of her symptoms, as well as parameters of AS and CHF, and she had a stable course for 2 years thereafter (Figure 1).

DISCUSSION

AS without bicuspid aortic valve occurring in patients of the present patient's age is rare⁵, let alone severe AS requiring TAVI or surgical aortic valve replacement in their 30s. Among the risk factors for AS are high leptin and low adiponectin^{6,7}, and indeed, the present patient showed a markedly high leptin level 3 h after administration of metreleptin accompanied by marked hypo adiponectinemia, yielding an extremely high leptin/adiponectin ratio of nearly 100, a marker of atherosclerosis whose average was 0.6 in the general population⁸. Hyperleptinemia could be partly an overestimation, possibly due to leptin bound to anti-leptin antibody or soluble leptin receptor remains, but we later confirmed that at least free leptin index was not lowered (leptin before administration of metreleptin 4.4 ng/mL; soluble leptin receptor 10.5 ng/mL; free leptin index 41.9). Furthermore, given that glucose and lipid metabolism showed marked improvement by LRT, sufficient leptin was deemed to be replaced in the present case.

We identified a heterozygous *LMNA* variant in this patient⁴, which was later proposed to cause lipodystrophy and progeria or GLPS⁹. Although none of the 11 patients with GLPS were reported to have undergone TAVI or surgical aortic valve replacement for AS, valvular disease was observed frequently, and three of them developed severe calcification of aortic valve, two of whom had received LRT for more than a decade⁹. We thus hypothesized that the present patient might have been susceptible to progeria-associated disorders, including AS, which was exaggerated by the prolonged 'imbalanced adipokines' caused by LRT, although the treatment led to a definite improvement in her prognosis.

In the present case, refractory foot ulcer due to delayed wound healing prompted us to avoid open-heart surgery and select TAVI, and, thus, it is vitally important to prevent restenosis of the implanted biological valve. In addition to controlling risk factors for atherosclerosis, one of the potential

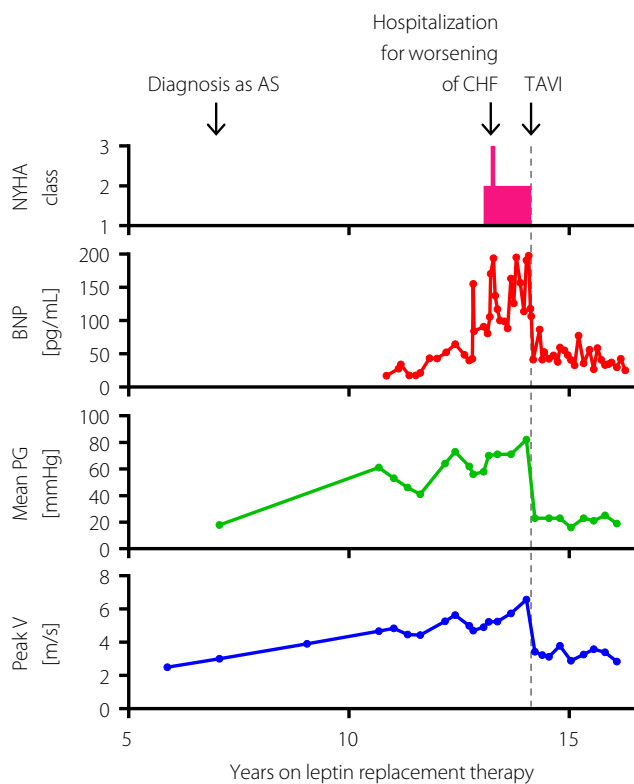


Figure 1 | The course of aortic stenosis (AS) and congestive heart failure (CHF) of the patient after initiation of leptin replacement therapy. BNP, brain natriuretic peptide; Mean PG, mean pressure gradient; NYHA, New York Heart Association functional classification; peak V, peak velocity; TAVI, transcatheter aortic valve implantation.

strategies is to optimize the dose of metreleptin, as far as hypertriglyceridemia and diabetes are well controlled. Furthermore, co-replacement of adiponectin might prove a better approach than replacement of leptin alone¹⁰, as it could attenuate the pro-inflammatory effects of leptin, hopefully arresting the development of AS by resolving the 'imbalanced adipokines'.

In conclusion, the present case suggests a potential association between long-term LRT and AS, and the *LMNA* variant to cause GLPS and hypoadiponectinemia could constitute potential risk factors.

ACKNOWLEDGMENTS

The authors thank Dr Masao Suzuki (Yuzunokidai Clinic), Dr Katsuyuki Hoshina (The University of Tokyo, same as below), Dr Kenichiro Enooku, Dr Takemichi Fukasawa and Dr. Satoshi Toyama for the patient's care. The authors have no funding sources.

DISCLOSURE

TS reports grants from Shionogi & Co., Ltd. IK and TK report personal fees from Shionogi & Co., Ltd. TY reports grants and endowments from Shionogi & Co., Ltd. The other authors declare no conflict of interest.

Approval of the research protocol: N/A.

Informed consent: The patient provided written informed consent for publication of this report.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

REFERENCES

1. Oral EA, Simha V, Ruiz E, *et al.* Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 2002; 346: 570–578.
2. Ebihara K, Kusakabe T, Hirata M, *et al.* Efficacy and safety of leptin-replacement therapy and possible mechanisms of leptin actions in patients with generalized lipodystrophy. *J Clin Endocrinol Metab* 2007; 92: 532–541.
3. Ghantous CM, Azrak Z, Hanache S, *et al.* Differential role of leptin and adiponectin in cardiovascular system. *Int J Endocrinol* 2015; 2015: 534320.
4. Hosoe J, Miya F, Kadowaki H, *et al.* Clinical usefulness of multigene screening with phenotype-driven bioinformatics analysis for the diagnosis of patients with monogenic diabetes or severe insulin resistance. *Diabetes Res Clin Pract* 2020; 169: 108461.
5. Coffey S, Cox B, Williams MJ. The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis. *J Am Coll Cardiol* 2014; 63(25 Pt A): 2852–2861.
6. Glader CA, Birgander LS, Soderberg S, *et al.* Lipoprotein(a), chlamydia pneumoniae, leptin and tissue plasminogen activator as risk markers for valvular aortic stenosis. *Eur Heart J* 2003; 24: 198–208.
7. Mohty D, Piabarot P, Cote N, *et al.* Hypoadiponectinemia is associated with valvular inflammation and faster disease progression in patients with aortic stenosis. *Cardiology* 2011; 118: 140–146.
8. Norata GD, Raselli S, Grigore L, *et al.* Leptin:Adiponectin ratio is an independent predictor of intima media thickness of the common carotid artery. *Stroke* 2007; 38: 2844–2846.
9. Hussain I, Patni N, Ueda M, *et al.* A novel generalized lipodystrophy-associated progeroid syndrome due to recurrent heterozygous *LMNA* p.T10I mutation. *J Clin Endocrinol Metab* 2018; 103: 1005–1014.
10. Yamauchi T, Kamon J, Waki H, *et al.* The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 2001; 7: 941–946.