Early Atherosclerosis and Conduction Defect in a Rare Case of Dunnigan Type Familial Partial Lipodystrophy

Nadir Bir Dunnigan Tipi Ailevi Kısmi Lipodistrofi Olgusunda Erken Ateroskleroz ve İleti Bozukluğu

ABSTRACT
A 45-year-old female patient was admitted to the emergency department with syncope. Her medical history revealed a diagnosis of Familial Partial Lipodystrophy 2 (FPLD2). The patient’s electrocardiogram showed a complete atrioventricular (A-V) block, and she had a history of insulin-dependent diabetes mellitus and coronary artery bypass surgery. A severe stenosis was observed in the aortic right coronary artery saphenous vein graft during coronary angiography, which was successfully revascularized. Subsequently, due to persistant syncope attacks, a permanent pacemaker was implanted after an electrophysiological study. This case highlights that serious cardiac conduction defects in patients with FPLD2 may not only be related to coronary artery disease but can also present as direct conduction defects.

Keywords: Conduction defect, early atherosclerosis, familial partial lipodystrophy

ÖZET

Anahtar Kelimeler: İleti defekti, erken ateroskleroz, familial parsiyel lipodistrofi

Familial Partial Lipodystrophy (FPLD) is a rarely seen disease characterized by partial loss and abnormal distribution of adipose tissue. To date, six different types of FPLD have been described. The most common subtype is Dunnigan Type Familial Partial Lipodystrophy (FPLD2), caused by the lamin A/C (LMNA) mutations. Abnormal adipose tissue accumulation under the skin is a prominent phenotypic feature in these patients. Metabolic disorders such as lipid disorders and diabetes mellitus (DM) can be observed in these patients. In addition, non-ischemic cardiomyopathy (CMP) and cardiac conduction disorders may accompany.

This is a case report of a patient with Dunnigan disease, confirmed by mutational analysis of the LMNA gene. The patient, who had previously undergone a coronary artery bypass surgery, presented with cardiac conduction defect.

Case Report
A 45-year-old female was admitted to the emergency room with complaints of syncope, nausea, vomiting, and fatigue. The patient, with a medical history of FPLD type 2 (Dunnigan type), had insulin–dependent diabetes mellitus, had undergone coronary angiography and subsequent coronary artery bypass surgery eight years ago. A LMNA gene mutation was detected in exon 8 at position 482. Additionally, she had undergone coronary angioplasty with stent placement due to a myocardial infarction one year
ago. Laboratory tests performed in the emergency room (ER) showed that the high sensitive troponin I level was at the upper limit of the normal value. Electrocardiograms (ECGs) illustrated atrioventricular (A–V) block with 2:1 intermittent episodes of asystole (Figure 1). Other blood tests were within normal levels. The ejection fraction was 58%, pulmonary artery pressure was 29 mmHg, left atrium size was 37 mm, and no significant valve pathology was observed in echocardiography. The thickness of both interventricular septum and posterior wall was 10 mm.

During her follow-up in the coronary care unit, and repeated conduction defects were observed. The patient was taken to the angiography laboratory, where a lesion in the aorto-right coronary artery (RCA) saphenous graft was identified as suitable for revascularization. Consequently, a stent was implanted, and a temporary pacemaker was inserted (Figure 2). No critical lesions were observed in other vessels. The patient’s beta-blocker treatment was discontinued. Her symptoms decreased after the intervention, and she did not require any pacemaker within the first 12 hours. She was discharged after 72 hours of sinus rhythm monitoring. Nevertheless, the patient presented to the ER with syncope at 24th hour of hospital discharge. A–V complete block and sinus pauses were observed in the electrocardiography.

**ABBREVIATIONS**

- A–V: Atrioventricular
- CMP: Cardiomyopathy
- DM: Diabetes mellitus
- ECGs: Electrocardiograms
- EPS: Electrophysiological study
- ER: Emergency room
- FPLD: Familial partial lipodystrophy
- RCA: Right coronary artery
- SNRT: Sinus node recovery time

![Figure 1. Patient’s admission and follow-up electrocardiograms.](image-url)
Bradyarrhythmia and progressive A-V block were the only causes of the syncope that could be identified. Electrolytes and thyroid function tests were normal. A permanent pacemaker insertion after an electrophysiological study was scheduled, however, it was postponed for ten days after a positive test for COVID-19 was obtained. The electrophysiological study (EPS) was performed 15 days later, during which she was under a temporary pacemaker. In the electrophysiological study, the sinus node recovery time (SNRT) and corrected SNRT (cSNRT) were 1,280 ms and 613 ms, respectively. Tachycardia was not induced by programmed stimulations. After the permanent pacemaker implantation, the patient was followed up without any cardiac problems.

Discussion

FPLD2 is a disease characterized by a disorder of subcutaneous adipose tissue in the extremities and hips. It most commonly results from a missense mutation in the LMNA gene located on chromosome 1 q21-22.6. Clinical findings usually appear in adolescence.6 They include the loss of subcutaneous adipose tissue from the extremities and trunk and its deposition in the head and neck.7 Similar features were also present in our patient (Figure 3). The degree of fat loss is associated with metabolic complications, such as insulin resistance, diabetes, hypercholesterolemia, hypertriglyceridemia, and low high-density lipoprotein levels. Our patient had developed coronary artery disease and diabetes in her third decade. Atherosclerotic disease, including coronary artery disease, is more frequent among women and is often associated with metabolic complications, as described in our case. Atherosclerotic disease is thought to arise from the presence of risk factors rather than a direct effect of the disease. Cardiomyopathies and conduction system problems, such as atrial fibrillation and A-V block, are also more frequently encountered.7 It was noteworthy that our patient, who exhibited all cardiovascular complications of lipodystrophy, was complicated by coronary artery disease, diabetes, and a conduction defect.

Mutations in the LMNA gene have been more commonly associated with muscular dystrophy and/or cardiomyopathy than FPLD2.4 Additionally, LMNA mutations resulting in FPLD2 do not usually lead to cardiomyopathy. The co-occurrence of both cardiomyopathy and/or conduction defects with FPLD2 due to LMNA mutations is very rare, although some cases have been reported.

In our patient, as in 75% of FLDP2 patients, there is a mutation in a single allele at position 482. Apart from abnormal fat distribution, insulin resistance, and other metabolic complications can be observed in these patients. While the LMNA mutation is associated with both CMP and FLDP2, CMP is rare. The strongest association with dilated CMP was seen in patients with typical FPLD with mutations between exons 1 and 3.4 Cardiac arrhythmias are more prominent in FPLD patients with exon 9 mutations. Additionally, FPLD has been associated with hypertrophic CMP and aortic stenosis.5

Patients with mutations in exons 1 and 3 have been reported to exhibit a pattern of body fat loss similar to that observed in patients with typical FPLD with mutations in exon 8.6 Other phenotypic manifestations include insulin resistance, diabetes, hepatic steatosis, hypertriglyceridemia, acanthosis nigricans, and polycystic ovary syndrome. Our patient had a mutation in exon 8 at position 482.

Some LMNA mutations are associated with early-onset and severe heart disease, including conduction system disease requiring pacemaker implants.8 In a median follow-up of 57 months of over 60 affected individuals, there were 15 heart transplants, 15 sudden cardiac arrests, 12 defibrillator implants, and one death from end-stage heart failure in patients with
LMNA mutations. Pacemaker data showed that 42% of these subjects received appropriate therapy for ventricular tachycardia and ventricular fibrillation, suggesting that these patients are at a high risk of developing arrhythmias. The authors conclude that, in patients with LMNA mutations requiring pacemaker implantation, implantable cardioverter-defibrillator (ICD) implantation should be considered as a primary preventive measure instead of pacemaker implantation.8

Conduction defects may develop as a result of the toxic effects of abnormal lipotoxic products on myocytes and conduction system cells, which occur due to changes in glucose metabolism.

Our limitation was that we did not perform cardiac Magnetic Resonance Imaging (MRI) and speckle-tracking echocardiography analysis to show myocardial involvement, since the patient had a genetic diagnosis and clinical cardiac manifestations.

An electrophysiological study was performed in our patient after coronary revascularization due to accompanying episodes of A-V block and asystole attacks. Since her ejection fraction (EF) was normal and ventricular tachycardia was not induced in the electrophysiological studies, ICD was not considered. Our patient underwent an uncomplicated permanent pacemaker and was followed up without symptoms for about six months.

**Conclusion**

Our patient exhibited characteristic findings of lipodystrophy with a diagnosis of premature and recurrent coronary artery disease, diabetes, and A-V conduction defect. Presence of LMNA mutation and possibly lipotoxicity in conduction system cells were the two important contributors for the development of conduction abnormalities in the patient who had no overt cardiomyopathy.
Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.


Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study received no financial support.

References