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Siblings With Familial Dwarfism Presenting With Acute Myocardial Infarction at Adolescence

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ABSTRACT

We encountered siblings with familial Majewski osteodysplastic primordial dwarfism type II (MOPD II) with acute myocardial infarction in adolescence and in their early 20s. We successfully performed percutaneous and surgical coronary interventions. From these cases, we were able to better understand coronary artery disease of MOPD II and provide better management. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2021;3:795–800) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

PATIENT 1

HISTORY OF PRESENTATION. A 23-year-old man visited the hospital due to week-long exertional chest pain. The pain had a squeezing characteristic and was provoked after walking for 5 min. He did not complain of ongoing chest pain.

LEARNING OBJECTIVES

- To be aware of the rare but fatal coronary artery complications in young patients with MOPD II.
- To understand the pathogenesis of coronary artery complications in MOPD II.

MEDICAL HISTORY. The patient was born at the gestational age of 37 weeks and weighed 1.07 kg at birth. Despite growth hormone therapy for poor growth, his final height and weight were 104 cm and 19.5 kg (body mass index: 18 kg/m^2), respectively. Insulin resistance (homeostatic model assessment for insulin resistance [HOMA-IR]: 3.5 to12.9; cutoff: >2) was detected at 12 years of age when skin pigmentation mimicking acanthosis nigricans was observed on his neck, genitalia, and nipples. At 18 years of age, he was diagnosed with Majewski osteodysplastic primordial dwarfism type II (MOPD II) with pathogenic compound heterozygous variants of the pericentrin gene (*PCNT*) on whole-exome sequencing. He underwent several transarterial or surgical interventions for multiple intracranial aneurysms with

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CAG = coronary angiography

ECG = electrocardiogram

HOMA-IR = homeostatic model assessment for insulin resistance

LAD = left anterior descending artery

LCX = left circumflex artery

MOPD II = Majewski osteodysplastic primordial dwarfism type II

PCNT = pericentrin gene

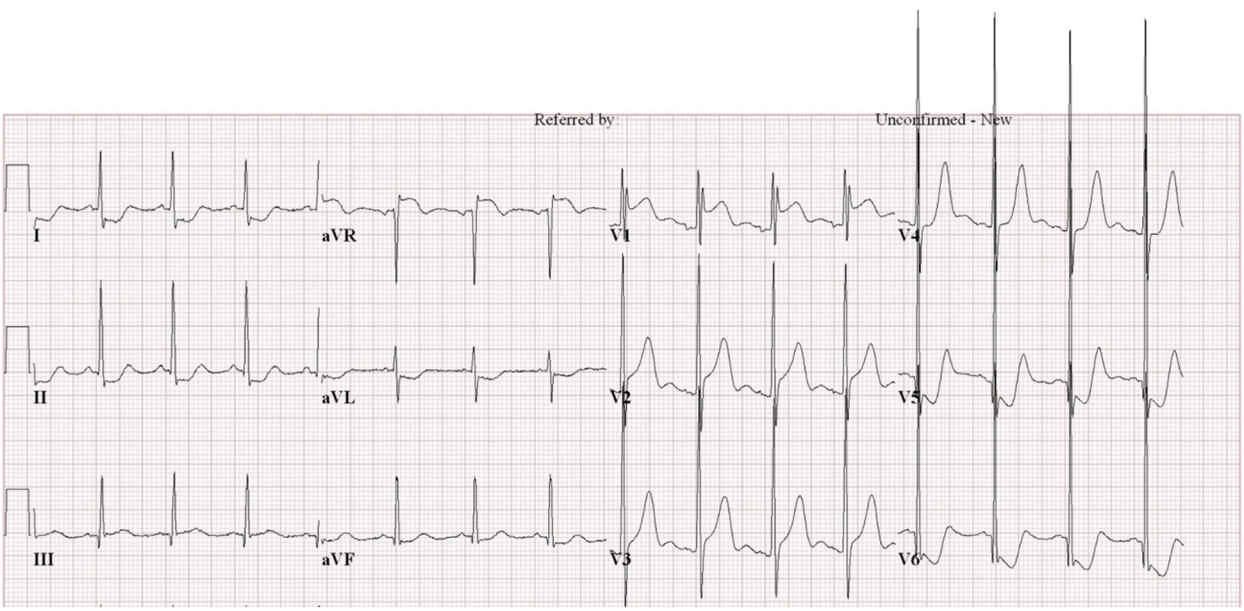
or without rupture since 20 years of age. In addition, he developed dyslipidemia, mainly hypertriglyceridemia (up to 567 mg/dl), at 18 years of age. Mild fatty liver with hepatitis, chronic kidney disease with proteinuria, and thrombocytosis (427 to 985 $\times 10^3/\mu l$) were also detected at 20 years of age. He did not have any history of hypertension, diabetes mellitus, or smoking.

DIFFERENTIAL DIAGNOSIS. The initial electrocardiogram (ECG) demonstrated inferior and lateral ST-segment depression and high QRS voltage in the precordial leads that indicated left ventricular hypertrophy (**Figure 1**). Troponin I level was slightly increased, and echocardiography demonstrated decreased left ventricular contractility (ejection fraction: 35%) with hypokinesia of the basal septal and inferior wall that correlated with the region of ST-segment depression on ECG. Initial laboratory investigations are summarized in **Table 1**. Because the initial elevation of cardiac enzymes was modest, and the patient was young, both acute coronary syndrome and acute myocarditis were considered.

INVESTIGATIONS. Coronary angiography (CAG) revealed 90% focal stenosis of the proximal left circumflex artery (LCX) and 50% stenosis of the left anterior descending artery (LAD) (**Figure 2A**). Successful coronary stenting was performed for the proximal LCX lesion with a Resolute Onyx (Medtronic, USA) Zotarolimus-eluting stent (Medtronic, Korea, 2.5 × 15 mm) under intravascular ultrasound guidance (**Figure 2C**).

MANAGEMENT. Thirteen months later, the patient complained of exertional pain over the left scapula and arm with ST-segment elevation on ECG. Emergency CAG revealed 80% in-stent restenosis of the proximal LCX combined with 80% diffuse stenosis of the distal LCX (**Figure 2B**). We performed drug-coated balloon angioplasty for both lesions. However, after 5 months, even with dual antiplatelet therapy, the patient developed left wrist pain with ST-segment changes on ECG. CAG revealed diffuse in-stent restenosis in the LCX and a de novo lesion in the LAD (Video 1). During coronary artery bypass grafting (CABG), the cardiovascular surgeons discovered thick fat tissue surrounding the entire myocardium, thereby hindering the identification of coronary arteries. When the diagonal branch was incised, small atheroma plaques were detected inside the vessel. The left internal thoracic artery was anastomosed to the major proximal diagonal branch, and a right saphenous vein graft was used to

FIGURE 1 Initial Electrocardiogram of Patient 1



Initial electrocardiogram of Patient 1 shows inferior and lateral ST-segment depression and high QRS voltage in precordial leads that correlate with left circumflex territory ischemia.

connect the ascending aorta to the major obtuse marginal branch.

FOLLOW-UP. The patient was well without any symptoms and regional wall motion abnormalities on echocardiography for 8 months.

PATIENT 2

HISTORY OF PRESENTATION. A 15-year-old male, who was the younger brother of patient 1, was rushed to the emergency room because of chest pain and left arm pain.

MEDICAL HISTORY. He was diagnosed with MOPD II with the same pathogenic variants of the *PCNT* gene as his sibling at 9 years of age. His final height and weight were 101 cm and 16 kg (body mass index: 15.7 kg/m^2), respectively. At 14 years of age, he underwent encephaloduroarteriosynangiosis after diagnosis of Moyamoya disease following repetitive and prolonged transient ischemic attacks. Initial cardiac screening at the time revealed normal left ventricular function. He was followed-up and treated for insulin resistance (HOMA-IR 2.5 to 5.8), hypertriglyceridemia (up to 390 mg/dl), thrombocytosis (395 to 814 $\times 10^3/\mu l$), and mild proteinuria. However, he had no history of hypertension, diabetes mellitus, or smoking.

DIFFERENTIAL DIAGNOSIS. Initial ECG revealed right bundle branch block and ST-segment elevation in leads V_2 to V_4 (**Figure 3A**) along with modest elevation of serum troponin I without creatine kinase-MB elevation (**Table 1**). During follow-up, creatine kinase-MB and troponin I levels increased gradually. Further progression of ST-segment elevation on ECG (**Figure 3B**) and dyskinesia of the left ventricle anterior and septal wall on echocardiography were also detected. The diagnosis of acute myocardial infarction (AMI) was considered.

INVESTIGATIONS. On CAG, the proximal LAD was completely occluded with a collateral flow from the LCX (**Figure 4,** Video 2).

MANAGEMENT. Drug-coated balloon angioplasty for the LAD was performed successfully.

FOLLOW-UP. The patient was discharged on aspirin and clopidogrel. However, myocardial infarction recurred due to restenosis of the previously treated proximal LAD, approximately 10 months after ballooning. He also underwent CABG with left internal thoracic artery and LAD anastomosis.

TABLE 1 Laboratory Investigations

Test	Value		Reference Range
	Patient 1	Patient 2	
Platelet ($\times 10^3/\mu l$)	548	734	130–400
BUN (mg/dl)	29	19	10–26
Creatinine (mg/dl)	1.21	0.71	0.70–1.40
AST (IU/l)	38	33	1–40
ALT (IU/l)	78	21	1–40
Albumin (g/dl)	4.0	3.9	3.3–5.2
Total bilirubin (mg/dl)	0.3	0.5	0.2–1.2
Total cholesterol (mg/dl)	193	175	0–240
TG (mg/dl)	395	129	0–200
HDL (mg/dl)	45	43	35–55
LDL (mg/dl)	95	106	0–130
HbA_{1C} (%)	6.3	5.7	4–6.4
BNP (pg/ml)	168	122	0–100
Initial/peak			
CK (IU/l)	124/ND	220/2,392	20–270
CK-MB (ng/ml)	1.5/1.8	4.4/108.5	<6.6
Troponin I (ng/ml)	0.94/0.96	0.26/10.85	<0.028

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; BUN= blood urea nitrogen; CK = creatine kinase; CK-MB = creatine kinase-MB isoenzyme; HbA_{1C} = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ND = no data; TG = triglyceride

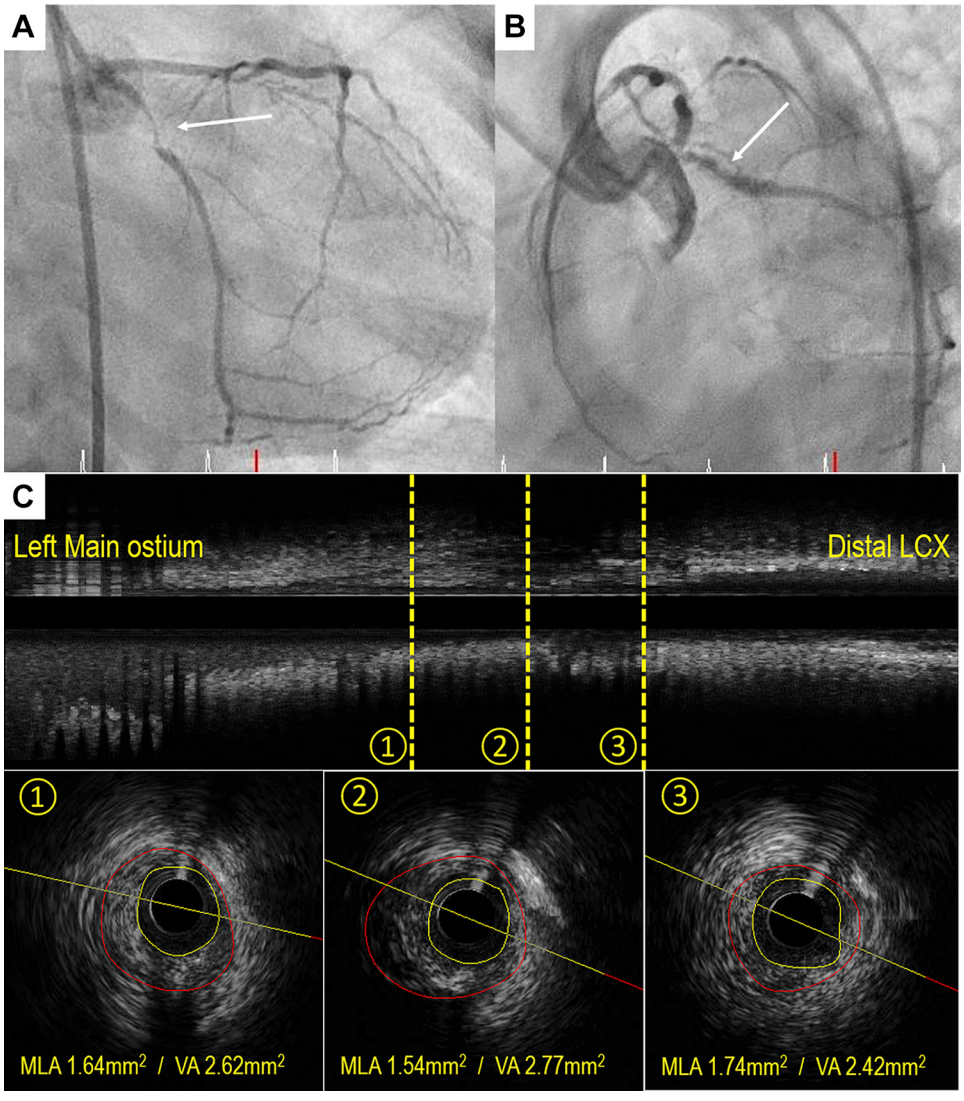
DISCUSSION

MOPD II is ultra-rare but 1 of the most common forms of microcephalic primordial dwarfism, with >150 cases identified worldwide (1). This disease is now understood as a distinct clinical entity caused by biallelic loss-of-function mutations in the *PCNT* gene (2,3). Although the protein pericentrin is an integral component of the centrosome, the relationship between the underlying pathogenesis and symptoms remains unclear.

Although the lifelong prevalence of cerebrovascular disease in patients with MOPD II has been estimated to be 19% to 52% (1), coronary artery disease (CAD) is so rare that only 5 cases have been reported so far (1,4–6). The prognosis of these patients is poor, with 4 deaths in the 5 reported cases. However, based on our experience, we were able to determine other characteristics of CAD in these patients.

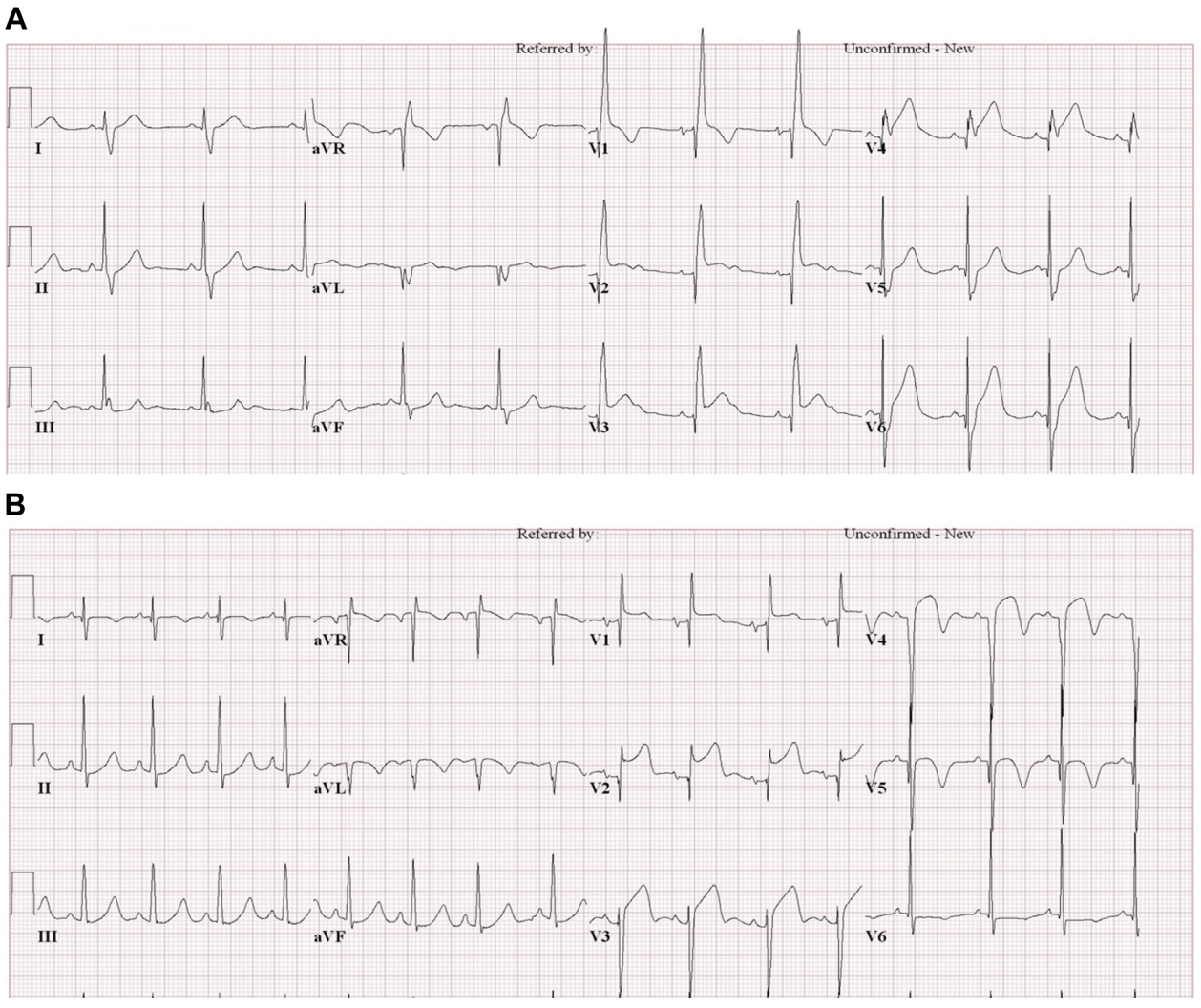
First, the pathogenesis of CAD is not consistent with the classic explanation of cerebrovasculopathy in MOPD II (5) and CAD in typical Moyamoya disease (7). The gross morphology of coronary arterial lesions in patient 1 was similar to that of atherosclerotic disease. Furthermore, insulin resistance is a well-known clinical feature of MOPD II (1); moreover, patient 1 had severe hypertriglyceridemia and high

FIGURE 2 Coronary Angiography and Intravascular Ultrasound Images of Patient 1



(A) The first coronary angiogram shows severe stenosis of proximal left circumflex artery (LCX) **(arrow)**. **(B)** The second coronary angiogram reveals in-stent restenosis **(arrow)** that occurred 13 months after stenting for the LCX lesion. **(C)** Intravascular ultrasound evaluation of the LCX (after plain ballooning) reveals diffuse stenosis with a large eccentric fibrofatty plaque (annotated as cross-section number 2). MLA = minimal luminal area; VA = vessel area.

FIGURE 3 Electrocardiograms of Patient 2



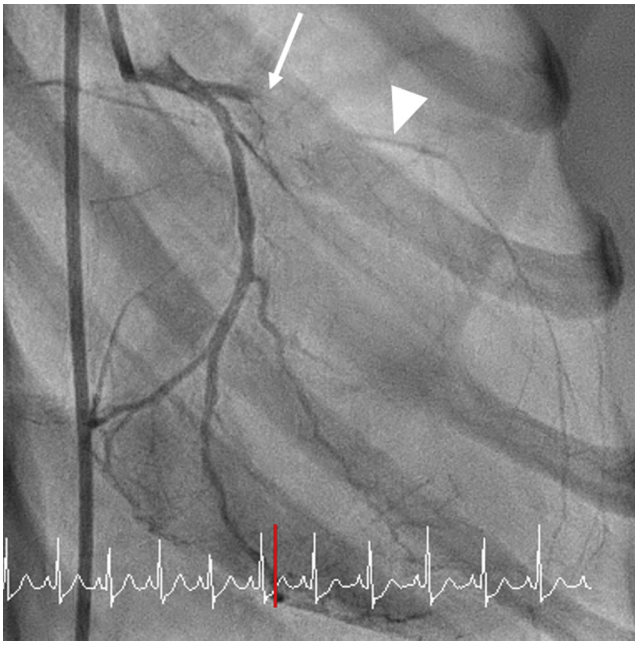
(A) Initial electrocardiogram shows right bundle branch block, mild ST-segment elevation in leads V_2 to V_4, and tall T-waves in leads V_4 and V_6. **(B)** The last electrocardiogram before intervention shows progressed elevation of ST-segment in leads V_1 to V_4 without definite reciprocal changes.

HOMA-IR for several years. These observations suggest that atherosclerosis may play a key role in the pathogenesis of coronary lesions. In addition, thrombocytosis, another clinical feature of MOPD II, can play a role in the onset of AMI (1).

Second, the onset of significant CAD was very early. In both the cases, the patients were too young to experience such a severe acute coronary event. We supposed that our patients' susceptibility to CAD might have originated from their short stature. From earlier reports, dwarfs are known to have an increased risk for cardiovascular disease. This was hypothesized to be due to a narrower cross-sectional diameter of the vessels (8). Our 2 patients not only had extremely short stature but also possessed powerful risk factors, such as hyperlipidemia and thrombocytosis, as previously described.

Bober and Jackson (1) suggested follow-up guidelines for patients with MOPD II, including echocardiography to screen for heart anomalies. However, they did not propose screening for CAD, which can be fatal if missed. It is reasonable that ECG should be obtained annually or biannually in adolescent patients for early detection of CAD. CAG should be considered

FIGURE 4 Coronary Angiography of Patient 2



Coronary angiography of Patient 2 shows total occlusion of proximal left anterior descending artery **(arrow)** with delayed visualization of distal part **(arrowhead)** from the collateral vessels.

in cases of clinical suspicion of acute coronary syndrome.

CONCLUSIONS

We described familial cases of MOPD II with AMI at an early age. Although both cerebrovasculopathy and CAD maybe life-threatening complications of MOPD II, active surveillance and intervention can effectively save lives, as proven in our cases. Despite the rarity of the acute coronary syndrome, physicians must closely monitor patients for the development of any symptoms and perform ECGs regularly.

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KEY WORDS coronary artery disease, insulin resistance, pediatric, primordial dwarfism

APPENDIX For supplemental videos, please see the online version of this paper.