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Case Report

Camptodactyly-arthropathy-coxa vara-pericarditis syndrome and an unusual association with mitral stenosis

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ABSTRACT

Background. Campotodactyly-artrhropathy-coxa vara-pericarditis (CACP) syndrome is a very rare autosomal recessive genetic disorder. It is characterized by flexion contracture of the fifth finger (camptodactyly); non-inflammatory arthropathy; decreased angle between the shaft and the head of the femur (coxa vara) and pericarditis. Its association with mitral stenosis has not yet been reported. Hereby we report this unique association with CACP syndrome.

Case. An eleven-year-old girl presented with non-productive cough, dyspnea, and orthopnea. She was diagnosed CACP syndrome at the age of seven and a biallelic frameshift mutation in the *PRG4* gene was determined. The physical examination revealed pectus excavatum, camptodactyly, genu valgum, tachypnea and orthopnea. The functional capacity was NYHA III-IV. She had 2/6 soft pansystolic murmur at 4th left intercostal space and a rumbling diastolic murmur at apex. Echocardiography revealed an enlarged left atrium, severe stenotic mitral valve with a mean diastolic transmitral gradient of 22.5 mmHg, mild mitral regurgitation and mild apical pericardial effusion. The patient had mitral comissurotomy and partial pericardiectomy operation. Her post-operative transmitral gradient decreased to 6.9 mmHg and the pulmonary pressure was 30 mmHg. Her functional capacity increased to NYHA I-II.

Conclusions. The main defect is the proteoglycan 4 protein which acts like a lubricant in articular and visceral surfaces. Therefore, the leading clinical feature is arthropathy. Cardiac involvement other than clinically mild pericarditis is not usually expected. Three types of proteoglycans (decorin, biglycan, and versican) are present in the mitral valve. This could be the reason of mitral valve involvement in rare cases as like ours. It is important that these patients undergo echocardiographic examination regularly.

Key words: arthropathy, camptodactyly, coxa vara, *PRG4* gene, mitral stenosis.

Campotodactyly-arthropathy-coxa vara-pericarditis (CACP) syndrome was defined by Dr. Matthew Warman in 1999. It is a rare genetic disorder with an incidence of less than 1/1.000.000. It is characterized by deformities like camptodactyly and progressive coxa vara beginning during childhood. Arthropathy is non-inflammatory and secondary to synovial hyperplasia. Pericardial effusion is infrequent and has a non-inflammatory origin, rarely causing constrictive pericarditis. The disease is inherited autosomal recessively due to a mutation in the PRG4 gene.[1-4] The PRG4 gene is located in the long arm of the first chromosome at the 1q25-31 locus and codes for a mucine like glycoprotein, namely proteoglycan 4, which is a lubricating material of the synovial fluid in the articular joints and visceral cavities like pleura and pericardium.[5,6]

The cardiological component of the disease is usually manifested as a clinically mild pericarditis. Mitral valve prolapsus and mitral

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regurgitation is rarely reported, only in a few cases.[7,8] To the best of our knowledge, this is the first case of CACP syndrome associated with significant mitral stenosis.

Case report

A written informed consent was received from the family for publication of this case and the photographs.

An eleven-year-old female patient presented with dyspnea and non-productive cough which had progressed to exercise intolerance and orthopnea in the last 3 months. She was born at term to consanguineous parents (3rd degree consanguinity) after an uneventful pregnancy. She had no notable medical problems in infancy and grew normally until three years of age. At the age of three years she started experiencing arthritis which led to deformities. The initial diagnosis by pediatric rheumatology was "juvenile idiopathic arthritis". She was given various anti-inflammatory treatment regimens without a significant clinical benefit. She was diagnosed with coxa vara deformity at the age of seven years. Thereafter she was referred to a genetics department and the whole exome sequencing (WES) analysis revealed a homozygous pathological p.Thr399Profs*513 frameshift in the *PRG4* gene.[2] Genetic counseling noted that no other family member had a similar finding.

The patient was recently referred to pediatric cardiology department for having exertional dyspnea, orthopnea and non-productive cough. The physical examination revealed pectus excavatum deformity (Fig. 1), camptodactyly (Fig. 2), genu valgum deformity (Fig. 3), tachypnea and orthopnea. The functional capacity was NYHA III-IV. Her lungs were clear with auscultation. She had 2/6 soft pansystolic murmur at 4th left intercostal space and a rumbling diastolic murmur at apex. In the echocardiographic examination, enlarged left atrium, (diameter: 47X41 mm, volume 42 ml); thickened and restricted movement of the posterolateral mitral leaflet, shortened posterolateral chorda tendinea were noted (Fig. 4). Mean diastolic transmitral gradient was 22.5 mmHg, indicating severe stenosis and there was mild mitral regurgitation (pressure half time: 83 msec; valve area 2.7 cm^2). The systolic velocity of the tricuspid regurgitation was 4m/sec, therefore the systolic pulmonary arterial pressure was estimated as 75 mmHg. There was also 9 mm pericardial effusion at the apical region.

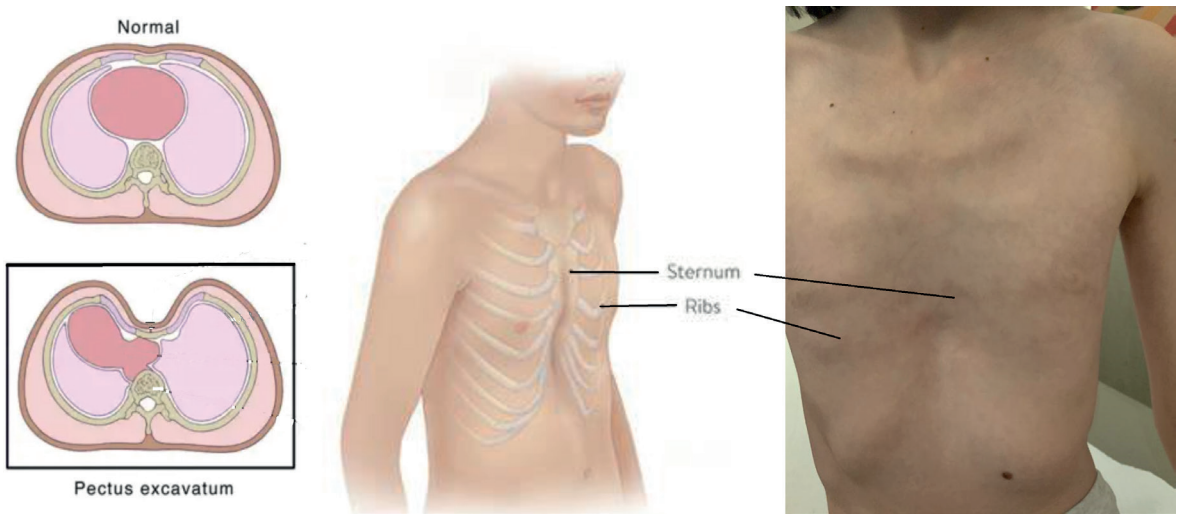

Fig. 1. Pectus excavatum deformity.
The caved-in appearance of the thorax in symmetric / central pectus excavatum deformity.

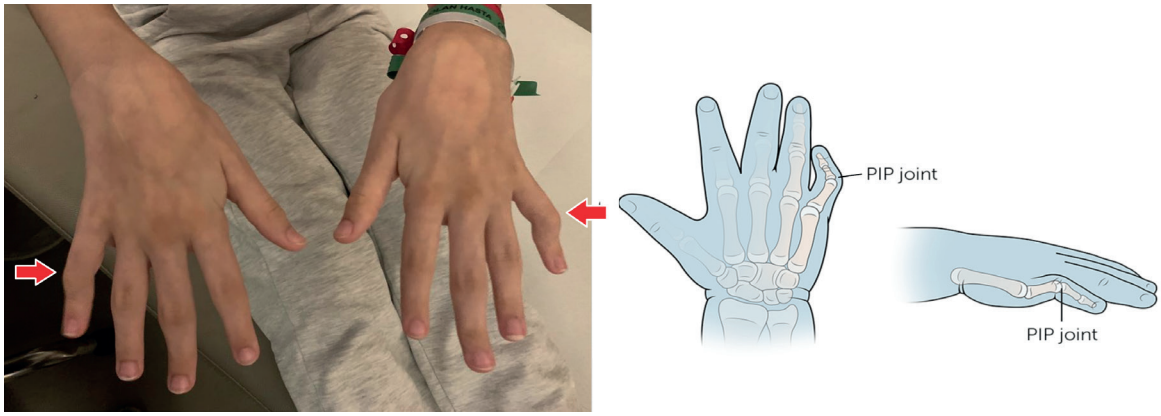

Fig. 2. Camptodactyly.
The fifth fingers are typically bent at the proximal interphalangeal joints (PIP) bilaterally.

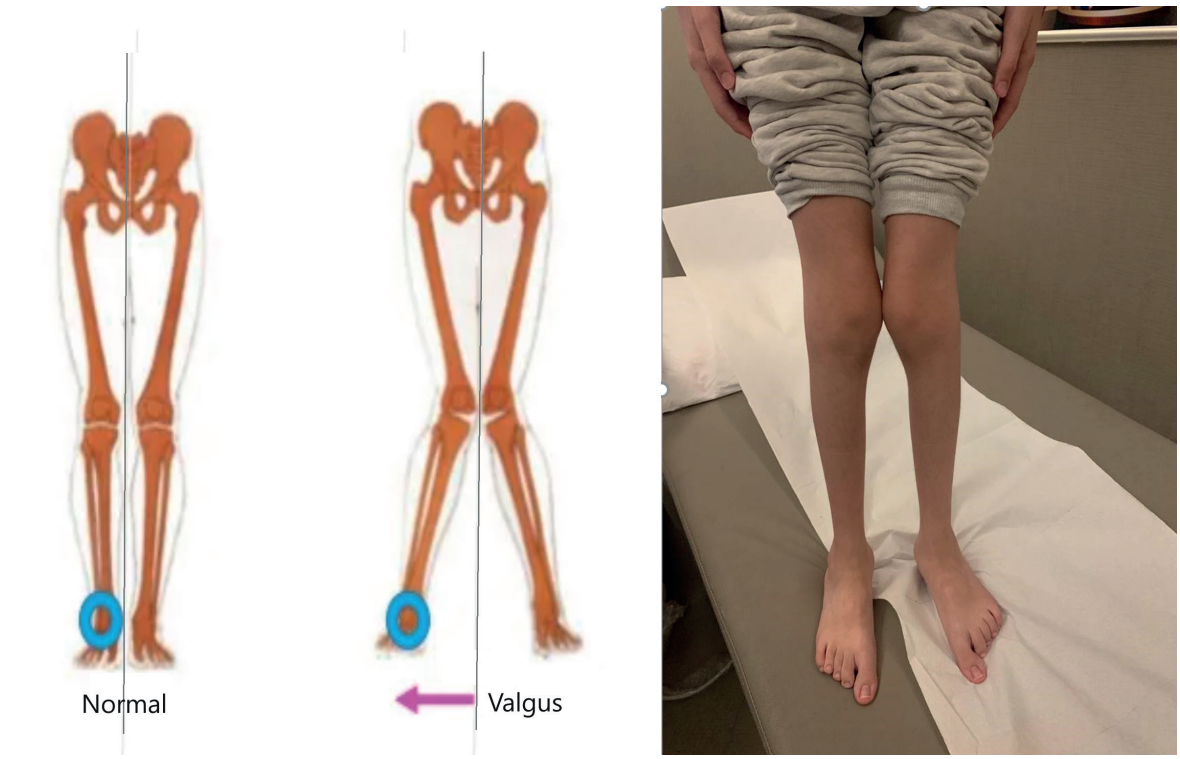

Fig. 3. Genu valgum deformity.
The distal end of the tibia deviates away from the midline, laterally. This is seen because of the coxa vara deformity.

The patient underwent a mitral comissurotomy operation and partial pericardiectomy was performed to prevent a possible constrictive pericarditis. The pericardial biopsy revealed acute fibrinous pericarditis with no elements of inflammation or infection. In the post-operative echocardiography, the diastolic mean transmitral gradient decreased to 6.9 mmHg. Mitral regurgitation was mild-moderate and the estimated systolic pulmonary arterial pressure was 30 mmHg. Her symptoms of orthopnea and dyspnea decreased and functional capacity increased to NYHA I-II.

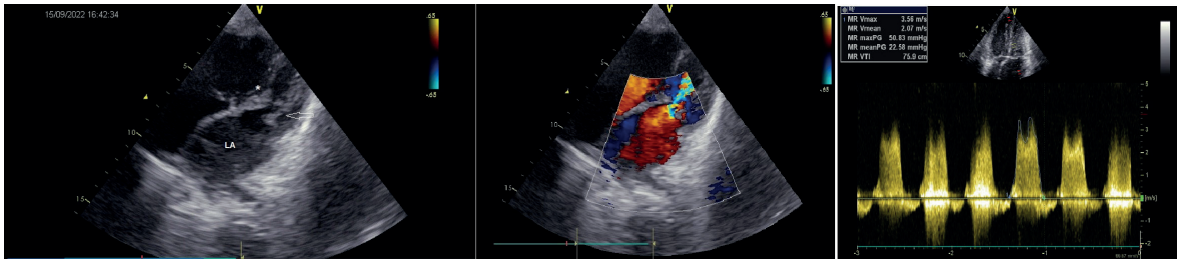

Fig. 4. Echocardiographic evaluation.

Left: Thickened mitral valve leaflet (star), thickened and shortened chorda tendinea are shown (arrow). Middle: Color Doppler diastolic flow pattern of the stenotic mitral valve. Right: CW Doppler diastolic flow pattern of the mitral valve.

Discussion

CACP syndrome is a rare single gene mutation disease with autosomal recessive inheritance. Its incidence may be relatively high in populations where parent consanguinity is frequent. The main defect is the proteoglycan 4 protein which acts like a lubricant in articular and visceral surfaces. Therefore the leading clinical feature is arthropathy with deformities. The polyarthropathy seen in early childhood has systemic involvement. The joints mostly affected are knee, wrist, elbow, and hip joints. Many patients complain about morning stiffness. Therefore it is frequently misdiagnosed as juvenile idiopathic arthritis, however the acute phase reactants and inflammatory parameters remain normal in CACP. In patients with childhood polyarthropathy resistant to anti-inflammatory treatment and with early deformities, CACP syndrome should be in the differential diagnosis list.

Other than clinically mild pericarditis, mitral valve prolapse and mitral regurgitation have rarely been reported. It is known that three particular proteoglycans (decorin, biglycan, and versican) are present in the mitral valve.[9] Extracellular matrix changes are seen in many heart valve pathologies. Myxomatous degeneration of the mitral valve is the leading cause of mitral valve prolapse and regurgitation. Myxomatous mitral valves are reported to contain excess proteoglycans and hyaluronan.[10] This could shed light on the unexpected mitral valve involvement in a patient with *PRG4* mutation, and classifying the variations in the mutation of PRG4 gene may help identify the possible associated anomalies in CACP syndrome. Our patient also indicates that other valvular anomalies like mitral stenosis may also be associated with this disease. Therefore it is important that in patients with CACP syndrome, cardiologic evaluation and echocardiographic examination should be performed regularly.

Ethical approval

We confirm that a written informed consent was received from the family for the publication of this case and the photographs.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: YKY, AA; data collection: AO, VM; analysis and interpretation of results: CA; draft manuscript preparation: DŞ, CA. All authors reviewed the results and approved the final version of the manuscript. They take public responsibility for it.

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Conflict of interest

The authors declare that there is no conflict of interest.

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