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Brothers with constrictive pericarditis – A novel mutation in a rare disease



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ABSTRACT

Familial constrictive pericarditis is extremely rare. We report a case of two brothers both suffering constrictive pericarditis along with having multiple painless joint deformities. Genetic workup confirmed the clinical diagnosis of camptodactyly-arthropathy-coxa vara-pericarditis (CACP) syndrome CACP syndrome and also revealed a rare mutation in the causative gene.

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1. Case history

A 13-year-old male presented with chronic systemic venous congestion since the age of four years. He also was unable to obtain squatting posture and had started developing bending deformities of fifth finger, elbow joint, and toes since the age of three years. There was no history of joint swelling, erythema, tenderness, and constitutional symptoms like fever, anorexia, and loss of weight. Interestingly, his 9-year-old younger brother also had similar complaints (Fig. 1A). Clinical examination was remarkable for elevated jugular venous pressure with no inspiratory fall (Kussmaul sign) and with prominent x and y descent, massive hepatomegaly, and a palpable spleen. Auscultation revealed pericardial knock.

Musculoskeletal examination revealed bilateral coxa vara, genu valgus, and elbow contractures. There was bilateral flexion deformity of the fifth finger at proximal interphalangeal (PIP) joint and interphalangeal flexion deformities of multiple toes (Fig. 1B). The hemogram, and liver and renal function assays were unremarkable. Radiography demonstrated short femur neck, flattened acetabulae, and nonerosive arthropathy without periarticular osteopenia at involved joints (Fig. 1C and D). There was moderate right-sided pleural effusion and no cardiomegaly (Fig. 1E). Transthoracic echocardiography revealed pericardial thickening and with features of constriction. Cardiac catheterization supported the diagnosis of constrictive pericarditis (Fig. 1F and G). Knee joint synovial fluid biopsy revealed synovial hyperplasia with minimal inflammatory cells (Fig. 1H). Genetic studies

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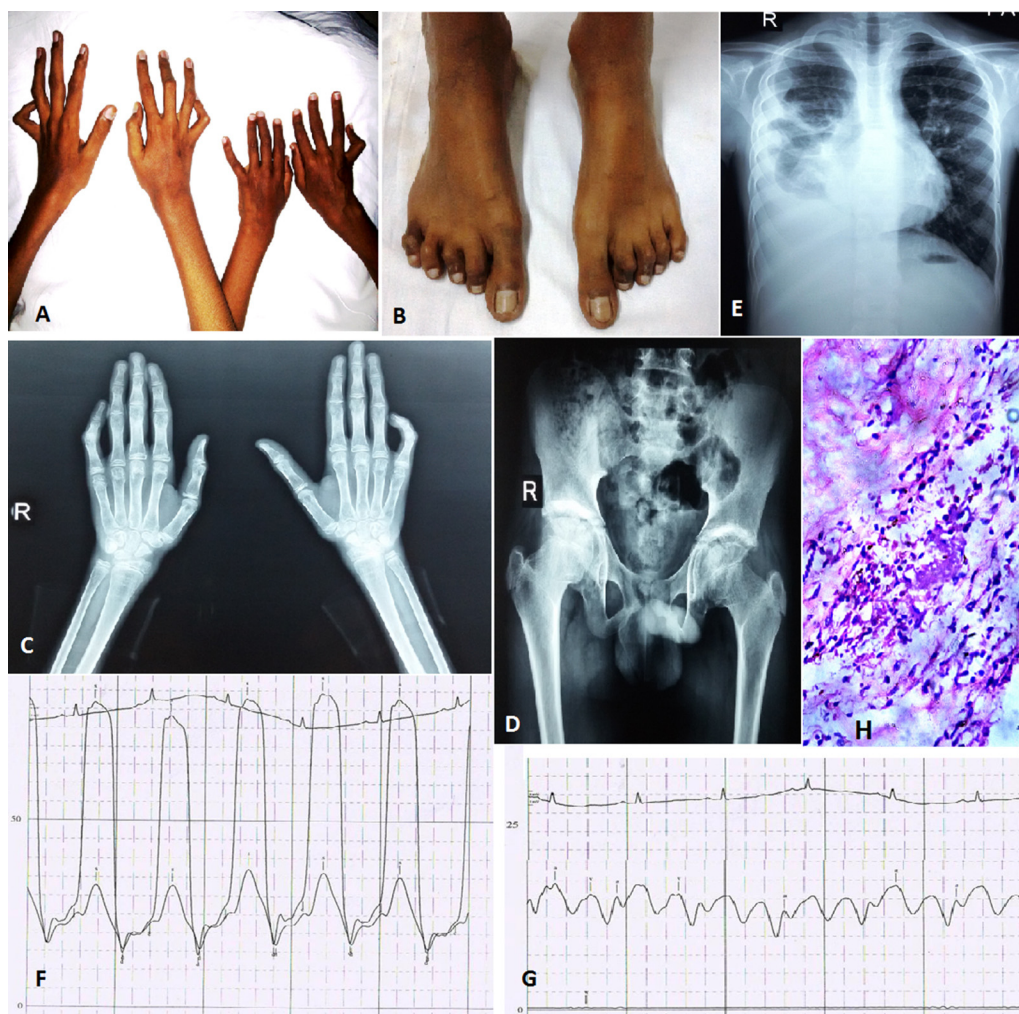


Fig. 1 – Photograph demonstrating (A) bilateral camptodactyly in upper limbs of both the brothers; (B) flexion deformity in toes. Radiographs demonstrating (C) bilateral fifth finger camptodactyly; (D) bilateral hip joint showing short femur neck, flattened acetabulae, and nonerosive arthropathy without periarticular osteopenia and (E) chest radiograph showing right pleural effusion. Pressure tracing showing (F) ventricular interdependence in simultaneous right and left ventricular tracing and (G) prominent x and y descent in jugular venous pressure tracing. Microphotograph of knee synovial biopsy under high magnification (H) demonstrating noninflammatory arthritis and synovial hyperplasia.

confirmed the diagnosis of the clinical diagnosis of camptodactyly-arthropathy-coxa vara-pericarditis syndrome (CACPS) and also revealed a novel homozygous deletion c.884_885delAG in exon 6 of the PRG4 (proteoglycan4) gene. The pedigree analysis clearly demonstrated that both the brothers were harboring the homozygous mutation, the parents were heterozygous, and their unaffected sister did not have this mutation (Fig. 2). Our patient underwent total pericardiectomy and knee synovectomy.

2. Discussion

CACPS (Online Mendelian Inheritance in Man OMIM number 208250) is an autosomal recessive disorder caused by mutations in the PRG4 gene; the locus is assigned to a 1.9-cM interval on human chromosome 1q25-31, encoding for

lubricin, a surface lubricant.¹ Till date, only up to 15 disease-causing mutations in the PRG4 gene have been listed in the Human Genome Mutation Database (www.hgmd.cf.ac.uk).¹ Deletion of two nucleotide bases in our patient lead to a shift in the reading frame and forming a premature stop codon after four amino acids from the position of mutation. This premature termination may lead to shortening of the protein length from 1404 amino acids to 299 amino acids, leading to loss of the functional domain. Although functional studies have not been done to prove this conclusively, the Mutation-Taster software predicted it to be pathogenic.

This mutation is distinct from the mutations identified in the two previously described Indian families.¹ Interestingly, though all these families are unrelated and there was absence of actual consanguinity, inbreeding within small communities was common to all. The husband and wife in all these families hailed from the same village and belonged to the same religion

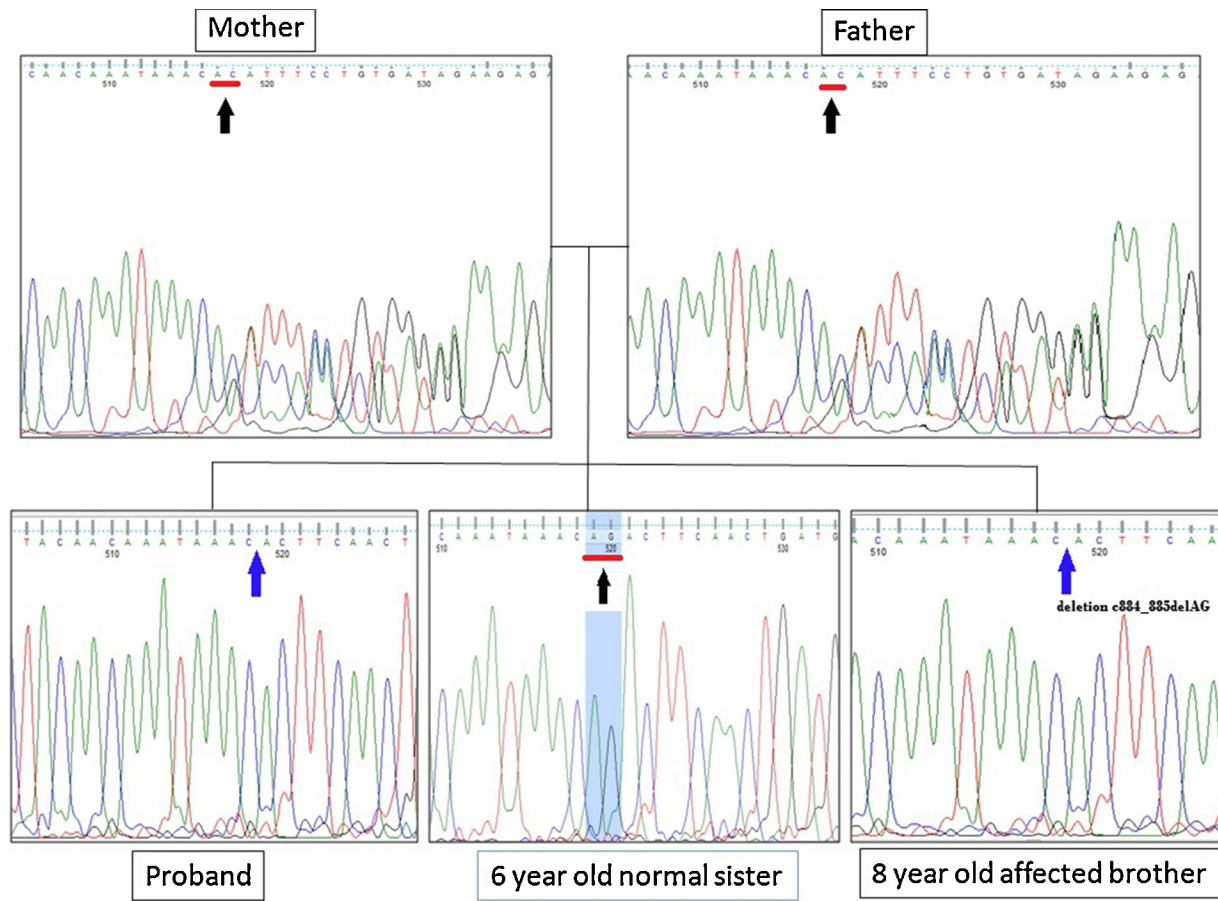


Fig. 2 – Pedigree chart built using partial electropherograms that demonstrate the DNA sequence of the exon 6 of the PRG4 (proteoglycan4) gene. It demonstrates the presence of heterozygous dinucleotides AG deletion mutation (underlined in red with black arrows below in upper panel) in both parents. The presence of dinucleotides AG in the sister has also been similarly highlighted. The absence of dinucleotides AG at the 884_885 position is clearly demonstrated (blue arrows in lower panel). This suggests homozygous nucleotides AG deletion mutation in both the brothers.

and caste. The genetic analysis in our patients also supports the previous reports that mention that only frame shift and nonsense mutations in the PRG4 gene trigger the phenotype.¹

CACP consists of congenital or early-onset camptodactyly (nontraumatic flexion deformity of the PIP joint of one or several fingers), noninflammatory arthropathy with synovial hyperplasia, progressive coxa vara deformity, and noninflammatory pericardial effusion. These patients develop pericarditis (in up to 30% cases) and joint contractures due to insufficient surface lubrication between visceral and parietal pericardium as well as tendon and tendosynovium, respectively. The joint deformities are the principal presenting complaints and it is very rare for patients with CACP syndrome to present primarily with features of constrictive pericarditis as in our case. In CACP, camptodactyly is usually bilateral and is so since birth or early childhood. The degree of contracture may be unequal and progressive. Arthropathy principally involves large joint, such as elbows, hips, knees, and ankles. Synovial fluid analysis reveals noninflammatory findings. Unlike rheumatoid arthritis, histopathologic analysis of synovial tissue reveals pronounced hyperplasia of synovium without evidence of inflammatory cell infiltration

or vasculitis.² CACP can be misdiagnosed as juvenile rheumatoid arthritis. The absence of constitutional symptoms, noninflammatory arthropathy, and characteristic radiological findings helps differentiate between the two.³ Treatment revolves around pericardiectomy, multiple synovectomies, splints, and physiotherapy.

Authors' contribution

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Guarantor: Devendra V. Patil; Milind S. Phadke; Jivtesh S. Pahwa; Ashwin B. Dalal.

Conflicts of interest

The authors have none to declare.

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