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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.

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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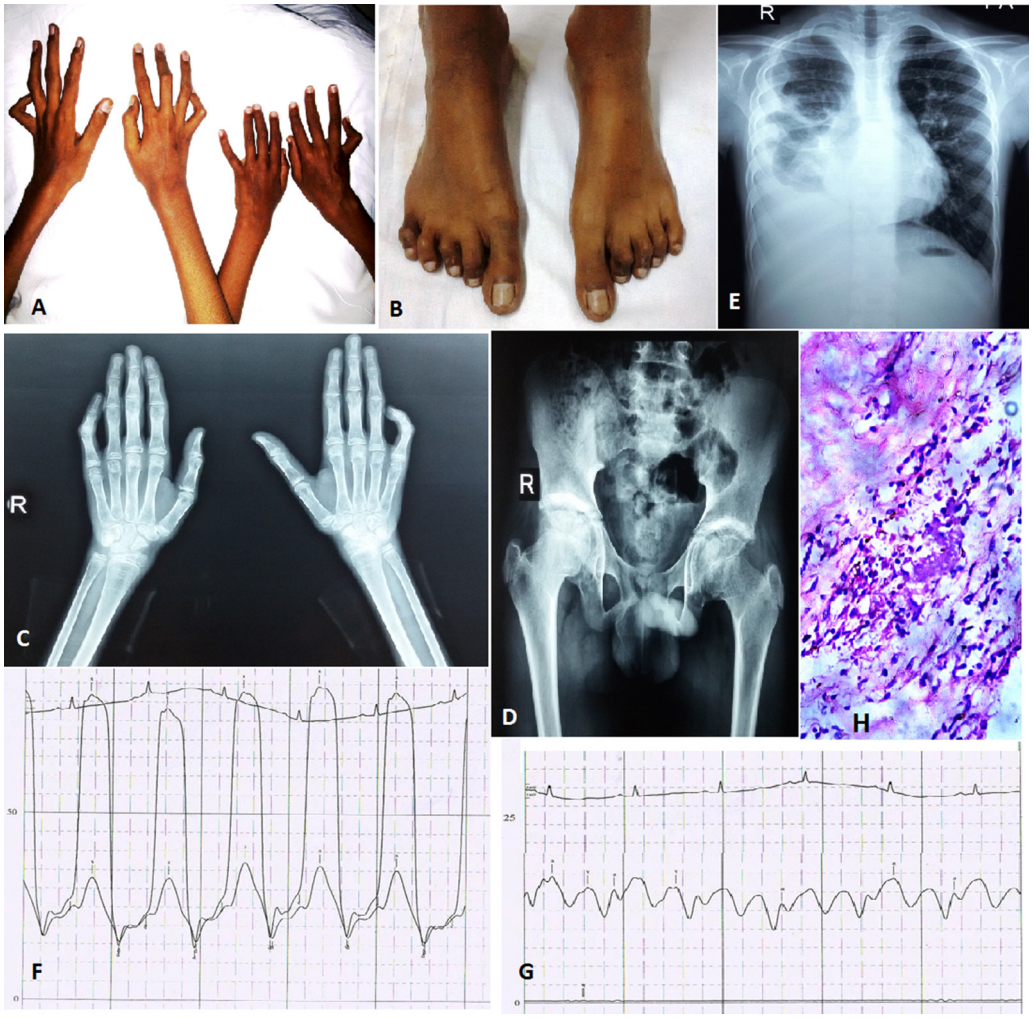

Fig. 1 – Photograph demonstrating (A) bilateral camptodactyly in upper limbs of both the brothers; (B) flexion deformity in toes. Radiographs demonstrating (C) bilateral fifth finger camptodactyly; (D) bilateral hip joint showing short femur neck, flattened acetabulae, and nonerosive arthropathy without 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 (CACP) 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

CACP (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 MutationTaster software predicted it to be pathologenic.

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

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