# Jammed joints and constricted heart: The science of tribology and missing lubricin. A case report on camptodactyly-arthropathy-coxa vara-pericarditis syndrome

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## ABSTRACT

**An autosomal recessively inherited noninflammatory arthropathy known as camptodactyly, arthropathy, coxa vara, and pericarditis (CACP) syndrome was discovered in 1999. It is distinguished by synoviocyte hyperplasia and subcapsular fibrosis of the synovial capsule, which results in a shortage of lubricin production. The resulting lack of joint lubrication induces increased mechanical stress, causing progressive deformities that become evident with weight-bearing and heightened joint activity. Animal models with a lubricin gene knock-out display similar traits, underscoring the impact of mechanical stress on disrupting type II collagen on the articular surface. The gradual development of pericarditis and constriction often results in misdiagnosis as juvenile rheumatoid arthritis with cardiac involvement, but the defining feature remains the noninflammatory nature of the disease. Early recognition is pivotal, as interventions such as pericardiectomy and recombinant human lubricin hold promise for altering the disease's natural course. In our familial case of CACP, two siblings exhibited distinct phenotypic variations – one with fibrosis-dominant features and pericardial constriction and the other displaying synovial hyperplasia without pericardial involvement.**

**Keywords:** Camptodactyly, arthropathy, coxa vara, pericarditis syndrome, constrictive pericarditis, lubricin deficiency, pericardiectomy

## INTRODUCTION

An autosomal recessive, noninflammatory arthropathy known as camptodactyly, arthropathy, coxa vara, and pericarditis (CACP) syndrome was discovered in 1999. It is distinguished by synoviocyte hyperplasia and subcapsular fibrosis of the synovial capsule, which results in a shortage of lubricin production.[1] The lack of lubrication of the joints leads to increased mechanical stress on the joints and progressive deformity. The joints appear normal at birth, and the characteristics of the syndrome appear gradually as weight-bearing and increased joint activity occurs. Animal models with lubricin gene knock-out develop similar features with load bearing with disruption of type-II collagen on the articular surface and increased activity of caspase-3, indicative of mechanical stress.[2] The pericarditis and the constriction also develop gradually, and these children frequently are misdiagnosed as juvenile rheumatoid arthritis with cardiac involvement. The defining feature, however, is the noninflammatory nature of the disease,

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with no clinical or laboratory evidence of inflammation. Early clinical recognition is important as pericardiectomy and recombinant human lubricin have the potential to alter the natural history of the disease.[3]

We present cases of CACP syndrome in a family where the siblings' phenotypic presentations differed. One youngster exhibited restricted joint spaces and pericardial constriction, whereas the other had joint swelling but no pericardial involvement.

## CASE REPORT

A 7-year-old boy born of a consanguineous marriage had undergone surgery for flexion deformity of the hands at 2 years of age. Subsequently, he had difficulty sitting cross-legged, could not squat, and walked with an unsteady gait.

He had been under follow-up at multiple clinics with a history of abdominal distension since he was 5 years of age and pedal edema for 2 months. Cardiac examination demonstrated elevated jugular venous pulse with no inspiratory fall, prominent x and y descents, a bilateral dull note on chest percussion, muffled heart sounds on auscultation, and gross hepatomegaly.

He underwent two-dimensional echocardiography suggestive of mild left ventricular dysfunction and moderate pericardial effusion with thickened pericardium. A provisional diagnosis of constrictive pericarditis was made. Laboratory tests showed normal complete blood counts, C-reactive protein, and erythrocyte sedimentation rate. Rheumatology workup done elsewhere, including antinuclear antibodies, was negative. In view of gross hepatomegaly and poor pericardial windows for planning pericardiocentesis, the child was initially managed with antifailure medications – milrinone infusion and diuretics. The abdominal distension reduced over the next 2 days, and the child showed symptomatic improvement. A repeat echocardiogram demonstrated persistent pericardial effusion; hence, he was planned for surgical pericardiocentesis and pericardiectomy.

He was taken for pericardiectomy through median sternotomy. Pericardial pressure at induction was 25 mmHg, which dropped to 12 mmHg following pericardiectomy. While inflammatory constriction predominantly affects the cavoatrial junctions and atrioventricular grooves, this child had involvement in the anterior and inferior surfaces of the pericardium [Figure 1]. He also underwent pericardial window creation and drainage, after which 200 ml of pericardial fluid was aspirated. Pleural fluid analysis, adenosine deaminase levels, rheumatoid factor, and polymerase chain reaction test for tuberculosis suggest noninflammatory effusion. Postoperatively, the child was hemodynamically stable, and pericardial drains were removed the next day.

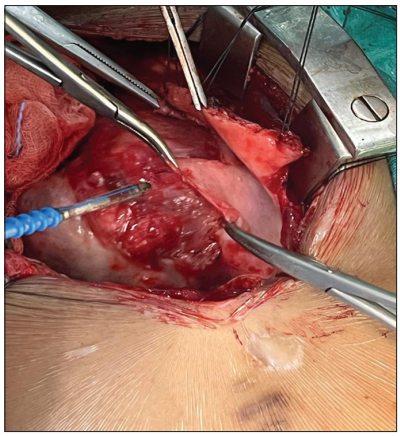

**Figure 1: Intraoperative photograph showing noninflammatory pericardial constriction; notice the constricting visceral pericardium is being removed and the potential space between the visceral and parietal pericardium**

A biopsy (2 × 1 flattened tissue bit) showed mild fibrosis of the pericardium with a few thin-walled congested capillaries. There was no vegetation, granulomas, or deposits in the section.

As a part of the genetic workup, clinical exome sequencing was done. He was detected positive for pathogenic variant PRG4 (ENST00000445192.7) gene located on Exon 7 variant c. 983insT (p. Ala329GlyfsTer2), causative for autosomal recessive CACP syndrome.

His younger sibling (5 years old) is beginning to show hand deformities and an inability to sit cross-legged. He has no features of pericardial constriction at the time of reporting, and his joints show more features of synovial hyperplasia than fibrosis, as noticed in the index case [Figures 2a-c]. He also showed the same genetic mutation.

## DISCUSSION

CACP is a genetic syndrome characterized by camptodactyly (contractures of proximal interphalangeal joints), arthropathy, coxa vara (which is a hip deformity where the angle between the head and shaft of the femur is reduced to <120° with shortening and inability to sit cross-legged) and pericarditis. The protein involved has been named variously as lubricating glycoprotein 1, superficial zone proteoglycan (PRG), the 32 kDa amino terminal end can stimulate platelet growth, and the gene has also been called megakaryocyte stimulating factor gene, showing the relation between platelets and joint surfaces.[4] Lubricin is a 227 kDa surface active glycoprotein produced by synovium. This coats the cartilage and prevents cell and protein adhesion. This glycoprotein is responsible for making the joint movement essentially frictionless. The coefficient of friction of a normal joint is < 0.01, which is better than the best achieved artificially with Teflon (0.04). Artificial joints have low wear, but their friction is higher than normal joints. Trauma, inflammatory arthropathies, osteoarthritis, and genetic syndromes finally act through

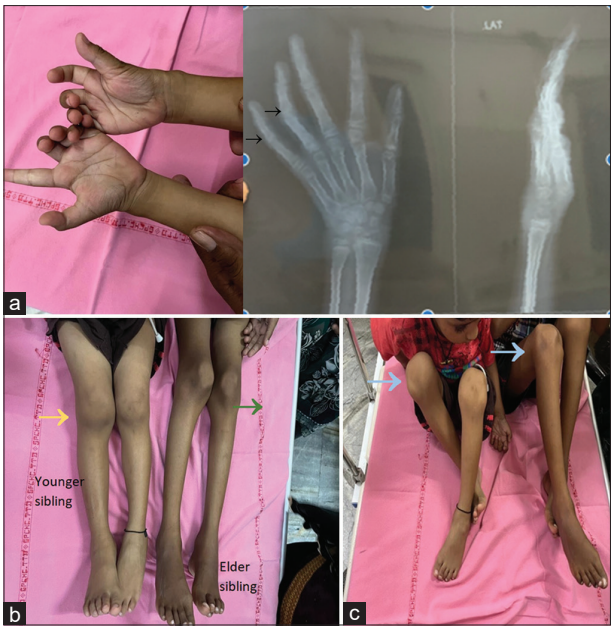


**Figure 2: (a) Figure depicting camptodactyly – joint deformity, (arrow marks are camptodactyly) (b) Knee joint showing the elder sibling (having pericardial constriction) having predominantly synovial fibrosis (green arrow) and the younger sibling who has no constriction at the time of writing having predominantly synovial hyperplasia/boggy knee joint (yellow arrow), (c) Coxa vara – the inability to sit cross-legged by both siblings (blue arrow)**

lubricin to exert its influence on the joint surfaces. Lubricin was discovered by David Swann in 1975, and even after digestion with hyaluronidase, the joint fluid had near-normal lubricating properties.[4]

The presence of lubricin/PRG-4 has been shown in a human pericardial fluid produced by pericardial mesothelial cells. It can potentially reduce adhesion formation primarily due to fibrosis induced by cardiomyofibroblast activation. However, further studies are required, and lubricin has not yet been therapeutically used.[5]

Inflammatory pericardial constriction occurs after an exudative stage, unlike noninflammatory constriction. These exudates tend to gravitate toward the region of the superior vena cava-right atrial junction and in the atrioventricular grooves. In these areas, relieving the constriction and removing the thick postexudative fibrotic material is important and sometimes challenging. Unlike this, noninflammatory constriction, as in our case, has a uniform thickness of the adherent pericardium, as there is no stage of exudation before the occurrence of constriction.

Recombinant human lubricin can potentially reduce and prevent the progressive joint damage these children endure, resulting in the requirement for joint replacement in their late 20s and 30s. Work on these glycoproteins also has the potential to have widespread ramifications in the clinical and industrial arena. Tribology (Greek–tribo means "rub") is the science of interacting surfaces in relative motion. The wear and tear induced by friction majorly contributes to power and energy loss. This science, applied in transport and power generation, is now applied to studying biological surfaces to create artificial polymers that mimic natural PRGs. Biotribology is a relatively new branch of biomechanics that studies friction in biological systems.[6]

Through this case report, we would like to draw attention to noninflammatory constriction of the heart and joint deformities caused by loss of the PRG4/lubricin gene. Although recombinant human lubricin has been available, we have not been able to procure it at the time of writing, and it is not yet approved for intra-articular/clinical use. We also see that this glycoprotein has the potential to reduce postcardiotomy adhesions, and a biomimetic product developed as a product of biotribology research could result in the development of a lubricant with widespread clinical and industrial applications.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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