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## EDITED BY

Ozgur Kasapcopur,  
Istanbul University-Cerrahpasa, Turkey

## REVIEWED BY

Oya Koker,  
Istanbul University, Turkey  
David Piskin,  
Lawson Health Research Institute, Canada

## \*CORRESPONDENCE

Maria Vincenza Mastrolia  
maria.mastrolia@unifi.it

## SPECIALTY SECTION

This article was submitted to Pediatric  
Rheumatology, a section of the journal  
Frontiers in Pediatrics

RECEIVED 01 July 2022

ACCEPTED 04 November 2022

PUBLISHED 05 December 2022

## CITATION

Maniscalco V, Pizzetti C, Marrani E, Perrone A,  
Maccora I, Pagnini I, Artuso R, Simonini G and  
Mastrolia MV (2022) Pseudo-rheumatic  
manifestations of limping: Camptodactyly–  
arthropathy–coxa vara–pericarditis syndrome:  
Single case report and review of the literature.  
*Front. Pediatr.* 10:981938.  
doi: 10.3389/fped.2022.981938

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# Pseudo-rheumatic manifestations of limping: Camptodactyly–arthropathy– coxa vara–pericarditis syndrome: Single case report and review of the literature

Valerio Maniscalco<sup>1</sup>, Camilla Pizzetti<sup>1</sup>, Edoardo Marrani<sup>2</sup>,  
Anna Perrone<sup>3</sup>, Ilaria Maccora<sup>2</sup>, Ilaria Pagnini<sup>2</sup>,  
Rosangela Artuso<sup>4</sup>, Gabriele Simonini<sup>5</sup> and  
Maria Vincenza Mastrolia<sup>2\*</sup>

<sup>1</sup>Department of Health Sciences, University of Florence, Firenze, Italy, <sup>2</sup>Rheumatology Unit, Meyer Children's University Hospital, Firenze, Italy, <sup>3</sup>Radiology Unit, Meyer Children's University Hospital, Firenze, Italy, <sup>4</sup>Medical Genetics Unit, Meyer Children's University Hospital, Firenze, Italy, <sup>5</sup>NEUROFARBA Department, University of Florence, Rheumatology Unit, Meyer Children's University Hospital, Firenze, Italy

Camptodactyly–arthropathy–coxa vara–pericarditis (CACP) syndrome is a rare genetic disease characterized by tetrad camptodactyly, noninflammatory arthropathy, coxa vara deformity, and pericardial effusion. Arthropathy typically affects large joints and presents with joint swelling in the absence of other signs of inflammation. We described the case of a girl affected by CACP syndrome caused by a novel compound heterozygous variant in proteoglycan 4 gene (c.2831\_2832insT; c.3892C>T) and associated with temporomandibular involvement. The patient received treatment with intra-articular hyaluronic acid injections, which presented rapid but transient improvements of pain and range of motion. A literature review of previously reported CACP patients has been performed. Of the patients, 69.2% (101 out of 146) were Middle Eastern, and 65.7% (96) were consanguineous. The median age of onset was 24 months (interquartile range of 12–36 months), and median age of diagnosis was 96 months (interquartile range of 48–156 months). Arthropathy was always present, mainly involving hips (95.2%), knees (92.4%), wrists (87.7%), elbows (79.5%), and ankles (57.5%). Camptodactyly and pericardial effusion were described, respectively, in 97.3% (142) and 15.1% (22) of patients. The main radiological findings were coxa vara (95.2%), femoral changes (64.4%), intraosseous cysts (14.4%), and bone erosion (5%). Of the patients, 32.9% (48) had received a previous juvenile idiopathic arthritis diagnosis. CACP syndrome can be easily misdiagnosed with juvenile idiopathic arthritis. A prolonged lack of response to immunosuppressive therapy associated with typical clinical and radiological features should prompt consideration of this rare syndrome.

## KEYWORDS

CACP syndrome, limping in children, temporo mandibular joint, juvenile idiopathic arthritis, coxa vara

## Introduction

Camptodactyly–arthropathy–coxa vara–pericarditis (CACP) syndrome is a genetic condition with autosomal recessive inheritance due to various mutations leading to the inactivation of the proteoglycan 4 (PRG4) gene on chromosome 1 (1). CACP syndrome has been found in different ethnic populations. Due to its rarity, CACP syndrome is probably underdiagnosed, making it difficult to estimate its real prevalence. PRG4 gene encodes for lubricin, a secreted glycoprotein produced by synoviocytes and chondrocytes, which lubricates the articular joints. Clinical manifestations of CACP syndrome can vary, even within families. The syndrome clinically manifests with congenital or early onset camptodactyly and noninflammatory arthropathy characterized by synovial hyperplasia and clear synovial fluid, low in cell count (2). Progressive coxa vara deformity and/or noninflammatory pericardial or pleural effusions are typical manifestations (3). CACP syndrome is commonly characterized by arthropathic involvement of large joints, such as elbows, hips, knees, and ankles (4). Typically, no temporomandibular joint (TMJ) involvement has been reported. Differential diagnosis with juvenile idiopathic arthritis (JIA) is challenging at disease onset, leading to frequent delays in the identification of the condition and prolonged ineffective therapeutic courses with immunosuppressive drugs. The absence of clinical and biochemical signs of inflammation and peculiar radiological features are the primary elements of a proper diagnosis. A prompt recognition may prevent the patient's exposure to unnecessary therapies with immunomodulatory drugs. To date, no specific treatment is available, and the therapeutic management is symptomatic.

In this regard, we report the first CACP syndrome case with TMJ arthropathy and we describe a novel compound heterozygous variant in the PRG4 gene. A literature review of previously reported CACP patients was also performed.

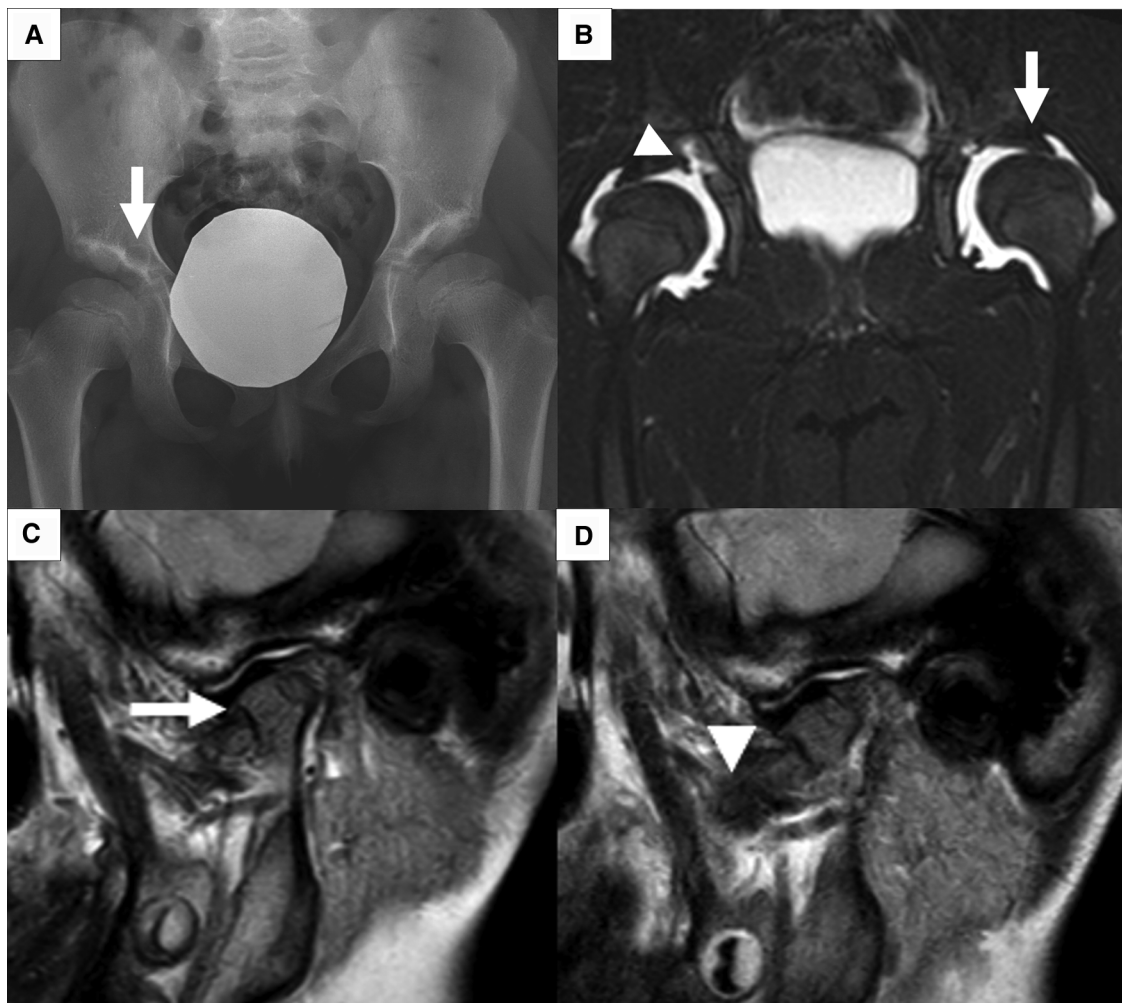
## Case report

A 4-year-old girl was referred to the Rheumatology Unit of Meyer Children's University Hospital, Florence, in June 2015 because of asthenia, knee pain following trivial effort, and an unsteady gait since she started walking at 18 months of age. She was the first child of nonconsanguineous Caucasian parents with no relevant family history, except for autoimmune thyroiditis in the mother. Past medical history was unremarkable. Physical examination revealed bilateral arthritis of the ankles, knees, metacarpophalangeal and proximal interphalangeal joints, camptodactyly, and genu valgus. Laboratory tests displayed normal values of blood

count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and negativity of antinuclear antibodies (ANA). The girl, diagnosed with polyarticular JIA, started subcutaneous methotrexate (15 mg/m<sup>2</sup>/week) and underwent intra-articular steroid injections in ankles and knees. She continued the multidisciplinary follow-up with clinical, laboratory, and instrumental evaluations. The patient never developed uveitis in serial ophthalmologic examinations, and inflammatory laboratory markers were always negative. During the evaluations, radiological scans of different skeletal segments were performed. Pelvis and lower limbs x-ray in weight-bearing position (October 2016) showed coxa vara and stubby and short femoral necks; and wide acetabulum with joint space enlargement, acetabular cyst, and signs of erosion (Figure 1). Spine radiography (November 2016) reported a mild reduction in lumbar lordosis and left convex thoracolumbar scoliosis (Figure 2). Bone densitometry (October 2016) revealed normal bone mineral density values. Pelvis and knee magnetic resonance imaging (MRI) (December 2016) identified synovial hyperplasia accompanied by joint effusion and bone erosions in both the coxofemoral joints and knees (Figure 1). Ankle-foot MRI (December 2016) showed bilateral effusion in the tibiotarsal joints.

Due to persistent disease activity, the girl underwent several intra-articular steroid injections and oral corticosteroid courses. In addition, different treatments with biological drugs were attempted but proved ineffective. In December 2015, the patient started etanercept; then, due to lack of efficacy, on April 2016, etanercept was replaced by abatacept together with an oral course of corticosteroid (August 2016–September 2016). In January 2017, because of the occurrence of pseudotumor cerebri, methotrexate was interrupted. In February 2017, after abatacept discontinuance, tocilizumab was started along with an oral steroid course until October 2017 without a beneficial response. Subsequently, a partial improvement was only observed with oral and intra-articular steroid administration.

Due to her peculiar clinical features, with no disease remission and no response to treatment, trios whole exome sequencing (WES) was performed in September 2018. All identified variants have been classified as potentially pathogenic or benign variants in accordance with the interpretation guidelines of the American College of Medical Genetics (ACMG) (5). The analysis revealed a compound heterozygous mutation in the PRG4 gene (c.2831\_2832insT; c.3892C>T); both mutations were point nonsense-mutations not previously reported in the literature. The first mutation c.2830\_2831insT, inherited from the mother, caused the insertion of one thymine nucleotide in exon 7, producing a premature truncation of the protein's 34 amino acids downstream to codon 944 (*p*.Thr944IlefsTer34). The second variant c.3892C>T, inherited from the father, caused the substitution of glutamic acid in position 1,298 with a stop



**FIGURE 1**

Main radiological feature. (A) X-ray of the pelvis shows flattening of femoral heads, stubby and short femoral neck, and bilateral coxa vara. Acetabular roofs are irregular with sclerotic surfaces and radiolucent lytic areola (*arrow*) as per acetabular cyst. (B) Short tau inversion recovery sequence of pelvis MRI shows effusion at coxofemoral joints resulting in partial femoral head dislocation (*arrow*); acetabular cyst connected with joint effusion (*arrowhead*). (C, D) MRI of left TMJ in close and open mouth shows little/no excursion of the condyle. The condyle has an enlarged and flattened morphology (*arrow*) with irregular surface. A slim layer of intra-articular effusion is present. The articular disc (*arrowhead*) has normal morphology and signal.

codon in exon 11. According to ACMG guidelines, both variants were classified as likely pathogenic. To date, stop mutations and small insertions or deletions in PRG4 gene are described in the literature as associated with CACP syndrome (OMIM#208250). Our patient has never experienced pericarditis, but considering these genetic results, a cardiological evaluation was performed resulting normal. Since the diagnosis (June 2019), the patient received monthly intra-articular injections of hyaluronic acid in knees and ankles and started a tailored rehabilitative program with a team of rheumatologists, physiatrists, and physiotherapists. The girl referred reduced pain soon after every infiltration with an improvement in the range of motion. However, this effect was transient since the pain returned after 3 weeks from each

hyaluronic acid injection. In September 2019, the patient reported a left-sided TMJ pain associated with an impairment in the opening of the mouth. TMJ MRI revealed bilateral anterior dislocation of the articular disc more evident on the left side, irregular and flattened condyle articular surface with erosive images on the posterior face (**Figure 1**). Slim intra-articular fluid and thickened posterior tissues were seen on the left side. After orthodontic evaluation, a tailored appliance was later pursued with prompt reduction of mandibular pain.

Currently, the girl continues her multidisciplinary follow-up through an integrated physiatric, physiotherapeutic, and rheumatologic management. Pain and reduced range of motion had improved but persisted. No adverse events were reported.



**FIGURE 2**  
Radiography of the spine. X-ray of the spine shows on the coronal plane the presence of wide-radius convex left curvature of the thoracolumbar vertebrae.

## Discussion

CACP syndrome is a rare autosomal recessive condition caused by the mutation of the PRG4 gene. The syndrome was first described in 1986 by Bulutlar et al. and is characterized by tetrad camptodactyly, noninflammatory arthropathy, coxa vara deformity, and pericardial effusion (6). The arthropathy typically starts during childhood and involves large joints, such as knees, wrists, elbows, ankles, and hips, while shoulder and spine involvement are

described sporadically (7, 8). We reported the first case of temporomandibular involvement in CACP syndrome. A literature search was carried out using PubMed/Medline and Embase databases. English language reports of CACP syndrome reported from 1986 until 1 April 2022 were retrieved and analyzed. Twenty-eight studies (12 case series, 11 case reports, 5 retrospective multicenter cohort studies) had previously described CACP patients, recording a total of 146 patients, 94 males and 52 females (Table 1) (2–4, 6–30). Double-reported patients were excluded from the total account (2, 11, 15).

CACP syndrome is a rare clinical condition, and its real prevalence is still unknown. Our patient was a Caucasian girl with nonconsanguineous parents. However, this genetic disorder has been observed in patients of different ethnicities, especially in Middle Eastern families, and is frequently associated with consanguinity. As regards the previously reported cases, 69.2% (101) of patients were of Middle Eastern descents (41 from Saudi Arabia, 39 from Turkey, 16 from north Africa, 4 from the United Arab Emirates, and 1 from Jordan), 16.4% (24) were Caucasian (10 from Italy, 4 from France, 2 from Albany, 2 from Netherlands, 2 from England, 2 from United States, 1 from Ireland, and 1 from Switzerland), 13.7% (20) were from south Asia (11 from India, 9 from Pakistan), and 1 from east Asia (Korea) (2–4, 6–30). Consanguinity was reported in 65.7% (96) of CACP cases (2, 3, 15–17, 23, 25, 27–29).

The articular involvement first appears in early childhood, leading to an incomplete clinical picture. Moreover, polyarticular arthropathy can mimic JIA, often leading to a delayed diagnosis and inappropriate treatments.

Our patient presented articular symptoms at 18 months of age, received a mistaken diagnosis of polyarticular JIA at 4 years of age and received a final diagnosis of CACP when she was 8 years old. The median age of symptom onset in CACP patients is 24 months (interquartile range, IQR, 12–36 months) with a median age of diagnosis of 96 months (IQR 48–156 months); one-third of them (32.9%, 48 patients) were diagnosed as JIA (2–4, 6–30).

Our girl presented camptodactyly, hip, knee, and ankle arthropathy complaining pain after trivial efforts. In addition, subsequent temporomandibular involvement was observed. Polyarticular arthropathy represents a constant finding in CACP syndrome, mainly affecting the large joints bilaterally, the hips (95.2%), knees (92.4%), wrists (87.7%), elbows (79.5%), and ankles (57.5%). Patients typically present joint swelling without any other sign of inflammation. Pain was reported in only one-fifth of patients (35) and 37% (54) presented a limited range of motion. Camptodactyly, usually bilateral and congenital, affected 97.3% (142) of patients, although it may appear in the first months of life (2–4, 6–30). Pericardial and pleural effusions were described in 15.1% (22)

TABLE 1 CACP syndrome patients reported till date.

Publication	Country	Number of patients (M/F)	Consanguinity	Mutations reported	Age of diagnosis (months)	Clinical features			Therapy	
						Camptodactyly	Large joint arthropathy	Coxa vara		
Bulutlar 1986	Turkey	4 (0/4)	4	NA	7–16	3	4	4	2	NA
Laxer 1986	Canada	1 (1/0)	1	NA	60	1	1	0	1	NSAID, intra-articular steroid, physiotherapy
Bahabri 1994	Saudi Arabia	3 (1/2)	0	NA	84–156	3	3	3	0	Oral gold, physiotherapy
Bahabri 1998 <sup>a</sup>	Saudi Arabia	8 (5/3)	1	NA	24–156	8	8	7	2	Surgery (femoral osteotomy, repair of hallux valgus deformity)
Favre 2000	Europe, North Africa	12 (10/2)	8	NA	24–180	12	12	10	0	Surgery (6 patients)
El-Garf 2003	Egypt	10 (7/3)	10	NA	36–204	10	10	9	0	NA
Choi 2004	Korea	1 (1/0)	0	NA	120	1	1	0	1	NA
Offiah 2005	United Kingdom	1 (1/0)	0	NA	156	1	1	1	1	NSAID, methotrexate, systemic steroids, anti-TNF
Alazami 2006	Saudi Arabia	7 (5/2)	4	c.3139_3140delAA c.4078A>T c.923_924delAA c.3125_3128delGAGT c.3276_3277delAA	18–60	7	7	5	0	NA
Al-Mayouf 2007 <sup>a</sup>	Saudi Arabia	16 (11/5)	16	NA	44	16	16	14	2	NA
Basit 2011	Pakistan	9 (8/1)	9	c.2816_2817delAA	NA	9	9	9	0	NA
Akawi 2012	United Arab Emirates	4 (2/2)	4	c.1320dupC	60–144	4	4	4	0	Surgery (correction of flexion contracture)
Murphy 2012	United States	2 (1/1)	0	NA	168–204	2	2	2	1	Intra-articular steroid, surgery (hip arthroplasty)
Albuhairan 2013 <sup>a</sup>	United Arab Emirates	22 (15/7)	16	NA	12–168	22	22	22	2	NSAID, methotrexate (10 patients), systemic steroid
Emad 2013	Egypt	1 (0/1)	0	NA	96	1	1	1	1	NA
Kakkar 2013	India	1 (0/1)	1	NA	39	1	1	1	1	NA
Ciullini Mannurita 2014	Italy, Albania, Netherlands	13 (8/5)	0	c.2754_2758delGACAA c.3636p3A4G c.3894_3898delGGTTA c.1982_1983delCT c.3648C4A c.2153delA	1–180	10	13	11	4	NA
Nandagopalan 2014	India	3 (2/1)	0	c.2883_2886delAAGA c.2883_2886delAAGA 2645_2646delGA	60–192	3	3	0	0	NA

(continued)

TABLE 1 Continued

Publication	Country	Number of patients (M/F)	Consanguinity	Mutations reported	Age of diagnosis (months)	Clinical features			Therapy
						Camptodactyly	Large joint arthropathy	Coxa vara	
Tasar 2014	Turkey	1 (1/0)	0	NA	84	1	1	1	Physiotherapy, surgery
Madhusudan 2016	India	2 (2/0)	0	NA	48–96	2	1	2	NSAID, physiotherapy
Patil 2016	India	2 (2/0)	0	NA	108–156	2	2	1	NA
Peters 2016	Netherlands	1 (0/1)	1	c.1290de	120	1	1	1	Pericardiectomy, cotrimoxazole prophylaxis, immunoglobulin supplement iv
Vutukuru 2016	India	1 (1/09)	0	NA	96	0	1	1	NA
Yilmaz 2017	Turkey	35 (20/15)	28	c.1194delC c.73934del c.3276_3277delAA c.4101C>G c.3276_3277delAA c.1192delC c.1911delT c.2215A>T c.1910_1911delCT c.2837_2838delAA c.849delA c.4101C>G	12–624	35	35	3	Surgery
Al-Mayouf 2017 <sup>a</sup>	United Arab Emirates	6 (3/3)	NA	NA	NA	NA	6	NA	Medical synovectomy (radiosynovectomy) using radioactive isotope with no benefit
Albtoush 2018	Jordan	1 (0/1)	0	NA	132	1	1	1	Surgery (tendon-lengthening of fingers)
Kisla Elkinci 2021	Turkey	3 (0/3)	3	c.538C>T, c.1194delC, c.1194del	36–156	3	3	1	NSAID, methotrexate, anti-TNF, physiotherapy, surgery
Johnson 2021	India	2 (1/1)	1	c186275834dupT p.Ser1085Ter	144–156	2	2	2	NA

NSAID, nonsteroidal anti-inflammatory drugs; anti-TNF: anti-tumor necrosis factor; NA: not available.

<sup>a</sup>Studies that included patients who have been already reported.

and 4.8% (7) of cases, respectively (2, 3, 8, 9, 12, 13, 15, 18, 19, 22, 23, 25, 27, 30). Other associated conditions have been reported, although they are certainly not related to this syndrome. Two patients presented hepatomegaly and ascites, and two had constrictive pericarditis complicated by portal hypertension and protein-losing enteropathy in one case (12, 23, 25, 27, 30). Congenital cataract was observed in one patient (17).

As with our girl, all CACP patients had normal inflammatory marker values (i.e., ESR and CRP) in contrast to polyarticular JIA children, in which they are typically elevated.

Concerning the radiological features, our case presented characteristic CACP findings: the pelvic x-ray showed coxa vara deformity associated with femoral changes (stubby and short femoral necks) and increased joint space secondary to joint effusion. The pelvis and knee MRI reported synovial hyperplasia with joint effusion and bone erosions. An MRI of the TMJ showed intra-articular fluid associated with signs of bone erosion and thickening of periarticular soft tissue. Moreover, the patient presented with left convex thoracolumbar scoliosis.

In this regard, coxa vara deformity was almost always present in CACP patients (95.2%) associated with femoral changes (e.g., short femoral neck, flat and irregular femoral head) in more than half of cases (64.4%) (2–4, 7, 8, 13, 16–18, 21, 22, 24, 25, 27). Bone cysts, secondary to joint capsule herniation, are characteristic of the syndrome and occasionally reported (14.4%) (2, 4, 7, 9, 13, 21, 24, 25, 28, 29). Osteoporosis was observed in 36.3% of cases (53), while spine abnormalities (e.g. kyphosis, lordosis, scoliosis) were described in 24.7% of cases (36) (2–4, 12, 16, 20, 23, 25, 27). Signs of bone erosion are rarely described (5% of cases), as in our patient (7, 19). Conventional radiographs also revealed periarticular soft tissue swelling and osteopenia (15). Imaging findings of articular effusion and synovial hyperplasia were reported in 40.4% patients (59) at ultrasound sonography or MRI (2, 4, 7–9, 12, 13, 17, 19, 20, 24, 28, 29).

The synovial tissue histology, performed in 20 patients, revealed little or no mononuclear infiltration with typical multinucleated giant cells (CD68+) infiltration. Synovial fluid was always noninflammatory (clear, honey-colored, and low in cell count) (3, 4, 9, 10, 12, 13, 22, 23, 28).

The patients received several immunosuppressive therapies, including biologic agents, without any significant improvement, and multiple systemic and intra-articular corticosteroid courses with only transient relief. Indeed, CACP syndrome typically shows no response to immunomodulatory treatment with only symptomatic therapy. In some cases (eight patients), physiotherapy allowed a recovery of range of motion and a reduction in joint pain (9, 21, 24, 29).

Because CACP syndrome is caused by the mutation of the PRG4 gene that encodes for lubricin, a proteoglycan secreted by synoviocytes and chondrocytes acts as a lubricant in joint space and protects cartilage surfaces (31). Hyaluronic acid, similar to lubricin, may supply joint lubrication and protect the cartilage from mechanical degradation (32). Intra-articular hyaluronic acid is used in the elderly with osteoarthritis and has been shown to have beneficial effect on pain and joint function without presenting safety risk (32–34). Starting from these considerations, we decide to treat our patient with intra-articular hyaluronic acid injections with partial benefit. The girl presented with pain reduction soon after each infiltration and an improvement in range of motion, although with a transient effect of 3 weeks. A surgical approach has been attempted with variable effects in 29 CACP cases (19.9%). Four patients underwent surgical corrections of flexion contractures of fingers with success, and two patients underwent hip arthroplasty with pain relief and improved joint function (17, 18). Six children underwent radiosynovectomy with no benefit (26). Finally, one patient underwent right femoral osteotomy and surgical repair of hallux valgus deformity, and two patients underwent pericardiectomy (9, 23, 28). In 14 cases, the type of surgical intervention was not reported (3, 25, 29).

In conclusion, CACP syndrome is a rare disorder that can be incorrectly framed as JIA causing a delay in diagnosis and inappropriate treatment with immunosuppressive drugs including biologic agents. The association with camptodactyly and coxa vara (almost always present), the involvement of large joints, and the absence of clinical and biochemical inflammatory signs are hallmarks of the syndrome. These findings associated with a prolonged lack of response to immunosuppressive therapy should induce the physician to reconsider an earlier JIA diagnosis. Typical radiological features identified by x-ray and ultrasonography can support the diagnosis. Synovial pathology may be helpful even if not mandatory. Genetic testing definitively confirms the diagnosis and allows for genetic counseling for the family members. Currently, no specific treatment is available, and therapeutic management is only symptomatic and requires a multidisciplinary approach.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual (s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

## Author contributions

GS, EM, and MVM conceptualized the study. VM wrote the first draft. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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