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Case Report
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Camptodactyly-Arthropathy-Coxa Vara-Pericarditis Syndrome: Important Differential for Juvenile Idiopathic Arthritis: A Report of Ten Cases

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ABSTRACT

The main objectives of this study is to describe the clinical features in patients with campatodactyly-arthropathy-pericarditis-coxa vara syndrome (CACP); highlight the important clinical and radiological features that allow differentiation of CAPA from juvenile idiopathic arthritis; and to recognize the importance of differentiating CAPA from juvenile idiopathic arthritis.

Ten affected children with CAPA from five different families following in pediatric rheumatology clinic, Tripoli children hospital underwent complete history, complete clinical examinations, laboratory and radiological investigations and histological study of synovium in one case.

All cases were Libyans, age 6 to 19 years, 3 cases were male and 7 cases were female. Campatodactyly developed at birth in 3 cases, 5 cases developed campatodactyly before the age of 5 years and 2 cases do not have it. Coax vara was present in 5 cases, carditis was detected in 3 cases with varying severity, and arthropathy was present in all cases with multiple joint involvements. Consanguinity was positive in 8 cases, 2 cases have no consanguinity but they came from the same village. Family history of same disease was positive in all cases. All the cases were diagnosed wrongly as acute rheumatic fever or juvenile idiopathic arthritis and treated accordingly. Laboratory investigations (CBC, ESR, CRP, ANA, RF) were normal in all cases.

Plain hip radiology revealed short broad femoral neck and widening of joint space in all cases; no evident cartilage destruction excited in any case, MRI of the hips was done in two cases, showed rim-like enhancement of the lining of the fluid filled bursa in both of them. Histopathology revealed non inflammatory synovial hyperplasia with multinucleated giant cell in the only case in which synovial biopsy was performed.

Our cases represent a familial autosomal recessive syndrome of non-inflammatory arthropathies associated with campatodactyly and coax vara, the complete picture of the disease may be related to the disease duration. Plain X rays, MRI and synovial biopsy are useful tools in the diagnosis.

Physicians should be aware of the symptoms to avoid mis diagnosis with pediatric rheumatology conditions especially juvenile idiopathic arthritis, and CACP should be considered in all patients who present with non-inflammatory arthropathy particularly if radiograph reveal absence of erosions.

Keywords - *CACP; Campatodactly; Coxa-vara; Familial arthropathy.*

INTRODUCTION

The international league against rheumatism (ILAR) introduced the term juvenile idiopathic arthritis (JIA) in 1997 to replace the previous classification of juvenile chronic arthritis and juvenile rheumatoid arthritis.[1] Juvenile idiopathic arthritis is an umbrella term that includes all forms of arthritis lasting more than 6 weeks and occurred before the age of 16 years. JIA is a diagnosis of exclusion and there are a number of disease entities affecting the joints that may present in a similar way, a genetic disorder has been recognized and termed Camptodactyly-Arthropathy-Coxa vara-pericarditis (CACP) syndrome, a rare autosomal recessive disorder caused by mutation in the Proteoglycan PRG4 gene on chromosome 1.[2] It characterized by congenital or early-onset flexion camptodactyly, childhood-onset of non-inflammatory arthropathy, often associated with non-inflammatory pericarditis or pericardial effusion and progressive coxa vara. The causative gene is located on chromosome band 1q25-31.[3,4] This gene encodes for "proteoglycan-4" (PRG-4), which is a surface lubricant for joints and tendons. This syndrome has distinct radiological and histological features, which are important to recognize since it may clinically mimic juvenile idiopathic arthritis and genetic analysis may not be easily available.

CACP may mimic not only polyarthritic subtype of JIA, but also some of the clinical features of systemic JIA in which pericarditis may occur.

Management of the two conditions is very different: JIA requires anti-inflammatory drugs, often with methotrexate and steroids, whereas CACP syndrome dose not respond to these therapies as it is not an inflammatory disorder.

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Jacob in 1965 was the first to recognize familial association of congenital campatodactly with arthropathy as a distinct clinical entity.[5] Since then several authors have reported a description of cases with CACP syndrome. Recently, etiology of the syndrome was attributed to a gene that was mapped to a chromosome 1q.[6-13] Marcelino *et al.*[14] identified a mutation in a gene (CAPA) encoding a secreted proteoglycan as the cause of CAPA.

The CAPA protein has been also known as megakaryocyte stimulating factor precursor, a superficial zone protein and lubricin.[15,16] This protein appeared to be a major joint lubricant and an intimal cell growth regulator.

Case Report

We evaluated 10 cases (3 males and 7 females) with CACP, from 5 families. All cases were Libyans. Mean age at presentation was 12 years and 6 months (age range from 6 to 19 years). Table 1 summarizes the clinical features of patients.

All were referred to the Rheumatology Clinic, Tripoli Children Hospital with a diagnosis of acute rheumatic fever or juvenile idiopathic arthritis. All cases underwent a complete evaluation including detailed history, clinical examination including loco- motor system examination, ophthalmic and cardiac consultation. Laboratory tests including erythrocyte sedimentation rate, complete blood cell count, antinuclear antibody and rheumatoid factor done to exclude other connective tissue diseases. Skeletal survey was conducted for all patients. Echocardiography to detect pericardial disease was performed to all patients. Magnetic resonance imaging (MRI) of the hips was done in 2 cases; synovial hypertrophy, effusion and state of cartilage were evaluated with gadolinium. Arthroscopic synovial biopsy from the knee joint was performed in one case.

***Family 1*:** Fourth child to consanguineous parents. Female (patient 1 in table 1), presented to rheumatology clinic at the age of 14 years was born with bilateral flexion contraction of 2nd-5th proximal interphalangeal joints (PIP) of both hands. At the age of 5 years she developed painless swelling and limitation of motion of both knees. At the age of 10 years she had chronic pericardial effusion necessitated pericardial biopsy that shows chronic pericarditis. Pericardial peritoneal tunnel was performed due to massive effusion. At the age of 14 years Coxa vara was noticed.

***Family 2*:** Consanguineous parents. Male child (patient 2 in table 1) affected presented at the age of 9 years. Bilateral flexion contractures of fingers of both hand was developed before first birthday. At 7 years he developed painless swelling with limitation of motion in multiple joints including the wrists, knees, elbows and ankles during clinical evaluation found to have pericarditis with pericardial effusion, diagnosed and treated as acute rheumatic fever. No Coxa vara could be detected during evaluation.

***Family 3*:** Consanguineous parents, had 2 affected children (patient 3, 4 in table 1, 2), boy 11 years old at presentation to rheumatology clinic. He had bilateral flexion contractures of 2nd, 3rd, 4th, and 5th PIP at birth, at age of 3 years she developed painless swelling of the knees and ankles. Cardiology evaluation including echocardiography confirms absence of pericarditis. While radiological assessment confirms the presence of coxa vara. The 2nd child female, 7 years at presentation, she had flexion contractures of left 3rd and both 2nd PIP by the end of first year of life and painless joint swelling in knees, elbows and ankles. Coxa vara was confirmed radio logically; however evaluation for pericardial involvement was negative.

***Family 4*:** Parents are non- consanguineous but they came from the same village. They have 2 affected children (patient 5, 6 in tables 1, 2): female aged 6 years with no clear history of fingers flexion, start to suffer from painless swelling of both knee joint at the age of 3 years. Her cardiology evaluation was negative for pericarditis as well as her radiological evaluation for coxa vars. Second child, female was 16 years at presentation, no clear history of finger contractures; start to have painless joint swelling affecting knees, ankles and wrists. Her cardiology evaluation confirms the presence of pericarditis and radiologically coxa vara was evident.

***Family 5*:** Consanguineous parents, have 4 affected children, one male and three females (patient 7-10 in tables 1, 2): male child, 9 years at time of referral, born with flexion contractures of all fingers, and had painless swelling of both knee joints at the age of 3 years. At 8 years of age he had chest pain, his echocardiography shows presence of pericarditis with pericardial effusion. No coxa vara detected during evaluation. Second child female was 11years when referred because of bilateral knee swelling with limitation of motion, her history revealed flexion contractures of 3rd, 4th PIP of both hands started at the age of 1 year. No pericarditis can be detected on evaluation, coxa vara detected radiologically. 3rd child, female 12 years old, born with fingers flexion, at the age of 3 years she had bilateral knee swelling with limitation of motion. Her evaluation excludes the pericarditis and confirms presence of coxa vara. 4th female 16 years old with history of finger contractures started at age of 2 years and involve 2nd, 3rd PIP of both hands, at 3 years she got painless swelling of both knees, ankles and left wrist. Her evaluation was positive for coxa vara and negative for pericarditis.

Table 1: Clinical features of cases

Patient	Age* (in years)	Sex	Campatodactly	Arthropathy	Coxa-vara	Pericarditis
1	14	F	+At birth	+	+	+
2	9	M	+1st year	+	-	+
3	11	M	+At birth	+	+	-
4	7	F	At 1st year	+	+	-
5	6	F	-	+	-	-
6	16	F	-	+	+	+
7	9	M	At birth	+	-	+
8	11	F	At 1st year	+	+	-
9	12	F	At birth	+	+	-
10	16	F	At 2nd years	+	+	-

*Age at time of referral.

Table 2: Description of campatodactly and arthropathy of cases

Patient	Campatodactly	Arthropathy
1	Both 2nd, 3rd, 4th, 5th	Both knees, both hips
2	All fingers	Both wrists, elbows, knees and ankles
3	Bilateral 2nd,3rd,4th,5th	Knees and ankles
4	Left 3rd,both 2nd	Knees, elbows 'hips and ankles
5	-	knees
6	-	Knees, ankles and wrists
7	Bilateral 1st,2nd,3rd,4th,5th	knees
8	Bilateral 3rd, 4th	knees
9	All fingers	knees
10	Bilateral 2nd, 3rd	Knees, ankles and left wrist



Figure 1: CACP syndrome: Per articular osteopenia, almost complete loss of joint spaces, campatodactly, no erosions.

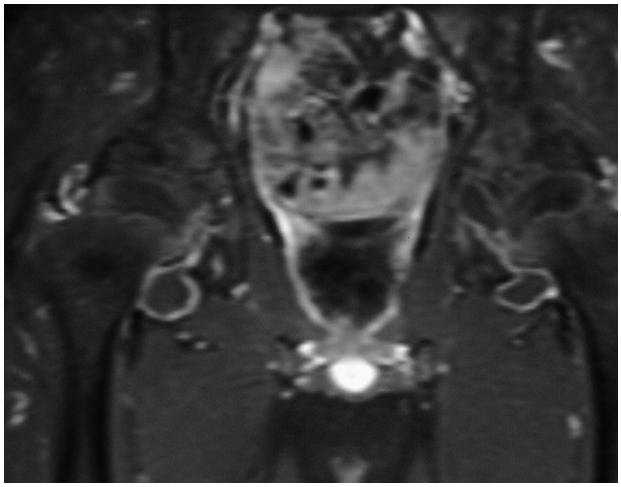


Figure 2: MRI with gadolinium: rim enhancement of joint capsule.

DISCUSSION

In this study we evaluate 10 cases with CACP, relatively large series. CACP is characterized by wide clinical variability. Campatodactly refers to congenital or acquired non traumatic contractures of the proximal inter phalangeal joint of one or several fingers.[17] Although campatodactly considered to be constant features of CACP, two of our patients (2 sisters in family 4) had no clear history and this may be explained by mild degree of contractures and improvement over time. no cases reported without campatodactly. The onset of campatodactly in our study was at birth in 4 cases, the other 4 cases developed it before age of 5 years. Campatodactly was bilateral in most cases with variable distribution (Table 2).

Arthropathy begins during childhood and primarily affects large joints as knees, ankles, elbows and hips. Clinically it is characterized by joint swelling without warmth, but with synovial thickening. Histologically, there is pronounced hyperplasia of synovium and multinucleated giant cell is present. Synovial hyperplasia is also commonly seen in juvenile idiopathic arthritis; however in contrast to JIA hyperplasia in CACP is not accompanied by inflammatory cell infiltrate or vasculitis. In our study arthropathy was present in all cases and mainly affects the big joints; hips, knees, ankles, elbows and wrists (Tables 1, 2). The involvement was bilateral and mostly symmetrical. Synovial biopsy performed in one case (patient 2), histopathology revealed non inflammatory synovial hyperplasia with multinucleated giant cell, no evidence of inflammatory cells. Many authors reported similar pathological finding.[7-9,11]

Coxa vara, reduction of angle between femoral neck and shaft were radio logically evident in 50% of published cases.[18] In one study, 90% of cases had coxa vara deformity[22], in our study it was evident in 7 cases (70%). Bahabri, *et al.*[19] suggested that coxa vara deformity becomes clinically apparent with increasing age and cited that the actual percentage of the previously described patients in whom the hip may ultimately becomes involved is uncertain. Plain hip radiology revealed short broad femoral neck and widening of joint space in all cases; no evident cartilage destruction excited in any case, MRI of the hips was done in 2 cases, showed rim-like enhancement of the lining of the fluid filled bursa in both of them. Rim like enhancement can distinguish between CACP and JIA based on homogenous or multinucleated enhancement in JIA.[20,21] Therefore, MRI is regarded as a useful diagnostic tool which differentiate CACP from JIA.[22]

Non inflammatory pericarditis has been reported in30% of published cases.[7,10,11] In one study no cases with pericarditis had been reported[22] pericarditis may be mild and self-limited[19] or life- threatening, necessitating pericardiocentesis or pericardiotomy.[7, 10,11] In our study, 4 cases had pericarditis, 2 males and 2 females. Pericarditis was mild in two cases no treatment was needed, one with moderate disease and needs medical treatment and the 3rd had severed persistent pericarditis needs pericadio-peritoneal shunt.

Although some cases with CACP were reported in Egyptian, Saudi Arabia children, but no cases have been reported from Libya and our cases are the first to publish.

CONCLUSION

We described 10 cases with CACP syndrome, which was relatively large proportion with such a rare disease. All cases were misdiagnosed as acute rheumatic fever or juvenile idiopathic arthritis and most of them receive unnecessary drugs as non-steroidal anti-inflammatory and methotrexate for variable durations of time. Good history, careful examination, a lack of clinical and laboratory evidence of inflammation help to differentiate CACP from the more common and treatable, juvenile idiopathic arthritis. Radiological evaluation including MRI is very helpful to distinguish the two conditions.

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