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Review Article

A Brief Review on Calcium Pyrophosphate Deposition Disease (Pseudogout)

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Abstract

Calcium pyrophosphate deposition disease (CPDD) or pseudo gout is a metabolic arthropathy caused by the deposition of calcium pyrophosphate dihydrate in and around joints especially in articular cartilage and fibro cartilage. Pseudo gout is a joint disease that can cause attacks of arthritis. Like gout, the condition involves the formation of crystals in the joints. But in pseudo gout, the crystals are formed from a salt instead of uric acid. Almost any joint may be involved by CPDD, although the knees, wrists, and hips are most often affected. Exact mechanism for the development of CPDD is still not known, but increased adenosine triphosphate breakdown which leads to increased inorganic pyrophosphate in the joints results from aging, genetic factors, or both. CPDD is a common condition that occurs with aging in all races. About 50% of people above 85 years have chondrocalcinosis in the United States. Physical examination findings show an acutely inflamed joint with swelling, effusion, warmth, tenderness and pain on motion similar to acute gouty arthritis and occur in the knee but may be present in the wrists, shoulders, ankles, hands and feet. Laboratory tests include serum calcium, phosphorus and magnesium, alkaline phosphatase levels, iron levels, total iron-binding capacity, transferrin saturation and ferritin, thyroid-stimulating hormone and free thyroxine levels. Imaging studies like radiography, magnetic resonance imaging (MRI) and Ultrasonography is done. Management of CPPD includes surgery and pharmacotherapy with Non-steroidal anti-inflammatory drugs (NSAIDs), anti-inflammatory agents like colchicine and corticosteroids such as prednisone and methylprednisolone.

Keywords: Calcium pyrophosphate deposition disease, Calcium pyrophosphate dehydrate, NSAIDs, Colchicine, Corticosteroids

1.Introduction

Calcium pyrophosphate deposition disease (CPDD) is a metabolic arthropathy caused by the deposition of calcium pyrophosphate dihydrate in and around joints, especially in articular cartilage and fibro cartilage. Although CPDD is often asymptomatic, with only radiographic changes seen (chondrocalcinosis), various clinical manifestations may occur, including acute pseudo gout and chronic arthritis. Pseudo gout is a joint disease that can cause attacks of arthritis. Like gout, the condition involves the formation of crystals in the joints. But in pseudo gout, the crystals are formed from a salt instead of uric acid. Almost any joint may be involved by CPDD, although the knees, wrists, and hips are most often affected. This condition is the most common cause of secondary metabolic osteoarthritis. According to McCarty, five most common presentations of CPDD are asymptomatic (lanthanic) CPDD, acute pseudo gout, pseudo-osteoarthritis, pseudo rheumatoid arthritis and pseudo neuropathic joints.

2.Etiology

Exact mechanism for the development of CPDD is still not known, but increased adenosine triphosphate breakdown which leads to increased inorganic pyrophosphate in the joints results from aging, genetic factors, or both. Changes in the cartilage matrix also promote CPPD deposition. Rare hereditary forms of CPDD occur, generally inherited in an autosomal dominant mode. Over activity of enzymes that break down triphosphates, such as nucleoside triphosphate pyrophosphohydrolase are seen in the cartilage of patients with CPDD. It showed that inorganic pyrophosphate can bind calcium, leading to CPPD deposition in the cartilage and synovium [1, 2]. Various cartilages are affected like mostly Hyaline cartilage and fibro cartilage like meniscal cartilage of the knee [3]. In vitro studies hypothesized that pyrophosphohydrolase activity and inorganic phosphate content are generalized phenomena that occurs in fibroblasts [4]. However, these phenomena are generalized but how it is involved only in joints is still not known. Genetic defects have been identified as specific gene mutations in a few families [5]. The mutations occurred in the genes ANKH and COL, which may be involved in crystal-induced inflammation. This is related to synovial tissue and direct cartilage activation, leading to the arthritis caused by CPPD. The ANKH gene has also been shown to be involved in cellular transport of inorganic phosphate.

3.Epidemiology

CPDD is a common condition that occurs with aging in all races. About 50% of people above 85 years have radiologic evidence of chondrocalcinosis in the United States. CPDD is slightly more common in women than in men. The exact female-to-male ratio is unknown but is about 1.4:1. CPDD usually occurs in individuals who are in the fifth decade of life or older with increasing prevalence as age increases. When it occurs early, before the fourth decade of life, it is usually associated with a secondary cause like underlying metabolic disease or familial cause. A study in England (1727 subjects, mean age 63) reported prevalence of chondrocalcinosis of 7%, with no difference between men and women, age, sex and knee pain. There was a strong association with age, the prevalence increasing from 3.7% in persons aged between 55–59 years to 17.5% in person aged between 80–84 years [6]. Framingham survey (sample of 1425 subjects) over the age of 63 years shows 8.1% prevalence of knee chondrocalcinosis [7]. In a Spanish primary care based study prevalence of chondrocalcinosis detected by radiographs of both knees and wrists was 10% in subjects aged >60 years [8]. In a population of elderly Italian subjects from Northeastern Italy, the prevalence of radiological chondrocalcinosis of the lower limbs was 10%, and this increased with age, rising from 7.8% in subjects aged 65-74 years, to 9.4% in those aged 75-84 years, and to 21.1% in subjects aged over 85 years [9]. In recent study, the comparison between chienese subjects (Beijing residents, ages >60 years) and US white subjects in Framingham (MA, USA) showed lower

prevalence of knee chondrocalcinosis in Chienese subjects (1.8% in men, 2.7% in women) than in US white subjects (6.2% in men, 7.7% in women). In elder chienese subjects, wrist chondrocalcinosis was rare about 0.3% in men and 1.0% in women [10].

3.1. Asymptomatic (lanthanic) CPDD

It is associated with radiographic findings of chondrocalcinosis in the absence of clinical manifestations and may be the most common form of CPDD. The classic radiologic findings include chondrocalcinosis of the hyaline cartilage and fibro cartilage of the knees, the fibro cartilage of the triangular ligament of the wrist, the fibro cartilage of the symphysis pubis and the acetabulum labrum of the hips.

3.2. Acute pseudo gout

It is characterized by acute monoarticular or oligoarticular arthritis. It involves the knee or the wrist and any joint can be involved including the first metatarsophalangeal (MTP) joint, as occurs in patients with gout. This form of CPDD accounts for 25% of cases. Glucose levels are usually normal. Clinical manifestations are similar to those of acute gouty arthritis presenting with an acute monoarthritis with less intense pain and swelling. Polyarticular attacks may occur on occasion. Pseudo gout may be precipitated by medical illness such as trauma, myocardial infarction, congestive heart failure, imbalance in serum calcium levels, cerebrovascular accident and after surgery. Pseudo gout may present as a pseudo septic syndrome with acute arthritis, fever and leukocytosis with a left shift.

3.3. Pseudo-osteoarthritis

It involves the metacarpophalangeal (MCP) joints, wrists, elbows, and shoulders, joints unlikely to be involved in primary osteoarthritis. It affects the knees and involves the proximal interphalangeal (PIP) joints and spine seen in patients with primary osteoarthritis. This form of CPDD accounts for 50% of all cases. Approximately half of patients have associated pseudo gout.

3.4. Pseudo rheumatoid arthritis

It is found in about 5% of patients with CPDD and associated with symmetrical inflammation of the PIP and MCP joints. Symptoms include morning stiffness and joint swelling.

3.5. Pseudo neuropathic joints

Neuropathic like arthropathy observed in fewer than 5% of patients with CPDD and it most commonly involves the knee. This is a severe, destructive arthropathy but no clear underlying neurologic disorder is present. The presence of chondrocalcinosis aids in making diagnosis.

4. Physical examination

The physical examination findings vary depending on the form of CPDD in a patient, who may present with an acute arthritis or different patterns of chronic arthritis.

4.1. Acute pseudo gout

Physical examination findings show an acutely inflamed joint with swelling, effusion, warmth, tenderness and pain on range of motion similar to acute gouty arthritis and typically occur in the knee but may be present in the wrists, shoulders, ankles, hands and feet.

4.2. Pseudo-osteoarthritis

Physical examination findings are similar to osteoarthritis, sometimes with an unusual joint predilection. If a patient has osteoarthritis involving the MCP joints and wrists, then consider that CPDD is associated with an underlying metabolic disease.

4.3. Pseudo rheumatoid arthritis

Physical examination findings are similar to rheumatoid arthritis with synovitis in a symmetrical, Polyarticular pattern involving the wrists and MCP joints.

4.4. Gitelman syndrome

Gitelman syndrome is associated with hypokalemic metabolic acidosis and hypomagnesaemia. Patients may have renal tubular acidosis and a history of pseudo gout. Gitelman syndrome has been shown to be associated with a mutation in the gene solute carrier family 12, member 3 (SLC12A3). The cause may be related to the thiazide-sensitive sodium chloride co transporter. It can mimic several other manifestations of CPDD including osteoarthritis, carpal tunnel syndrome and tenosynovitis with calcifications along the tendon sheath [11].

4.5. Septic arthritis

Septic arthritis present as monoarticular arthritis and can mimic acute pseudo gout. Therefore, a Gram stain of the fluid should be performed. The results of the Gram stain will be negative unless a concomitant infection is present. If septic arthritis is suggested clinically, even if crystals are seen on compensated polarized microscopy, it must be evaluated and possibly treated.

4.6. Other differentials

The differential diagnosis for pseudo-osteoarthritis includes hemochromatosis, hyperparathyroidism, hypothyroidism, Basic calcium phosphate deposition disease, Lyme arthritis and traumatic arthritis.

5. Diagnostic approach considerations

Primers on Rheumatic Diseases (1997) revised diagnostic criteria for CPDD and are used with permission from the Arthritis Foundation. The criteria are as follows [12]:

Criterion I: Demonstration of calcium pyrophosphate crystal deposition in tissue or synovial fluid by definitive means (Characteristic radiographs, diffraction analysis or chemical analysis)

Criterion IIa: Identification of monoclinic or triclinic crystals showing no or weakly positive birefringence by compensated polarized light microscopy

Criterion IIb: Presence of typical radiographic calcifications

Criterion IIIa: Acute arthritis of knees or other large joints

Criterion IIIb: Chronic arthritis of knee, hip, wrist, carpus, elbow, shoulder or MCP joint, particularly if accompanied by acute exacerbation. It shows the following features which are helpful in differentiating it from osteoarthritis:

a) Uncommon sites - Wrist, MCP joint, elbow, shoulder

b) Radiographic appearance - Radio carpal or patellofemoral joint-space narrowing, if isolated (Patella wrapped around the femur)

c) Subchondral cyst formation

d) Severity of degeneration - Progressive with Subchondral bony collapse and fragmentation with formation of intra-articular, radio dense bodies

e) Osteophytes formation - Variable and inconsistent

f) Tendon calcifications - Triceps, Achilles, Obturators

5.1. Categories

Criteria-based categories include the following:

Definite disease - Criterion I or IIa plus IIb must be fulfilled

Probable disease - Criterion IIa or IIb must be fulfilled

Possible disease - Criterion IIIa or IIIb should alert the clinician to the possibility of underlying calcium pyrophosphate deposition

5.2. Arthrocentesis

Arthrocentesis is the most important procedure to perform in patients with acute pseudo gout. The acquired fluid can be examined using compensated polarized microscopy and fluid cultures can be performed.

5.3. Histologic findings

Histologic changes associated with CPDD correspond to calcium deposits and to inflammation due to cartilage fragments. These changes are nonspecific but calcium deposits inside the

chondrocartilage are the most typical finding. The pathognomonic finding with compensated polarized microscopy is the presence of weakly positively birefringent crystals, typically intracellular that are usually rhomboid in shape.

6. Associated conditions

Various conditions have been associated with CPDD. When CPDD is diagnosed, in a patient younger than 60 years, a metabolic workup should be performed with measurements of serum calcium, magnesium phosphorus, alkaline phosphatase, iron, total iron-binding capacity, transferrin saturation, ferritin and thyroid-stimulating hormone. Associated conditions include the following:

True associations: Familial (autosomal dominant), prior trauma or prior surgery, hyperparathyroidism, hemochromatosis, hypophosphatasia, hypomagnesaemia, aging

Probable associations: Hypothyroidism, gout, familial hypercalciuria

Possible associations: Acromegaly, diabetes mellitus, ochronosis, Wilson disease

6.1. Laboratory studies

General laboratory studies usually are not helpful in CPDD. The white blood cell (WBC) count and erythrocyte sedimentation rate (ESR) may be elevated. In younger patients, underlying metabolic diseases are evaluated. Laboratory tests can include Serum calcium, phosphorus and magnesium, alkaline phosphatase levels, Iron levels, Total iron-binding capacity, Transferrin saturation and ferritin, Thyroid-stimulating hormone and free thyroxine levels.

6.2. Pseudo gout

Pseudo gout may present as a pseudo septic syndrome with acute arthritis, fever and leukocytosis with a left shift. The diagnosis of acute pseudo gout is made by performing compensated polarized microscopy after aspiration of fluid from the involved joint. Commonly involved joint is the knee followed by the wrist, the MCP joints, the elbows and the MTP joints. The crystals are rhomboid-shaped, weakly positively birefringent and difficult to see. If intracellular, an acute attack of pseudo gout is suggested. Aspiration of the fluid from affected joints during an acute attack yields mildly to moderately inflammatory fluid with 10,000-50,000 WBCs/μL, more than 90% of which are neutrophils. Appearance of calcium pyrophosphate dihydrate crystals obtained from the knee of a patient with pseudo gout. The crystals are rhomboid-shaped with weakly positive birefringence as seen by compensated polarized microscopy. The black arrow indicates the direction of the compensator is shown in Fig. 1.

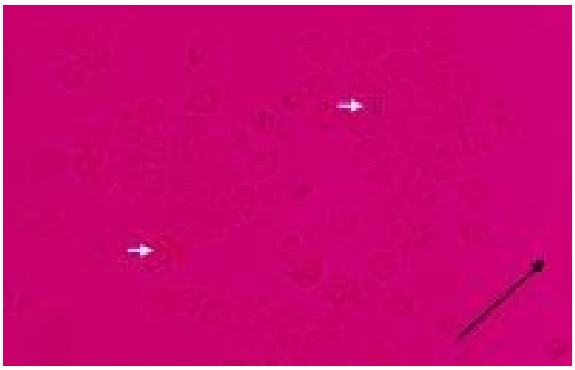

Fig. 1: Calcium pyrophosphate deposition

High-powered view of calcium pyrophosphate dihydrate crystals with compensated polarized microscopy. The black arrow indicates the direction of the compensator. Crystals parallel to the compensator are blue while those perpendiculars to the compensator are yellow as shown in Fig. 2. High-powered view of calcium pyrophosphate dihydrate crystals with compensated polarized microscopy. The crystals parallel to the compensator were blue, while those perpendiculars to the compensator were yellow as shown in Fig. 3.

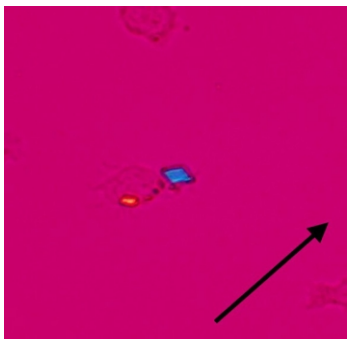

Fig. 2: Rhomboid-shaped Calcium pyrophosphate dihydrate crystals

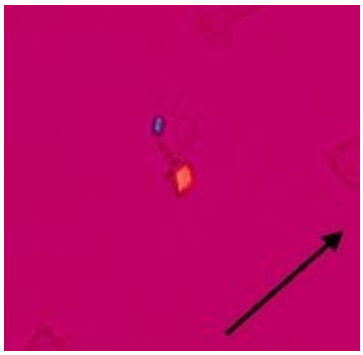

Fig. 3: Calcium pyrophosphate dihydrate crystals

The crystals have been rotated 90%, resulting in a color change in both of them. The direction of the compensator was not changed and is indicated by the black arrow. Gout and pseudo gout can coexist, even in the same joint. Therefore, the presence of gout does not rule out the possibility of pseudo gout and vice versa. Ultrasonography may be helpful in diagnosing pseudo gout.

6.3. Pseudo rheumatoid arthritis

The ESR is elevated in pseudo rheumatoid arthritis. The older age at onset for this condition, the lack of rheumatoid factor and the presence of chondrocalcinosis help to differentiate it from true rheumatoid arthritis. However, rheumatoid arthritis can occur in older individuals. In addition, older individuals may have low-titer–positive rheumatoid factor. Thus, the diagnosis must be made with care.

7. Imaging studies

7.1. Radiography

Radiologic studies are important in the diagnosis of CPDD with radiography being the criterion diagnostic standard. Imaging studies usually include the hands, wrists, pelvis, and knees. The pelvic radiograph should include an anteroposterior view that shows the symphysis pubis and hips. Radiograph of the knee showing chondrocalcinosis involving the meniscal cartilage, as well as evidence of osteoarthritis as shown in Fig. 4.

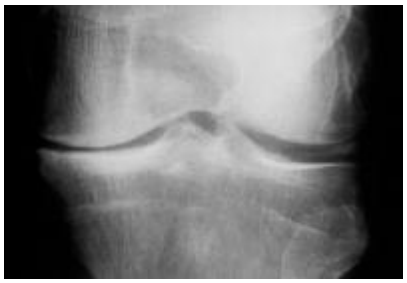

Fig. 4: Radiograph of knee

Radiograph of the wrist and hand showing chondrocalcinosis of the articular disc of the wrist and atypical osteoarthritis involving the metacarpophalangeal joints in a patient with underlying hemochromatosis as shown in Fig. 5 [8].

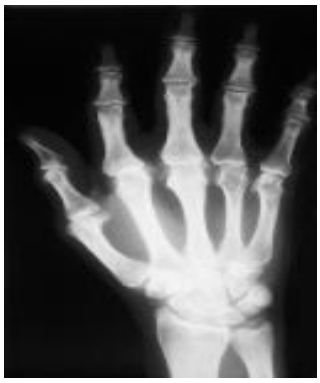

Fig. 5: Radiograph of the wrist and hand

Chondrocalcinosis is usually found in the articular cartilage or meniscal cartilage of the knee, the triangular ligament of the wrist, the symphysis pubis or the glenoid or acetabulum labra. Chondrocalcinosis has also been observed in other areas of the wrist aside from the fibro cartilage such as the distal radioulnar joint, midcarpal joint, pisotriquetral joint and in the spine as calcification of the ligamentum flavum [13]. In some situations, hemochromatosis can produce specific radiographic findings such as large, hook like osteophytes around the second to fifth MCP joints. These findings also occur in patients with CPDD alone. Hook like osteophytes are a common radiologic finding in patients with a pseudo-osteoarthritis condition and are usually present along the second and third metacarpal heads. Radiologically, erosions can be observed in pseudo rheumatoid arthritis but are usually associated with chondrocalcinosis [14].

7.2. Magnetic resonance imaging (MRI) and Ultrasonography

Routine MRI is not sensitive like radiography in detecting the presence of CPPD deposits. However, 4T MRI holds better promise in detecting CPPD crystals. Ultrasonography has been beneficial in the visualization of CPDD crystals as shown in Fig. 6 [15-16].

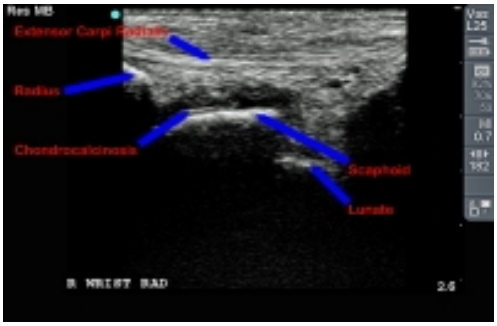

Fig. 6: Ultrasonography in CPPD

8. Management of CPPD

Management of CPDD depends on the clinical manifestations. Asymptomatic (lanthanic) CPDD should not be treated unless it is a possible manifestation of other syndromes, such as hyperparathyroidism or hemochromatosis. Acute pseudo gout may be treated by joint aspiration and intra-articular corticosteroid injection, systemic corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) or high-dose colchicine. Treatment for pseudo-osteoarthritis is similar to that for typical osteoarthritis. Patients with a pseudo rheumatoid arthritis can be treated with small doses of corticosteroids, such as prednisone 5mg daily. Methotrexate is effective in patients who had severe disease with joint destruction. This treatment is attempted only in patients with the pseudo rheumatoid presentation [17]. Studies suggested that the inflammasome complex plays a pivotal role for interleukin-1 in pseudo gout attacks. Anakinra is a potential alternative for treating patients with CPPD. This was reported in a single individual, a 71-year-old man with recurrent pseudo gout attacks in multiple joints that were resistant to therapy with anti-inflammatory drugs, including glucocorticoids. This could also be important in patients with renal insufficiency in whom non-steroidal drugs can be problematic [18]. Possible life style modifications include resting the joint and not to use the affected joint for a couple of days and cold packs can help reduce the inflammation associated with flare-ups. Surgically removing calcifications from an affected joint could be beneficial.

9. Pharmacotherapy of gout

Depending on the size of the joint, intra-articular corticosteroid injections 40-80 mg of methylprednisolone or triamcinolone into the affected joint have the advantage of avoiding the adverse systemic effects of NSAIDs. For Polyarticular attacks of pseudo gout short courses of systemic corticosteroids may be used. The NSAIDs in higher doses are used during the acute attack and in lesser doses for prevention. Toxicity is common in elderly patients includes gastrointestinal and renal toxicities. Cyclooxygenase-2 (COX-2) selective NSAIDs (COX-2 inhibitors) may be similar effective as traditional NSAIDs with less toxicity. Oral or intravenous (IV) colchicine can be use for the treatment of acute pseudo gout. Due to poor therapeutic ratio Colchicine is last option. Prevention of acute attacks of pseudo gout is difficult. The use of small doses of colchicine (0.6mg qd/bid) or NSAIDs are also used. NSAIDs or low-dose prednisone may be beneficial for chronic arthropathies due to CPDD. Medical therapy for acute pseudo gout is similar to that for gout, including the use of NSAIDs, intraarticular or occasionally, systemic corticosteroids, and, rarely, oral or IV colchicine. Variable success in preventing acute attacks of pseudo gout has been achieved with small doses of colchicine (0.6mg qd/bid) or NSAIDs.

NSAIDs are very effective for the treatment of acute pseudo gout and may be used for prophylaxis to prevent recurrent attacks of pseudo gout. It may also be useful for symptomatic treatment of chronic arthropathies associated with CPDD. NSAID use is limited by toxicity (renal, gastrointestinal) which is common in elderly patients. COX-2 selective NSAIDs may be as effective as traditional NSAIDs with less gastrointestinal toxicity. Treatment with NSAIDs is shown in Table 1.

Table 1. Treatment with NSAIDs

Drug	Description	Use
Indomethacin	Blocks COX and proinflammatory prostaglandins. Initially maximum dose, tapering it over 2 weeks depending on response	Acute gouty arthritis, acute pseudo gout
Ibuprofen	Inhibits inflammatory reactions and pain by decreasing prostaglandin synthesis	Mild to moderate pain

Drug	Description	Use
Naproxen sodium	Inhibits inflammatory reactions and pain by decreasing the activity of COX which results in a decrease in prostaglandin synthesis	Mild to moderate pain
Diclofenac	Inhibits prostaglandin synthesis by decreasing COX activity and decreases formation of prostaglandin precursors	Mild to moderate pain
Ketoprofen	Small dosages are indicated in small patients, elderly patients and patients with renal or liver disease. Doses higher than 75 mg do not increase the therapeutic effects. Administer high doses with caution and observe the patient's response	Mild to moderate pain and inflammation

Colchicine inhibits microtubules and may inhibit neutrophil chemotaxis and phagocytosis. It may also inhibit prostaglandin generation. It is given orally or intravenously to treat acute pseudo gout. Toxicity is significant. Low-dose colchicine may be useful for long-term prophylaxis of pseudo gout attacks. Corticosteroids are potent anti-inflammatory agent and very useful in the treatment of acute pseudo gout in patients who are not good candidates for NSAIDs and less toxic than colchicine. It can be given orally, intravenously or intra-articularly. Prednisone can be given orally or intravenously to prevent an attack of pseudo gout. Intra-articular corticosteroids are the first choice of therapy because of excellent safety profile. Low-dose prednisone may be used for long-term treatment of pseudo rheumatoid arthritis. Oral prednisone used for an acute attack of pseudo gout is generally tapered over a 2-week period. However, intra-articular dexamethasone promotes CPPD crystal formation by chondrocytes. Methylprednisolone decreases inflammation by suppressing the migration of polymorphonuclear leukocytes and reversing increased capillary permeability. Methylprednisolone in 20-80mg or its equivalent dose depending on the size of the joint is very effective for the treatment of acute pseudo gout and has minimal toxicity and few contraindications (septic arthritis) [19].

10. Conclusion

CPDD or pseudo gout is a metabolic arthropathy caused by the deposition of calcium pyrophosphate dihydrate in articular cartilage and fibro cartilage. Diagnosis of CPPD includes radiographs, MRI, Ultrasonography test. Several laboratory test are also done for measurement of Calcium, Phosphorus, Magnesium, Alkaline phosphatase levels, Iron, Total iron-binding capacity, Transferrin saturation, Ferritin, Thyroid-stimulating hormone and free Thyroxine levels to differentiate CPPD from other diseases. Treatment of CPPD includes surgery approach and pharmacotherapy includes use of NSAIDs and anti inflammatory agents like Colchicine and Corticosteroids.

Conflicts of Interest

The author declared no competing interests.

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