PSEUDOGOUT

Background

1. Definition
    - Clinical syndrome of acute synovitis with intraarticular (IA) Calcium pyrophosphate dehydrate (CPP) crystal deposition
2. Terminology
    - European League Against Rheumatism (EULAR) recommends replacing 'pseudogout' with Acute Calcium Pyrophosphate (CPP) crystal arthritis [1]
3. General Information
    - Most common joints knee and wrist
    - Chronic form referred to as calcium pyrophosphate deposition (CPPD) Disease

Pathophysiology

1. Pathology of disease
    - IA CPPD and mineralization leads to inflammatory response[2]
        - Hypertrophic chondrocytes generate more extracellular pyrophosphate which complexes with calcium in hyaline and fibrocartilage to form CPP crystals
        - Polymorphonuclear neutrophils (PMN) ingest CPP crystals which lead to PMN lysis and inflammatory response
        - CPP crystals may also have direct catabolic effects on chondrocytes and alter biomechanics of cartilage[3]
2. Incidence/prevalence
    - Incidence and prevalence uncertain [1,4]
    - Strong association with age (prevalence 3.7% in age 55-59yo, 17% in age 80-84yo)[4]
    - CPPD associated arthritis is third most common inflammatory arthritis and most common acute mono-articular arthritis in elderly; typically involves the knee
3. Risk Factors
    - Age is most important risk factor[4]
    - Osteoarthritis (OA) - threefold increased risk if CPPD present
    - Previous joint trauma/injury
    - Joint surgery/lavage promotes crystal shedding[4]
    - Metabolic disease
        - Hemochromatosis, 1˚Hyperparathroidism, Hypomagnesemia, Malabsorption syndromes
        - Consider in age <50-60yo, especially if polyarticular chondrocalcinosis (CC)[5]
    - Familial predisposition to CPPD
4. Morbidity/Mortality
    - Acute debilitating joint pain/edema
    - Chronic inflammatory arthritis with progressive joint destruction

Diagnostics

1. History/symptoms

- Rapid development severe joint pain, stiffness, swelling, and tenderness peaking at 6-24 hours
- Most common joints involved are knee, wrist and shoulder
- May have chronic, progressive pain in multiple joints
- 50% with low grade fever[6]

2. Physical Exam
   - Warm, erythematous, tender, swollen joint +/- effusion
   - Majority are mono or oligo-articular
3. Diagnostic Testing
   - Arthrocentesis
     - Gold standard: synovial fluid analysis under polarized light microscopy with rhomboid crystals, absent/weak positive birefringence[7]
     - Inflammatory Synovial Aspirate: mean leukocyte count of 24,000 cells/μL with neutrophil predominance[5]
     - Gram stain and culture necessary to rule out infectious arthritis[6]
   - Laboratory evaluation
     - Blood cultures and WBC if fever or systemic symptoms
     - If <55yo, screen for associated metabolic disease
       - Electrolytes, magnesium, calcium, iron, parathyroid hormone[5]
   - Diagnostic imaging
     - Radiograph of involved joint
       - Chondrocalcinosis (CC) = linear densities in joints; best seen on films of pelvis, hand and knee[3]
         - Only detects 40% articular CPPD disease[3]
           - Subchondral cysts – also seen in osteoarthritis
           - Aggressive joint degeneration; osteophyte formation
     - Ultrasound –CPPD in peripheral joints appears as punctuate pattern with thin hyperechoic deposits [3]
       - Specificity 86.7%, Sensitivity 96.4%; Sensitivity varies with joint[8]
       - Most accurate in mild cartilage degeneration[3]
     - MRI - insensitive for articular CPPD
     - CT – sensitive for CPPD; however not specific[3]

Differential Diagnoses

1. Key Differential Diagnoses
   - Gout - negative birefringent monosodium urate crystals; elevated uric acid; first attack usually in foot[6, 7]
   - OA: may be associated with CPPD; chronic symptoms
   - RA : positive serology (Rheumatoid factor, Anti-citrullinated peptide antibody) and elevated acute phase reactants; morning stiffness; polyarticular; symmetric arthritis of wrist, hand or finger joints; rheumatoid nodules; Symptoms >6 weeks [9]
   - Septic Arthritis: SF analysis with turbidity, >10,000 PMNs/mm^3, low glucose and elevated lactic acid; positive Gram stain and culture

- Trauma

2. Extensive differential diagnosis
   - Systemic Disease: Amyloidosis, Hyperparathyroidism, hyper/hypothyroidism, sarcoidosis, fibromyalgia
   - Infectious: viral/bacterial reactive arthritis, Lyme disease, tuberculosis, rheumatic fever
   - Rheumatologic: SLE, Reiter's syndrome, psoriatic arthritis, spondyloarthropathies

Therapeutics

1. Acute Treatment[10]
   - Ice
   - Rest
   - Joint aspiration
   - Intraarticular glucocorticosteroids (GCS)
     - May exacerbate CPPD; unclear if anti-inflammatory response outweighs potential CPPD[11]
   - Oral Nonsteroidal Anti-inflammatory Drugs
     - Indomethacin 25mg TID
     - Naproxen 500mg BID
   - Cyclooxygenase-2 selective agents
     - Use if GI intolerance with NSAIDs
   - Colchicine
     - Low dose colchicine (0.5mg TID – QID +/- 1mg loading dose PO)[10]
   - IV/IM/PO corticosteroids
     - Polyarticular attacks not amenable to IA GCS
     - GCS provide more instant relief of acute symptoms compared to NSAIDs, but no difference after 2-3 days[10]
   - Parenteral Adrenocorticotropic Hormone
     - May be a safe and effective alternative treatment option[10]
     - Adverse effects of mild hypokalemia, hyperglycemia, fluid retention and rebound arthritis
2. Further Management
   - Treat associated metabolic disease
3. Long-Term/Chronic Care
   - Prophylaxis against frequent recurrent acute attacks
     - Colchicine 0.6mg twice daily[10]
     - Low dose oral NSAIDs
   - Chronic CPP crystal inflammatory arthritis
     - Oral NSAIDs with gastro-protective treatment
     - Colchicine 0.5-1.0 mg daily decreases frequency of acute flares but not severity[12]
     - Daily low dose corticosteroids
     - MTX – benefit in refractory CPPD, but clinical trials underway[12]
     - Hydroxychloroquine – no trials specific for CPPD disease[12]
     - Magnesium –a cofactor for enzymes that break down pyrophosphate[12]

- Anakinra, IL-1 receptor antagonist; reserved for resistant disease due to cost [12, 13]
- Omega-3 polyunsaturated FA supplementation - evidence of improvement in inflammatory arthritites [10]

Follow-Up

1. Rheumatology if fluid-crystal analysis is inconclusive
2. Hospitalization for comorbid septic arthritis or inability to control pain
3. Orthopedic consult if septic arthritis cannot be ruled out

Prognosis

1. Acute attacks self-limited, resolve 7-10 days
2. Progressive joint damage; destructive arthropathy resembling neuropathic (Charcot's) joints[7]
3. Large joint arthropathy may require joint replacement.

Prevention

1. No known prevention for idiopathic pseudogout
2. Control of associated metabolic abnormalities

Patient Education

1. http://www.rheumatology.org/practice/clinical/patients/diseases_and_conditions/pseudogout.asp

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