Update on Calcium Pyrophosphate Deposition Disease

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Disclosures

• None
Learning Objectives

• Review and update of CPPD
• Know the most common joints involved by CPPD
• Recognize distinct patterns of inflammatory arthritis in CPPD
• Know risk factors associated with CPPD
• Understand treatment goals
Calcium Pyrophosphate Deposition Disease

CPPD   CPPDD

“Pseudogout”
Why think about CPPD?

• A common cause of acute or chronic inflammatory arthritis in older individuals

• CPPD disease is a great imitator
  o Mimics Gout
  o Frequently co-exists and can cause Osteoarthritis
  o Mimics Rheumatoid Arthritis
  o Can look like meningitis
Calcium Pyrophosphate

• Clinical features
• Pathophysiology
• Treatment
Calcium Pyrophosphate

- Pyrophosphate $\text{P}_2\text{O}_7$, $\text{PP}_i$
- $\text{ATP} \rightarrow \text{AMP} + \text{PP}_i$
- Positively birefringent, rhomboid crystal
- CPP forms in pericellular matrix of cartilage
Polarized Microscopy

Demonstration of rhomboid-shaped crystals with positive birefringence on polarized microscopy
Chondrocalcinosis
Radiographic vs Clinical disease

• Chondrocalcinosis is highly associated with clinical CPPD disease and precedes the development of clinical disease in familial CPPD.

• Clinical disease occurs in the absence of chondrocalcinosis
  o present in approximately 40% of patients
  o difficult to visualize with severe cartilage loss

• Chondrocalcinosis may occur in patients without arthritis
  o non-CPP mineral (e.g. calcium phosphate dihydrate)

• Meniscus, fibrocartilage of wrist, symphysis pubis, AC joint, intervertebral disks and spinal ligaments
CPPD Disease is Common

• Prevalence is 4 to 7% in Europe and the United States
• Rare under age 60
• Prevalence doubles each decade
• 44% of patients > age 84
• Familial CPPD
Distinct Clinical Patterns

1. Acute inflammatory arthritis (gout like)
2. Chronic inflammatory arthritis (RA like)
3. Chronic degenerative arthritis (OA like)
   • Severe destructive arthropathy (Charcot like)
   • Spinal involvement
   • Tumoral calcification
Acute inflammatory arthritis (Pseudogout)

- Acute monoarticular inflammatory arthritis
- Mimics acute gout and septic arthritis
- Knee is to pseudogout as great toe is to gout
- Pseudogout vs Gout
  - knee, wrist vs toe and ankle
  - weeks to months vs days to weeks
Chronic inflammatory arthritis (RA like)

- Chronic inflammatory oligo- or polyarticular inflammatory arthritis
- Synovitis typically present
- Frequently involving the hands and wrists (MCPs)
- CPPDD vs RA
  - Less symmetric
  - Sequential involvement of joints

- Chronic episodic inflammatory oligoarthritis
Pseudo-RA Pattern of CPPD Disease

Rosenthal AK and Ryan LA, CPPD, New Eng J Med, 374;2575-84

American College of Rheumatology Slide Collection
Pseudo-RA Pattern of CPPD Disease
Chronic degenerative arthritis (OA like)

CPPD:

• Causes OA
• Frequently co-exists with OA
• Is confused with OA
• CPPDD vs OA
  o Inflammatory features
  o Severe destruction
  o Specific Joint Involvement
    • Wrist, MCPs, Glenohumeral joint
Degenerative CPPD Arthritis

Patterns of Inflammatory Arthritis
Spine involvement

• CPP can deposit in intervertebral disks and along spinal ligaments
• Deposition and inflammation in and around C2 and C1 produces acute, severe neck pain, frequently with headache and fever. “Crown Dens Syndrome”
• High acute phase reactants
• Often confused with meningitis, epidural abscess or sepsis.
Crown Dens Syndrome
CPPD Disease

**Associated Conditions**

- Hemochromatosis
- Hyperparathyroidism
- Hypomagnesemia
- Hypothyroidism
- Hypophosphatasia
- Ochronosis
- Gout
- Diabetes
CPPD Disease

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Pathophysiology of CPPD Disease

• formation of CPP crystals in the pericellular matrix of cartilage by chondrocytes in articular cartilage vesicles
• Extracellular ATP is a rate-limiting for PP$_i$ formation
• ATP efflux regulated by membrane protein ANKH
• CPP crystals activate inflammatory responses and stimulate destructive metabolic changes that damage chondrocytes and synoviocytes
Innate Immune Response in Gout

- Liberation of uncoated MSU crystals
- C5 activated on crystal surface
- C5b-9 MAC
- Recognition by TLR2/4 → MyD88 signaling
- Induction of IL-1, TNFα and CXCL8
- Neutrophil infiltration
- MSU phagocytosis
- Release of chemotactic calgranulins
Induction of the NALP3 Inflammasome
CPPD “Pseudogout”

Typical Clinical Features

- Acute, inflammatory, gout-like attacks that occur secondary to calcium pyrophosphate dihydrate (CPPD) crystals.
- Patients are typically older (60’s-70’s).
- Male/female incidence is about equal.
- Knee is to pseudogout as big toe is to gout (wrist also common).
Calcium Pyrophosphate Deposition Disease

Objective Findings

- Radiographs typically show linear deposition of calcium pyrophosphate dihydrate (CPPD) in hyaline cartilage or fibrocartilage.
  - triangular cartilage of wrist
  - menisci of knee
  - symphysis pubis
  - acromicoclavicular joint
- Inflammatory synovial fluid.
- Rhomboid shaped, weakly positively birefringent crystals.
Basic Calcium Phosphate Disease

• More likely in OA joint
  o Positive birefringent rod shaped crystals
  o knee> wrist> MCPs>
    hips, shoulders, ankles; frequently including tendons

• Chondrocalcinosis

• Neuropathic joint
Treatment Considerations

• Pseudogout - treat like gout
  o NSAIDS, steroids
  o colchicine
    • Start immediately
    • Acute gout regimen: 1.2 mg followed by 0.6 mg one hour later
  o anakinra
    • SQ daily for 3-5 day
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Colchicine

- Reversible inhibition of microtubule assembly
- Inhibits NALP3 inflammasome activation
- Now an expensive medication
Colchicine - Side Effects

- Narrow therapeutic window
  - Neuropathy, myopathy, bone marrow suppression
- GI effects
  - Purgative effect
- IV colchicine
  - Tissue necrosis, acute renal failure, bone marrow aplasia
  - Don’t use it
AGREE Trial of Colchicine for Acute Gout

“Low-Dose” 1.8 mg over 1 hr (1.2 + 0.6)
“High Dose” 4.8 mg over 6 hrs (1.2 + 0.6/hr)

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Treatment Considerations

Pseudogout
- acute or intermittent mono- or oligoarticular
- treat like gout
  - NSAIDS, steroids
  - colchicine
    - Start immediately
    - Acute gout regimen: 1.2 mg followed by 0.6 mg one hour later
  - anakinra (Kinarex)
    - SQ daily for 3-5 day
Treatment Considerations

Degenerative Arthritis (OA)

Consider metabolic risk factors

- Hemochromatosis
- Hyperparathyroidism
- Hypomagnesemia
Treatment Considerations

Degenerative Arthritis (OA)
Consider metabolic risk factors
  - Hemochromatosis
  - Hyperparathyroidism
  - Hypomagnesemia
Hemochromatosis

• Clinical Manifestations
  o Liver function abnormalities – 75 percent
  o Weakness and lethargy – 74 percent
  o Skin hyperpigmentation – 70 percent
  o Diabetes mellitus – 48 percent
  o Arthralgia – 44 percent
  o Impotence in males – 45 percent
  o Electrocardiographic abnormalities – 31 percent

Hemochromatosis

- Clinical Manifestations
  - Liver function abnormalities – 75 percent
  - Weakness and lethargy – 74 percent
  - Skin hyperpigmentation – 70 percent
  - Diabetes mellitus – 48 percent
  - Arthralgia – 44 percent
  - Impotence in males – 45 percent
  - Electrocardiographic abnormalities – 31 percent

Hemochromatosis

• Lab Testing/Screening
  o Unexplained liver function test abnormalities
  o High serum ferritin
    • eg, >300 ng/mL in men or postmenopausal women; >200 ng/mL in premenopausal women
  o High transferrin saturation
    • (>45 percent for men or >55 percent for women)
  o *HFE* gene mutation

*UpToDate, Clinical manifestations and diagnosis of hereditary hemochromatosis*
Treatment Considerations

• Degenerative Arthritis (OA)
  o Consider metabolic risk factors
    • Hemochromatosis
    • Hyperparathyroidism
    • Hypomagnesemia
  o Symptomatic treatment
    • acetaminophen
    • NSAIDs
    • consider gabapentin
Treatment Considerations

- Chronic Inflammatory (pseudo-RA)
  - NSAIDs
  - Colchicine 0.6 QD – BID
  - Consider DMARDs
    - prednisone
    - hydroxychloroquine
    - methotrexate
CPPD Disease

- A common cause of chronic inflammatory and degenerative arthritis
- Appropriate treatment requires recognition of the distinct pattern of clinical disease
- Chronic inflammatory CPPDD is an unmet clinical need