THE NORTHERN HOSPITAL

CALCIUM PYROPHOSPHATE CRYSTAL DEPOSITION (CPPD) DISEASE (PSEUDOGOUT)

The breath-takingly beautiful Cat's Eye Nebula, (NGC 6543) in the Constellation of Draco, Advanced Camera for Surveys, Hubble Space Telescope, NASA, August 2017.

In the mid 18th century, the famous French comet hunter, Charles Messier decided to catalogue annoying fixed "nebulae" that could be confused with comets. This was to assist his fellow comet hunters, in their search for new comets. Nebulae could look like comets initially, but they did move like comets and so they were something different altogether. If these strange objects could be catalogued then, Astronomers, would know where they were and could avoid confusing them with comets. Just exactly what these nebulae were however, was a total mystery in the 18th century. Thus was born Messier's famous catalogue, of nebulous deep space objects, still in common use in the 21st century.

Over the next two centuries nebulae became much more interesting objects in their own right for Astronomers and it soon became clear that not all nebulae where the same. Indeed these mysterious glowing objects consisted of a range of totally different deep space phenomena. Originally the term "nebula" was simply a general name for any celestial object that appeared indistinct and misty, a faint fuzzy glow in deep space and was fixed in the sky in distinction to those "nebulae" which were seen to ***move*** *across the sky where well recognized since antiquity, as comets.*

By the early Twentieth century, with more powerful telescopes, "nebulae" were essentially resolved into three groups, star clusters (open and globular), galaxies, and true nebulae, (or vast clouds of interstellar gas and dust. One odd group remained, the so-called Planetary Nebulae, so named because of their similarity in appearance to the giant planets Jupiter and Saturn, when viewed through small optical telescopes. It was eventually appreciated that these objects were in fact dying stars that were in the process of periodically shedding immense amounts of their outer layers into space at incredible speeds. Knowing this it became obvious that the term "planetary" nebula was a complete misnomer, and so a misleading term. Planets have nothing to do with planetary nebulae. Planetary nebulae are actually old main sequence stars that have gone through their red giant stage of life, and now are shedding enormous amounts of their mass into interstellar space. Eventually enough mass will be lost so as to form a stable white dwarf star, a much diminished remnant of a former glorious life. Eventually even a white dwarf will burn out, to leave a theoretical ash like heap known as a black dwarf.

Astronomers know of over 3000 planetary nebulae in the Milky Way. About 500 of these are bright enough or close enough to be seen in backyard telescopes. Additionally quite a number of planetary nebulae have been catalogued in other nearby galaxies. Planetary nebulae are some of the most breath-takingly beautiful objects in the cosmos. A small central star is seen surrounded by immense and highly complex clouds of gas in fantastic kaleidoscopic arrays. In the broadest terms planetary nebulae can be classified morphologically into 3 types, round, elliptical and butterfly. The famous Cat's Eye Nebula in Draco is an example of an elliptical planetary nebula. But things can be more complex than this. The precise way in which planetary nebulae appear to us in fact depends on, four factors, their basic shape (round, ellipse or butterfly) as mentioned, but also, its age, (early, middle, late), its exact orientation is space with respect to the Earth and finally is distance from the Earth.

Planetary nebulae, quite apart from being simply beautiful, are also intensely interesting objects of study in their own right, despite the misgivings of the eminent Charles Messier. It is known that our own star, the Sun is a main sequence star. As such planetary nebulae represent visions of our Sun in the very far distant future, some billions of years. By studying planetary nebulae we are in fact studying the fate of the distant future of our own Sun and Solar System, and so they are a way of seeing into our own future.

In all fields of human intellectual endeavor, terminology is the end product of the preceding history of a particular field. With the accumulating knowledge of the passing generations, more prefect understandings are achieved which replace older misconceptions. Unfortunately, the common terminology however rarely keeps pace with this advancing knowledge and so many terms become archaic even downright misleading. In the noblest of all human intellectual endeavors, Astronomy, one such

famous example is, despite now rigorous processes, remains that of the planetary nebula, another more well known example to the lay public is the confusing status of the "planet" Pluto. In the endeavor of Medical Science one splendid example, amoung examples innumerable, is that of the condition known as "pseudogout". This is an unhelpful and confusing terminology, inherited from the past, and with the ever accelerating advancement of Medical Science, bringing a much better understanding of this condition, the more modern terminology of CPPD disease is now proposed.

The Cat's Eye Planetary Nebula, as seen by composite data from NASA's Chandra X-ray Observatory and the Hubble Space Telescope, (August 2017). It is estimated that its star, (NGC 6543) discovered by William Herschel on February 15, 1786, lies approximately, three thousand light years from Earth. It periodically, every 1500 years, ejects mass at the staggering rate of 20 trillion tons per second into interstellar space, at a velocity of over 4 million miles per hour. The star is expected to collapse into a white dwarf in a few million years - in cosmological terms, less than the blink of a cat's eye!

CALCIUM PYROPHOSPHATE CRYSTAL DEPOSITION (CPPD) DISEASE (PSEUDOGOUT)

Introduction

Calcium pyrophosphate crystal deposition (CPPD) disease is inflammation of the joints, cartilage and occasionally tendons that is caused by **calcium pyrophosphate crystals**.

Definitive diagnosis of calcium pyrophosphate deposition is made by identifying **calcium pyrophosphate dihydrate crystals** in synovial fluid

Treatment is along similar lines to that of gout and so essentially involves:

1. NSAIDs
2. Colchicine
3. Prednisolone

Terminology:

Older terminology (but still in relatively common use) for CPPD disease includes:

1. Pseudogout:
    - Pseudogout refers to the **acute clinical** presentations of monoarthritis due to calcium pyrophosphate crystal deposition.
2. Chondrocalcinosis:
    - Chondrocalcinosis refers to radiographic calcification in hyaline cartilage and/or fibrocartilage.

      It is commonly present in patients with CPPD disease but is neither absolutely specific for CPPD disease nor universal among affected patients.
3. Pyrophosphate arthropathy:
    - The term "**pyrophosphate arthropathy**" refers to the *structural damage in cartilage and bone.*

Epidemiology

Calcium pyrophosphate deposition is a disease of the older patient, with the mean age at presentation reported to be between 65 - 75 years.

Women are more commonly affected than men (ratio estimates are 2-7:1).

The prevalence is 8100 / 100,000 of the population in most countries where epidemiology has been done.

Pathophysiology

Calcium pyrophosphate deposition disease occurs when excessive calcium pyrophosphate production results in local supersaturation of tissues with subsequent crystallisation.

Deposition of **calcium pyrophosphate dihydrate crystals** occurs almost exclusively in the **joints** and is the most common cause of **chondrocalcinosis (cartilage calcification).**

Pyrophosphate is generated by chondrocytes and so the disorder is generally thought to be associated with **excessive cartilage pyrophosphate production**, leading to local CPP super-saturation and CPP crystal formation or deposition.

Causes:

These include:

1. Most cases of pseudogout are sporadic and idiopathic.

   The main risk factors for calcium pyrophosphate deposition are:

   - Increasing age
   - The presence of osteoarthritis

Less common associations include:

2. Familial chondrocalcinosis

   - Familial chondrocalcinosis is typically manifested by an autosomal dominant inheritance and by the occurrence of more severe and widespread arthritis earlier in life than is commonly observed in the typical patient with CPPD disease

3. Metabolic disease associations:

   - Haemochromatosis.
   - Primary hyperparathyroidism.
   - Hypomagnesaemia.

4. Gout

5. Previous joint trauma (including prior joint surgery).

6. Drug precipitants:

Oral bisphosphonates:

- These *may* precipitate attacks of acute CPP crystal arthritis

Loop diuretics:

- Loop diuretics but *not* thiazide diuretics, appear to be associated with the development of acute calcium pyrophosphate crystal arthritis. [1]

Clinical Features

Calcium pyrophosphate deposition is often **asymptomatic**.

Acute presentations

CPPD disease and gout cannot reliably be distinguished on **clinical grounds**.

Fever, chills, and malaise do not reliably distinguish cellulitis or septic arthritis from crystal-induced arthritis (CPPD disease or gout) because all 3 illnesses can produce these signs and symptoms.

Acute CPPD disease typically presents as:

1. Mild constitutional symptoms
   - Lethargy / malaise
   - Mild fever (may or may not be present)
2. Relatively insidious onset:
   - As a general rule, gout symptoms tend to develop rapidly over a few hours

   Whereas:
   - The onset of symptoms in **pseudogout** is usually more insidious and may occur over several days.
3. An acute monoarthritis:
   - Mimicking gout (hence the older terminology, “pseudogout”)
4. Sites involved:
   - The **knee** and the **wrist** are the most common sites of pseudogout, this being a point of difference from gout, (where it is the first **metatarsophalangeal joint** that is most commonly affected).

     Less commonly the wrist or shoulder are involved.

- Patients may also have calcifications in the soft tissues:
    - ♥ Tendons, (Achilles in particular)
    - ♥ Bursae.
- "Crowned dens" syndrome:
    - ♥ A **rare *but well documented*** manifestation of acute calcium pyrophosphate crystal arthritis is the "crowned dens" syndrome, which affects females more commonly than males.

      It presents as acute neck pain and stiffness, often accompanied by fever and elevated inflammatory markers.

      Typically, there is periodontoid "crown-like" calcification above the dens. This can be observed on coronal views on cervical computed tomography (CT) scan, but is *not* typically visible on plain X-rays.

      Clinically it is characterized by:

      ♥♥ Severe acute or recurrent axial neck pain

      ♥♥ Neck and shoulder girdle stiffness

      ♥♥ Associated fever on occasions

      The importance of identification of the crystal deposition basis of CDS lies both in the resemblance of its symptoms and signs to those of **polymyalgia rheumatica, giant cell arteritis, or, less frequently, meningitis, cervical discitis, or inflammatory spondyloarthritis;** and in the usually favorable response of CDS clinical features to treatment with nonsteroidal antiinflammatory drugs (NSAIDs) or colchicine.

Acute attacks of CPP crystal arthritis are typically self-limiting, ranging from **days to weeks.**

Chronic presentations

Rather than presenting with an acutely inflamed joint, the occasional patient may have more smoldering chronic disease, (*formerly* known as "pseudo-rheumatoid arthritis", a term now no longer used).

This presents as a very destructive osteoarthritis which is more **polyarticular**.

Commonly it involves:

- Knees

- Second and third MCP joints
- Wrists
- Shoulders
- Elbows
- Hips
- Mid-tarsal joints.

Chronic calcium pyrophosphate crystal inflammatory arthritis should be considered in the differential diagnosis of rheumatoid arthritis in older adults.

Investigations

Investigation as to the underlying cause will largely depend on the age at presentation. Metabolic or genetic causes are more likely younger patients.

Blood tests:

1. FBE
    - WCC may be mildly elevated.
2. U&Es/ glucose
3. Inflammatory markers
    - ESR and CRP may be mildly elevated
4. Calcium and phosphate levels (and PTH levels if calcium is elevated)
    - Due to the known association with hyperparathyroidism.
5. Serum iron levels
    - Iron levels (due to the association with hemochromatosis).

Plain Radiology:

Articular cartridge calcification:

The finding of **calcification of articular cartilage** on X-ray examination is usually termed **chondrocalcinosis**

Larger joints, such as the knee, wrist, elbow, shoulder, and hip, are most frequently involved in CPPD disease, but almost any diarthrodial joint may be affected *radiographically*.

CPPD typically appears as **punctate** and /or **linear** radio-densities in articular cartilage (fibrocartilage and/or hyaline cartilage)

Chondrocalcinosis is a finding that increases with age: [1]

- Age 65 - 74 the incidence is 15%.
- Age 75 - 84 it is 36%.
- After age 84 almost 50%.

While the presence of chondrocalcinosis **supports** the diagnosis of calcium pyrophosphate deposition, it is neither highly sensitive nor specific.

Furthermore, the finding of chondrocalcinosis on X-ray does not necessarily indicate the presence of clinical disease; it may be asymptomatic without need of management.

Chondrocalcinosis most commonly affects:

- **Fibrocartilage**, as punctate opacities:

  Particularly:

  - ♥ Knee joint; the menisci of the knee (usually bilaterally)
  - ♥ Triangular cartilage of the wrist.
  - ♥ The glenoid
  - ♥ Acetabular labra.

but may also occur in:

- **Hyaline cartilage**, as **linear** opacities separate from, but parallel to, subchondral bone.

  Mainly in :

  - ♥ Knee joint
  - ♥ Glenohumeral joint
  - ♥ Wrist
  - ♥ Elbow
  - ♥ Hip

The location of the chondrocalcinosis is also important for determining its relevance to clinical disease.

For example, chondrocalcinosis involving the triangular cartilage of the wrist is much more likely to be associated with clinical disease than chondrocalcinosis involving the knee.

Soft tissue calcification:

Articular capsule or **synovial membrane** calcification is usually fainter and more diffuse than cartilage calcification.

Linear calcifications involving the Achilles tendon or plantar fascia are also often seen in CPPD disease.

Degenerative changes:

CPPD is often associated with degenerative changes in joints, even in the absence of radiographic cartilage calcification.

Characteristic degenerative changes in CPPD disease include typical features of osteoarthritis, including:

- Subchondral cysts
- Osteophyte formation
- Bone and cartilage fragmentation.

CT Scan:

Dual energy CT scanning with color coded images has recently become available, which can diagnose **gout** directly by imaging, with a high degree of specificity and sensitivity.

It may be a useful technique for excluding gout in patients who present with possible gout.

The presence of articular joint cartilage calcification is suggestive of (CPPD) disease.

The presence of bony erosions is more consistent with gout.

In summary:

Modality	**CPPD Disease**	**Gout**
Plain Radiography	Chondrocalcinosis *May* see chondrocalcinosis	Acute - no changes Chronic - bony erosions

Colour coded Dual Energy CT Scan	Negative for urate crystals More sensitive than plain radiography in detecting chondrocalcinosis	Positive of urate crystals

Ultrasound:

Ultrasound, in expert hands, has promising utility in the diagnosis of calcium pyrophosphate deposition.

It may be useful to detect hyperechoic lesions in hyaline and fibrous cartilage, tendons, bursa and/or joints, but further study is needed before it can be routinely recommended.

Joint synovial fluid aspiration:

Definitive diagnosis is by the detection of **calcium pyrophosphate crystals** identified on polarised light microscopy of joint aspirate.

CPP Crystals:

The crystals appear rhomboidal and are weakly **positively birefringent in polarized light.**

CPP crystals differ from the **needle-shaped, and strongly negatively birefringent monosodium urate crystals** in **acute gouty arthritis**.

CPP crystals can be *more difficult* to detect than monosodium urate crystals because they are:

- Smaller (0.5 - 10 microns)
- Only *weakly* **positively** birefringent (or not birefringent at all)
- More polymorphic in shape with rod-shaped and cuboid crystals in addition to the usual rhomboidal form

Note that up to 20% of calcium pyrophosphate deposition disease patients also have hyperuricaemia.

Joint fluid may therefore sometimes contain both urate and calcium pyrophosphate crystals. [1]

Leukocyte counts:

Total **synovial fluid leukocyte concentration** in an acute attack is typically:

- 15,000 - 30,000 per mm^3,

90 % of which are neutrophils.

In chronically symptomatic joints, cell counts are typically lower.

Microscopy and culture of the synovial fluid should also be undertaken to exclude septic arthritis.

Management

There is a lack of good evidence to guide the optimal management of acute calcium pyrophosphate crystal arthritis and so current management recommendations are necessarily based on extrapolating the evidence from treatment of acute gout.

Treatment of acute pseudogout is therefore similar to that of gout, and so options include:

1. NSAIDs

2. Corticosteroids.

3. Colchicine

    - This may be added to either an NSAID or prednisolone if monotherapy is insufficient to relieve symptoms

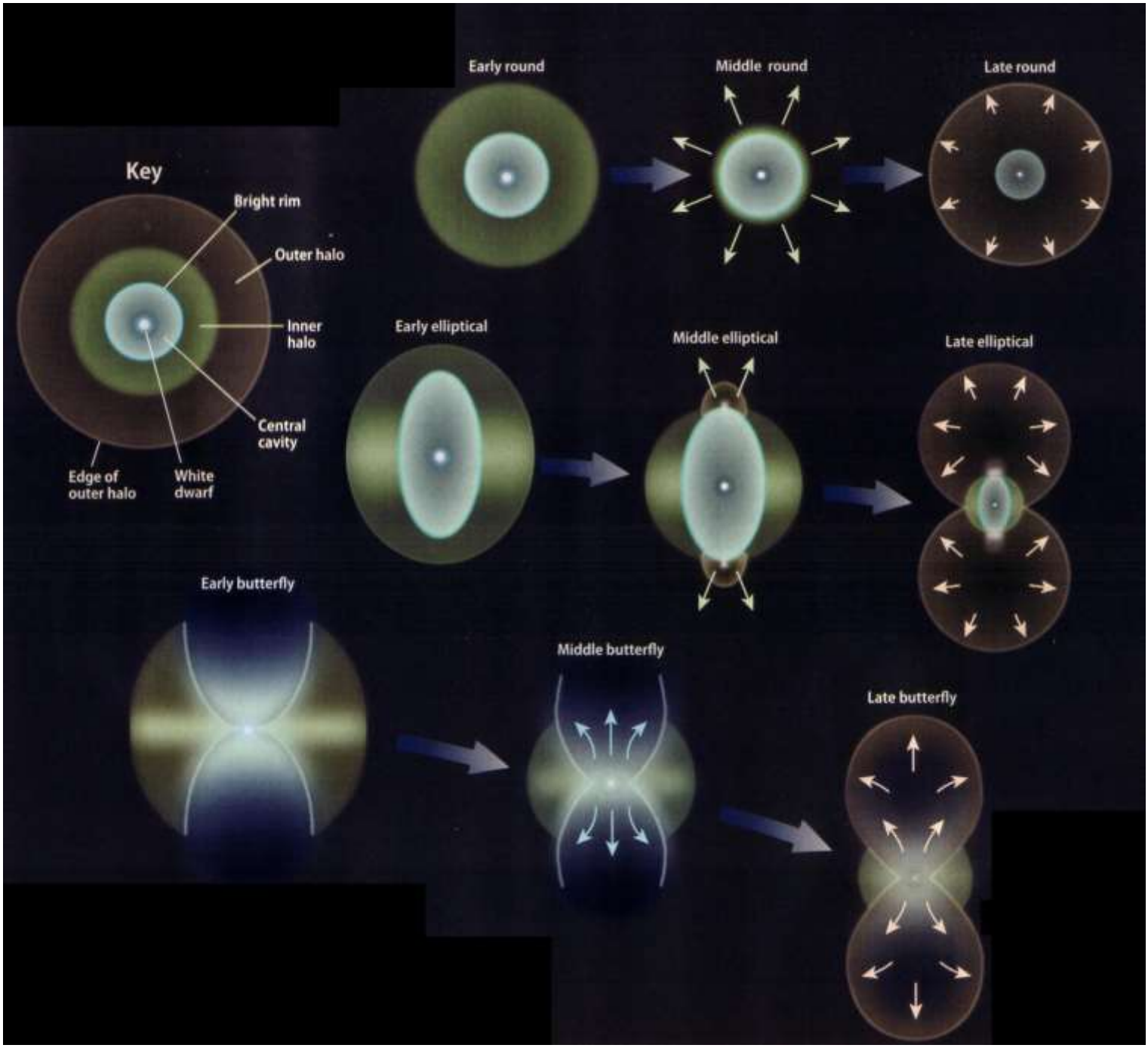
NSAIDS are often not the best choice in elderly patients however, and a short course of prednisolone will often be preferable.

In refractory cases further treatment options include:

4. Hydroxychloroquine.

5. Methotrexate

6. Intra-articular injection of corticosteroid, (as exclusion of infection).



A classification of Planetary Nebulae

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