ASK THE EXPERT

Calcium Deposition Disease

Calcium deposition disease—the disordered calcification of cartilage and/or periarticular soft tissue—"actually represents a heterogeneous group of musculoskeletal syndromes associated with calcium pyrophosphate dihydrate crystals and the hydroxyapatite-like trio of crystals known as basic calcium phosphate crystals," according to Dr. Anne K. Rosenthal.

ANNE K. ROSENTHAL, M.D.

The musculoskeletal conditions that fall under the calcium deposition disease umbrella are incompletely understood and are underdiagnosed, largely because of the conditions' heterogeneous clinical presentations and their propensity to mimic other disorders, as well as limitations in diagnostic technologies, said Dr. Rosenthal, who has written widely on this subject (J. Clin. Rheumatol. 2009;15:42-5; Arthritis Rheum. 2008;58:3270-4; Osteoarthritis Cartilage 2008;16:1395-402; J. Rheumatol. 2008;35:1108-17). Dr. Rosenthal provides insight into the pathogenesis, diagnosis, and management of these conditions in this month's column.

RHEUMATOLOGY NEWS: What is the estimated prevalence of calcium deposition disease?

Dr. Rosenthal: We do not know the prevalence. This lack of knowledge is a function of both varying clinical definitions and inadequate diagnostic techniques.

To add confusion, calcium crystals can occur alone or in the setting of osteoarthritis. Findings from recent studies suggest that at the time of knee replacement for osteoarthritis, almost 100% of patients will have basic calcium phosphate (BCP) and/or calcium pyrophosphate dihydrate (CPPD) crystal deposits in their articular cartilage.

About 60% of the time, synovial fluids from similar patients contain calcium crystals. Chondrocalcinosis, which is the typical radiographic correlate of CPPD deposition, increases dramatically with age.

Yet prevalence estimates range between 8% and 44% of the population older than age 60 years, based on knee radiographs.

BCP crystals are associated with a variety of musculoskeletal syndromes, such as calcific periarthritis and a bilateral, severely destructive shoulder arthropathy called Milwaukee shoulder syndrome. The prevalence of these syndromes is unknown.

RN: What is the epidemiology of CPPD and BCD deposition?

Dr. Rosenthal: The epidemiology of each differs somewhat, although these crystals can certainly coexist in a single joint and a single patient.

Pure CPPD deposition is associated with advanced age and a handful of metabolic syndromes, including hyperparathyroidism, hemochromatosis, hypophosphatasia, and hypomagnesemia. Rare familial forms of CPPD deposition also occur.

Articular BCP-crystal–associated syndromes are typically associated with joint degeneration, whereas periarticular syndromes such as pseudopodagra and calcific periarthritis can occur in younger patients. Whether renal disease and diabetes are additional risk factors for these syndromes remains poorly studied.

CPPD deposition disease typically presents with either an acute inflammatory monoarticular arthritis (known as pseudogout) or a chronic polyarticular syndrome similar to osteoarthritis, with or without superimposed episodes of inflammation. Less commonly, presentation can mimic that of rheumatoid arthritis, and rarely CPPD deposition disease resembles neuropathic arthropathy.

BCP crystal deposition frequently occurs in the setting of advanced osteoarthritis, but it is unclear if these patients can be clinically distinguished from patients without BCP crystals. Less commonly, BCP crystals cause Milwaukee shoulder syndrome, or an inflammatory periarthritis in the shoulder, or around the fingers and toes (pseudopodagra).

RN: How does the crystal deposition lead to arthritis?

Dr. Rosenthal: Both BCP and CPPD crystals can cause inflammation in the joint. The mechanism of this inflammatory response for CPPD crystals is through the NALP3 inflammasome—the same pathway that is activated by monosodium urate crystals.

Both CPPD and BCP crystals also have direct effects on articular tissues. For example, BCP crystals can elicit mitogenesis and the production of catabolic cytokines, growth, and prostaglandins from synovial cells. Similar effects may be seen in cartilage and with CPPD crystals.

CPPD crystal deposition clearly affects joints that are not typically affected by osteoarthritis, including the shoulder and wrist. There is some predilection for previously damaged joints, and damage to the meniscal cartilage of the knee is a strong risk factor for CPPD crystal deposition.

'We hope that a better understanding of crystal formation and their cellular effects will ultimately lead to the development of specific therapies' for these disabling conditions.

Less is known about the distribution of articular BCP crystals. They are best studied in the knee, but recent work also supports their presence in osteoarthritic hip cartilage. The reason that some joints are affected while others are not remains a mystery.

RN: How is crystal deposition disease diagnosed?

Dr. Rosenthal: CPPD crystals can be identified in tissues and synovial fluid with compensated polarizing light microscopy; they appear as positively birefringent rhomboid-shaped crystals. Unfortunately, they are easily missed because of their weak or absent birefringence and their small size.

There are no widely available accurate techniques to identify BCP crystals at the bedside. Stains such as alizarin red for BCP crystals in fluid and von Kossa's stain for crystals in tissues are used, but the results can be difficult to interpret. The lack of quick and accurate diagnostic techniques for calcium crystals has hampered studies designed to explore the prevalence and role of calcium crystals in arthritis.

RN: What are the current treatment options?

Dr. Rosenthal: Current therapies are limited and are largely aimed at treating symptoms.

Acute pseudogout is treated like acute gouty arthritis, with intra-articular corticosteroids, colchicine, NSAIDs, or short courses of systemic corticosteroids. Chronic CPPD deposition disease is more challenging to treat, and is typically managed in the same manner as osteoarthritis, with NSAIDs, intra-articular corticosteroids, and pain medications. Long-term colchicine therapy may be useful in selected patients. Increasing evidence suggests that rheumatoid arthritis–like CPPD deposition disease may respond to methotrexate. Articular and periarticular BCP-associated syndromes may improve with intra-articular corticosteroids or joint lavage. Some evidence also supports a role for therapies that involve dissolution of periarticular crystal deposits in a variety of ways.

RN: What is on the horizon?

Dr. Rosenthal: Recent work has shed some light on the mechanism of the formation of these crystals, implicating both extracellular matrix changes in cartilage and alterations in local phosphate and pyrophosphate levels, perhaps through alterations in membrane channels such as the ANK transporter. The development of drugs that may interfere with the effects of crystals on cells, such as phosphocitrate, is also exciting. We hope that a better understanding of crystal formation and their cellular effects will ultimately lead to the development of specific therapies for the common and disabling conditions associated with articular calcium crystal deposition.

—Diana Mahoney

DR. ROSENTHAL *is a professor of rheumatology at the Medical College of Wisconsin in Milwaukee. She has no conflicts of interest to disclose that are relevant to this interview.*

Acute Respiratory Failure Hits RA Patients Especially Hard

BY BRUCE JANCIN

SAN DIEGO — Much has been made recently of rheumatoid arthritis patients' substantially reduced life expectancy because of cardiovascular disease. Far less widely known is that they also have increased in-hospital mortality following acute respiratory failure.

A study of 22,121 adults in the U.S. Nationwide Inpatient Sample database who had an emergency hospitalization for acute respiratory failure from 2003 to 2006 showed that the 1,621 with comorbid rheumatoid arthritis or collagen vascular disease had an adjusted 21% increased risk of in-hospital mortality, Dr. David S. Kountz reported at the annual meeting of the American College of Chest Physicians.

The unadjusted in-hospital mortality rates in acute respiratory failure patients with or without rheumatoid arthritis or collagen vascular disease were closely similar: 25% in the rheumatologic group, and 24% in the 20,500 patients without such comorbidity. But the rheumatoid arthritis/collagen vascular disease group was younger, wealthier, and far more likely to be female.

After adjustment for these and other potential confounders, such as hospital teaching status, in a multivariate logistic regression analysis, the rheumatoid arthritis/collagen vascular disease group had a significantly greater in-hospital mortality risk, according to Dr. Kountz, senior vice president of medical and academic affairs at the Jersey Shore University Medical Center in Neptune, N.J. ■

Disclosures: *Dr. Kountz having no conflicts of interest in connection with this study.*