Image of the Month

Osteoarthritis and psoriatic arthritis do share some simple clinical characteristics. Both commonly affect the spine. More importantly, in the hand both osteoarthritis and psoriatic arthritis show a very strong tendency to afflict the distal interphalangeal joints.

"So when you look at it from a very simplistic, clinical perspective, there are strong similarities between psoriatic arthritis and osteoarthritis," said Dr. Dennis McGonagle of the University of Leeds (England).

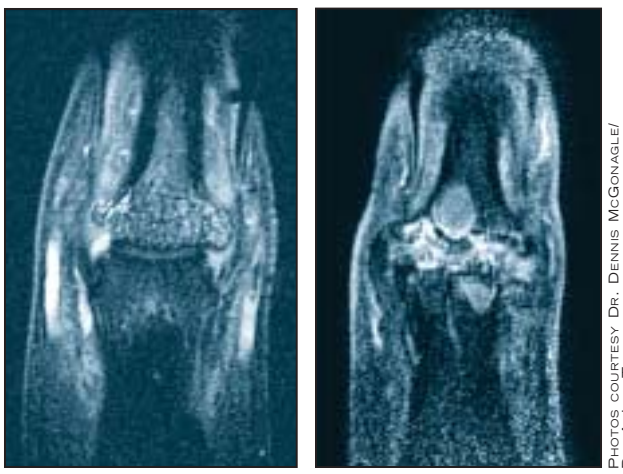
Dr. McGonagle, Dr. Ai Lyn Tan, and their colleagues have used high-resolution magnetic resonance imaging to look more closely at how psoriatic arthritis (PsA) and osteoarthritis (OA) affect the distal interphalangeal (DIP) joints (Arthritis Rheum. 2006;54:1328-33). This type of imaging involves conventional 1.5-T MRI scanners coupled with coils that are designed specially for hand imaging that give very high quality images.

Seeing patients with definite OA or PsA, "the most striking abnormalities that we saw were related to the ligaments and the adjacent attachments or entheses," he said.

Ligament and tendon insertions were involved in patients with either disease; however, enhancement on scanning (evidence of inflammation) of these structures was greater in patients with PsA. In these patients, ligament origins/insertions and extensor tendon insertions appeared to be the epicenter of the inflammatory response with diffuse involvement of adjacent structures. While ligaments tended to be thickened and abnormal in patients with OA, even when the cartilage appeared normal, there was less postcontrast enhancement compared with patients in the PsA group.

The ligaments are sites of very high mechanical stress, particularly in small joints. Both OA and PsA "are localized to sites of very high mechanical stress and 'wear and tear.' A simplistic explanation is that this mechanical stress leads to joint degeneration in osteoarthritis but joint inflammation in psoriatic arthritis," said Dr. McGonagle.

"Inflammation is well recognized in osteoarthritis but it's thought to be secondary to mechanical factors. Psoriatic arthritis is much more an inflammatory disease. What we speculate is that normal or low levels of microdamage and repair of joints—that damage is misinterpreted by the immune system as some sort of severe damage and then you get this autoimmune reaction."



Photos courtesy Dr. Dennis McGonagle/Dr. Ai Lyn Tan

Joint space in the distal interphalangeal PsA joint (left) is well preserved versus the OA joint (right).

There is evidence that most normal people walk around all of the time with low-grade microdamage of the joints, based on studies of insertions and ligaments, carried out in conjunction with Dr. Mike Benjamin of Cardiff University, Wales.

However, in the psoriatic phenotype, the body may misinterpret that damage, resulting in an overexaggerated immune response. After age 50 years, the cumulative microdamage to the joints becomes more pronounced, resulting in the secondary and less severe inflammation that accompanies wear and tear. This would fit with known data that PsA is a disease of younger individuals, while OA is a disease of older individuals said Dr. McGonagle.

It's unclear why the immune system is inadvertently activated in patients with PsA or why cumulative microdamage results in OA in some older individuals but not all. However, the hypothesis that microdamage may trigger both PsA and OA provides fertile ground for research. It is especially relevant for an appreciation that inflammation in the joints may not be primarily the result of immune system malfunction but could be a result of some intrinsic problem with the joints' response to normal locomotion.

—Kerri Wachter

Evolutionary Insights Suggest Novel Treatments for Gout

BY NANCY WALSH
New York Bureau

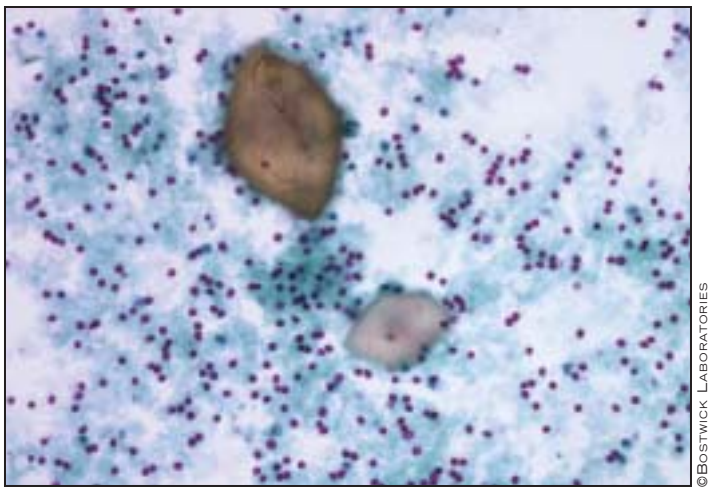
New York — Replacing the enzyme uricase may offer a new means of treating intractable gout.

Uricase—present in most mammals but lacking in certain primates since the Miocene era, when three mutations in the uricase gene rendered it inoperative—is responsible for breaking down uric acid to the soluble and easily excreted compound allantoin as a final step in the catabolism of purines. Without this enzyme hyperuricemia can, and does, develop in humans, chimpanzees, gorillas, orangutans, and gibbons, Dr. Michael Pillinger said at a rheumatology meeting sponsored by New York University.

Studies are evaluating the possibility of giving a pegylated, recombinant form of uricase to patients whose urate levels are not controlled with conventional antigout therapies. In a phase I trial that included 24 patients, the mean plasma urate concentration fell from 11.1 mg/dL to 1 mg/dL within 24-72 hours after intravenous administration of 4-12 mg pegylated uricase (Arthritis Rheum. 2007;56:1021-8).

After a 40-year hiatus during which few advances occurred in treatment or understanding of the disease, novel approaches to the treatment of gout also are being evaluated. In a recent report, the interleukin-1 inhibitor anakinra was administered to 10 patients with gout that was unresponsive to conventional anti-inflammatory drugs. After only three 100-mg doses of the drug, all 10 patients responded rapidly, with a 79% mean reduction in pain (Arthritis Res. Ther. 2007;9:R28 [Epub doi:10.1186/ar2143]).

Teleologic insights into gout's origins also are emerging, with consideration of questions about why uric acid should have been conserved through evolution at all, and why it is present in higher levels in humans and other primates than in other mammals, Dr. Pillinger said.



©Bostwick Laboratories

Uric acid crystals in the urine of a patient with gout. After decades of inactivity, treatment advances are on the horizon.

An explanation for evolutionary conservation of uric acid can be seen in the process of vaccination, where an adjuvant is needed to trigger the innate immune system to respond to the presence of a foreign antigen and overcome tolerance. Freund's adjuvant, for example, contains mycobacterial debris that provides this stimulus. Mammalian cell debris also can be used in an adjuvant capacity.

But there may be another means of providing the adjuvant stimulation, through endogenous "danger" signals from distressed or injured cells, a theory proposed by Dr. Polly Metzinger of the National Institute of Allergy and Infectious Diseases. In this hypothesis, infection or other cellular injury causes the secretion of some cellular danger signal that stimulates maturation of dendritic cells, upregulation of costimulatory molecules such as CD28, and antigen presentation. The result is an immunogenic response to an endogenous signal, said Dr. Pillinger of New York University, New York.

The precise nature of this danger signal remained unclear until a group of researchers from the University of Massachusetts conducted experiments in which they fractionated cytosol from ultraviolet-irradiated mouse fibroblasts. These researchers were able to identify a low-molecular-weight compound secreted in large amounts by dying cells as nucleotides break down—which turned out to be uric acid.

They then confirmed the role of uric acid by administering uricase to mice who had been immunized with uric acid and demonstrating a reduction in adjuvant activity. The authors wrote, "Up until now, [monosodium urate] crystals were viewed solely as pathogenic and the biological response to them as pathological. Our findings suggest that the formation of these crystals and the ensuing host response could have an important role in immune surveillance and the generation of adaptive immunity" (Nature 2003;425:516-21).

It also turned out that there was a threshold level for uric acid to begin upregulating CD28 on dendritic cells, at approximately 7 mg/dL uric acid—the level at which crystals begin to form. "Nature seems to have evolved this system, including a safety threshold, to play an important role in cell damage and the immune response," said Dr. Pillinger, who is also chief of rheumatology at the Veterans Administration Hospital and director of medical education, Hospital for Special Surgery, New York.

Support for the danger signal hypothesis also has been demonstrated in a mouse model, where uric acid levels were elevated during tumor rejection, and rejection was delayed if uric acid was inhibited by the administration of allopurinol or uricase (Cancer Res. 2004;64:5059-62).

"Another question is why we have so much more uric acid than other mammals," he said. Dogs and cats, for example, typically have levels of approximately 1 mg/dL, compared with the 5 or 6 mg/dL in normouricemic humans.

An answer to this question, if somewhat speculative, can be found in mutations of the uricase gene that occurred between 10 and 20 million years ago, at a time when many species of primates became extinct. Fossil records suggest that the primate diet at that time, consisting largely of fruit and grasses, was extremely low in salt, at approximately 0.6 g sodium chloride per day. In effect, vegetarian mammals were in a dietary hypotensive crisis that could be most problematic for those who had evolved to stand upright, Dr. Pillinger said.

Texas nephrologist Dr. Richard J. Johnson, who developed this hypothesis, said, "The uricase mutation may have provided an evolutionary advantage to early hominoids by maintaining blood pressure under the low sodium dietary conditions of that period" (Hypertension 2003;41:1183-90).

An association of gout with elevated blood pressure has long been noted, but these new findings suggest a causative role for hyperuricemia in hypertension, Dr. Pillinger said. One study of five adolescents with essential hypertension found that aggressive treatment with allopurinol normalized their blood pressure. Whether a causal link with uric acid can be found in all patients with hypertension remains to be seen but is intriguing, he said. A blinded trial investigating this question is currently underway. ■