

Rare Disease Offers Pediatric Rheumatology Insights

Report details genetic mutation in the joint condition camptodactyly-arthropathy-coxa vara-pericarditis.

BY DIANA MAHONEY
New England Bureau

The recent identification of novel gene mutations in seven Saudi Arabian children with camptodactyly-arthropathy-coxa vara-pericarditis syndrome has implications beyond the rare autosomal recessive joint condition, as it provides researchers with more pieces to fit into the genetic puzzle of pediatric rheumatic disease, Dr. Matthew Warman of Case Western Reserve University, in Cleveland, said in an interview.

Currently, because camptodactyly-arthropathy-coxa vara-pericarditis (CACP) syndrome mimics juvenile idiopathic arthritis, it is often mistakenly diagnosed and treated as such. However, “the management of the two conditions is very different,” said Amaka C. Offiah, Ph.D., of the Great Ormond Street Hospital for Children in London in an interview. While juvenile idiopathic arthritis is treated with anti-inflammatory medications, often in association with corticosteroids and methotrexate, “CACP does not respond to those therapies because it is not an inflammatory disorder,” she said. The estimated incidence of the syndrome is one case per 1-2 million individuals.

Previously, Dr. Warman and colleagues identified the CACP gene as proteoglycan, or PRG4, which maps to human chromosome 1. The PRG4 gene is switched on in human synovial cells and encodes for lubricin, which is a large, highly glycosylated secreted protein that has been identified as a key joint lubricant.

“Our studies have shown that most patients with CACP syndrome are missing lubricin from their synovial fluid,” said Dr. Warman. The PRG4 mutations in CACP patients suggest not only that inherited lubricin defects could lead to joint damage, he said, “but also that lubricin has an important role in healthy joints.”

In the aforementioned Saudi Arabian study, Anas M. Alazami, Ph.D., and colleagues at the King Faisal Specialist Hospital and Research Centre in Riyadh discovered five novel PRG4 mutations in seven children from four unrelated families (Human Mutation 2006;27:213). The

new findings confirm Dr. Warman’s observation that CACP may result from a loss of lubricin function.

In addition, “our paper suggests that PRG4 mutations are not uncommon, and that there may be a mutation hot spot within the gene, because each of the four families we examined in this fairly consanguineous population had a distinct mutation,” Dr. Alazami said in an interview.

Perhaps the most important conclusion from the new data “is that CACP syndrome is most likely based on a null phenotype, in other words, no synthesis of PRG4 protein at all,” said Dr. Alazami. This is because all of the mutations published thus far “predict a prematurely truncated protein and because the PRG4 gene appears to be under the control of the nonsense mediated mRNA decay pathway,” he said. “This suggests strongly that missense mutations, or in-frame deletions, may be associated with a less severe phenotype, perhaps one of the more common forms of arthropathy.”

Given that the disorder is associated with a null phenotype, “the obvious potential treatment target would be the injection of active PRG4 protein, or a synthetic substitute, into affected joints,” said Dr. Alazami. “But, from a genetic standpoint, the data are concerned more closely with prevention—in other words, the ability to identify carriers and offer genetic counseling—rather than treatment” at this juncture.

Toward this end, antibodies against lubricin could potentially be used to test synovial fluid from individuals suspected of having the disease for the protein’s presence, said Dr. Warman. “The data also suggest that antibodies could be used to look for transient deficiency of lubricin, as might occur when an individual sustains a joint injury that abrades the cartilage surface or has inflammation in the joint that results in degradation of lubricin.”

Because the mounting evidence of the genetic deficiency of lubricin in CACP points to this protein’s importance in maintaining human joint function, said Dr. Warman, “we can now ask specific questions about how this protein works within the joint. For example, what other proteins does it interact with? What leads

to its synthesis and degradation? What happens if we find a way to replace the protein, for example, through gene therapy or protein replacement therapy? When do we need to give lubricin back to a joint? Can lubricin reverse damage that may have already occurred in the presence of other joint-damaging diseases such as rheumatoid arthritis?”

To begin answering these questions, Dr. Warman and colleagues have genetically engineered mice that lack lubricin and are studying the consequences of this deficiency on joint development. While the joints of the genetically altered mice appear normal in the newborn period, abnormal protein deposits appear on the cartilage surface and underlying superficial zone chondrocytes disappear as the mice age, leading to joint damage.

“In addition to cartilage surface changes and subsequent cartilage deterioration, intimal cells in the synovium surrounding the joint space became hyperplastic, which further contributes to joint failure,” said Dr. Warman. The investigators hypothesize that, in the absence of lubricin, the synovial cells become much more aggressive, potentially invading the cartilage surface, in a process similar to that seen in rheumatoid arthritis, he said.

To determine whether it is feasible to prevent or slow joint disease by stimulating lubricin production within the joint, “we have also just recently developed a mouse in which we can turn lubricin expression on and off using doxycycline,” said Dr. Warman. The investigators are also conducting in vitro studies of different forms of lubricin to assess the effect of each different form on cell growth, tissue localization, and surface lubrication, with the ultimate goal being to replace protein function in humans, he said.

Dr. Warman’s team is hoping to apply the research findings to more common joint diseases as well. To determine whether lubricin replacement therapy could also be useful for patients with osteoarthritis and rheumatoid arthritis, Dr. Warman and his colleagues are investigating lubricin changes in the cartilage and

synovial fluid of patients with those conditions. “If we identify acquired changes in CACP protein among these patients, then therapies aimed at increasing endogenous protein synthesis or diminishing protein degradation may become valuable therapeutic adjuncts,” he said.

Although molecular testing to diagnose CACP or to identify unaffected characters is not yet available, the identification of the basic molecular components involved in the development of CACP is heading in this direction. Such tests will be especially useful for differentiating CACP from other conditions with which it shares many clinical features, such as polyarthritic

and systemic juvenile idiopathic arthritis, in which pericarditis occasionally occurs. The ability to identify the genetic cause of a constellation of symptoms can help direct appropriate treatment and avoid the use of ineffective agents and their potential side effects.

In the absence of definitive molecular testing, CACP is best differentiated from other conditions by the presence of certain clinical, laboratory, and radiologic features. Particularly important, according to Dr. Offiah, is the lack of clinical signs of inflammation. “[CACP syndrome] is not associated with inflammatory changes in the synovium. Also, erythrocyte sedimentation rate, C-reactive protein, and complete blood count are normal,” she said. In addition, autoantibodies, including antinuclear antibodies and rheumatoid factor, are negative.

Among the distinguishing radiologic features of CACP are nonerosive arthropathies with smooth flattening of the affected joint surfaces, squaring of the metacarpal and phalangeal heads, coxa vara, short femoral neck, osteopenia, and large acetabular cysts that can be seen on pelvic X-ray.

To date, no effective treatment has been developed for CACP. However, recognition of the condition is important in order to prevent the use of inappropriate and potentially dangerous medications, said Dr. Warman, as well as offer insight into optimal treatment strategies for more common joint conditions. ■

Mounting evidence of the genetic deficiency of lubricin in CACP points to the protein’s importance in maintaining human joint function.

Gelfoam Interposition Spares the Tendon in Osteoarthritis

BY PATRICE WENDLING
Chicago Bureau

TUCSON, ARIZ. — Gelfoam interposition is an effective, tendon-sparing alternative to the anchovy procedure for the treatment of trapeziometacarpal osteoarthritis, Dr. Ronald E. Palmer said at the annual meeting of the American Association for Hand Surgery.

The classic treatment for osteoarthritis of the trapezial metacarpal includes excision of the arthritic trapezium bone, with a ligament reconstruction using a forearm

tendon, typically the flexor carpi radialis tendon. The remainder of the tendon is then rolled up like an anchovy filet when packaged in a can for sale and interposed in place of the trapezium, where it serves as a biological cushion and minimizes collapse.

Gelfoam interposition “is an effective procedure that is much easier to do” than the anchovy procedure, said Dr. Palmer of the Orthopedic Institute of Illinois in Peoria.

“It has few of the complications that the other procedures have—certainly no syno-

vitis or osteolysis—and it spares the use of other tendons that may cause problems.” Dr. Palmer began using Gelfoam in 1996 and has now performed interpositions in 139 patients with symptomatic osteoarthritis of the trapezial metacarpal, Eaton classification stages II-IV.

All patients were evaluated with a clinical examination and questionnaire an average of 2 months after the procedure, said Dr. Palmer.

Pain relief was achieved in all cases, and all patients were satisfied with their postoperative results, he said, citing improved

function and strength as measured by thumb carpal-metacarpal extension and abduction, thumb opposition, grip strength, pinch tip, palmar pinch, and lateral pinch.

The first web space did not atrophy after the procedure. There were no complications or morbidity.

Dr. Palmer said the anchovy procedure provides excellent pain relief.

But in his experience, there frequently wasn’t enough tendon left with the anchovy procedure to adequately fill the space left by the excised trapezium. ■