# Surgery Lessens Pain in Juvenile Idiopathic Arthritis

BY DAMIAN McNAMARA
*Miami Bureau*

BIRMINGHAM, ENGLAND — Surgery can be an effective pain-relieving strategy for children with hip or knee joints severely disabled by juvenile idiopathic arthritis.

Total hip replacement is a good pain-relieving operation, and sometimes is indicated even in young patients, Dr. Johan Witt said at the annual meeting of the British Society for Rheumatology.

"Younger patients are better off getting a hip replacement while they still have bone to put this into," said Dr. Witt, a consultant orthopedic surgeon at the University College of London Hospitals.

Joint replacements have the potential to last a long time, but close monitoring of the patients is warranted.

Synovectomy is an option that can help some patients with juvenile idiopathic arthritis (JIA), but it is used less and less frequently. "I've probably done one in the past year," he said. "This requires intensive rehab to get anything out of it."

Another option for a subgroup of patients is hip resurfacing. "There has been a push from patients over time, including a group of JIA patients," he said. This procedure is indicated only for slightly older patients in whom the disease has largely resolved. "Some patients have an unrealistic view of what resurfacing can do. With some of the marketing around this, patients get confused."

Another choice, osteotomy, rarely is indicated for patients with JIA. In this population, the joint is too stiff and severely involved, and the bone too osteopenic.

Hip involvement is the most common cause of limited mobility in JIA, affecting 30%-60% of patients. The ultimate results of nontreatment include a fixed flexion deformity, adduction, and greater internal than external hip rotation. Other potential consequences of hip deformity are excessive lumbar lordosis, fixed flexion deformity of the knees, genu valgum, and external tibial torsion.

Therefore, early identification of JIA is essential. "The younger you are when arthritis starts, the more likely it is to lead to persistent disability in later life," he said.

Consider preoperative disease activity, upper limb involvement, and adjacent joint involvement, which can be important considerations for rehabilitation. Assess range of motion when a patient is under anesthesia.

In arthritic knees, Dr. Witt said that intra-articular steroids in combination with physiotherapy and rehabilitation are the front-line protocol. Surgery is a second-line option if the first interventions do not yield significant improvements.

Leg length discrepancies are common in children with knee involvement. A discrepancy or a valgus deformity can be corrected with epiphysiodesis.

"Remember this option," Dr. Witt said. "It is a painless way of correcting this condition. It takes advantage of growth potential."

Fixed flexion deformity (FFD) in combination with a valgus is a common presentation of an arthritic knee. "We are generally good at correcting the FFD. If it's a severe deformity, such as a 60-degree FFD, it may require some soft-tissue release in addition to knee replacement," Dr. Witt commented.

In addition, "extreme osteoporosis is associated with active disease and is the enemy," he said. "Many of these patients have been immobile for a long time, and immobility is bad for the skeleton."

Total knee replacement studies in children with JIA all have had short follow-up. Studies of long-term outcomes of knee replacement are needed, Dr. Witt said. ■

# DNA Microarrays May Pave the Way to Quicker JIA Diagnosis

BY JEFF EVANS
*Senior Writer*

BARCELONA — Genetic testing eventually may enable diagnosis of systemic-onset juvenile idiopathic arthritis before the onset of joint involvement, according to growing evidence from DNA microarrays and clinical studies.

Specifically, the testing looks for a particular gene expression profile of the disease. Such tests also have revealed pathways to explore for the prevention of arthritis or the inducement of remission, Dr. Virginia Pascual said at the annual European Congress of Rheumatology.

"One of the problems with this disease . . . is that many times, children have systemic symptoms but arthritis comes later, and not until arthritis shows up can we make the diagnosis. As opposed to [patients with] the majority of other forms of juvenile arthritis, these children do not have detectable autoantibodies and only very rarely do they present with uveitis," said Dr. Pascual, pediatric rheumatologist at the Baylor Institute for Immunology Research, Dallas.

It takes an average of 3 months to make a diagnosis of systemic-onset juvenile idiopathic arthritis (SoJIA) in her clinic.

To get an idea of which genes are being turned on or off abnormally in the active phase of SoJIA, Dr. Pascual and colleagues investigated the gene expression profiles of such patients with oligonucleotide microarray technology. They found serum from patients with SoJIA could induce the expression of interleukin-1β (IL-1β) protein in peripheral blood mononuclear cells (PBMCs) from healthy patients. The expression of IL-1β occurred in a pattern related to disease activity in which patients who had arthritis and already had passed the systemic phase of disease had lower upregulation of IL-1 protein expression than did those with active systemic symptoms.

The researchers found that inhibition of IL-1 with the IL-1 receptor antagonist anakinra (Kineret) induced complete remission in seven of nine patients with SoJIA, lowered fever in all nine, and lessened arthritis in seven of nine. Abnormal laboratory measurements in the patients (anemia, thrombocytosis, leukocytosis, and elevated erythrocyte sedimentation rate) also were corrected with anakinra treatment (J. Exp. Med. 2005;201:1479-86).

At the congress, Dr. Pascual reported on the treatment of an additional nine SoJIA patients with anakinra. In follow-up ranging from 6 to 36 months, 17 of 18 patients in her clinic have responded to the treatment. The sole nonresponder initially responded to anakinra for 3 months (after not responding in the earlier pilot study) but had a break-through flare; the patient now receives another therapy. A second patient who did not respond to anakinra in the pilot study is now in remission on the drug.

Many of these children could be tested for SoJIA in the hospital when they present with systemic symptoms, so Dr. Pascual and her associates set out to profile which genes are differentially expressed in the blood of patients with SoJIA, compared with healthy patients. These genes could then be whittled down to a more manageable set to use in diagnosing SoJIA. In a comparison of 16 patients with active SoJIA and 16 healthy control patients, the investigators found 874 differentially expressed gene transcripts in SoJIA patients. But when they took the 50 genes that best differentiated the SoJIA patients from the control patients and compared the expression pattern of SoJIA patients with those from children with other inflammatory conditions (influenza, systemic lupus erythematosus, PAPA [pyogenic arthritis, pyoderma gangrenosum, and acne] syndrome, or systemic infection with *Staphylococcus aureus*, *Streptococcus pneumoniae*, or *Escherichia coli*), they were disappointed to see that most of these children also differentially expressed the same genes.

Half of the patients with gram-positive bacterial infections, one-third of patients with gram-negative bacterial infections, and one-third of patients with PAPA syndrome identically expressed the same up- and down-regulated genes, she said.

Still in the hunt for a specific expression signature for SoJIA, Dr. Pascual and her associates then analyzed their microarray data differently by examining 88 genes that are differentially expressed in SoJIA patients compared with healthy control patients, but that are not dysregulated in comparisons between patients with other systemic inflammatory conditions and healthy control patients.

"These 88 genes are very stable over time," Dr. Pascual noted, giving an example of a SoJIA patient who had two disease flares but still had the same gene expression profile for these genes in two blood samples taken 2 years apart. The researchers then reduced those 88 genes to a set of 12 genes to diagnose SoJIA.

In newly hospitalized patients with a fever of unknown origin, this set of 12 genes correctly identified SoJIA in six of seven patients; the signature was correctly negative in another two patients who had SoJIA ruled out. The 12-gene set also correctly excluded 19 of 20 patients with infectious or other inflammatory diseases. This 12-gene expression signature of SoJIA went away in nearly all patients after treatment with an IL-1 blocker. The expression signature "seems to be linked in a way to the blocking of the IL-1 pathway," she said.

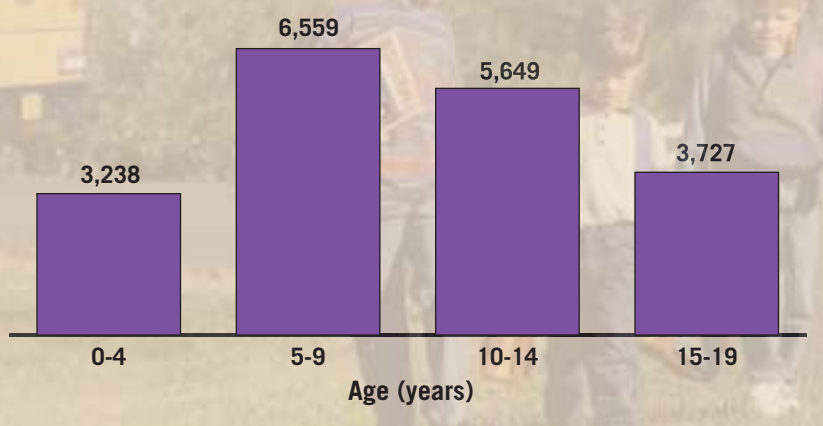
The 12-gene expression signature proved to be specific to the systemic phase of SoJIA, as it correctly identified 22 of 23 patients in the systemic phase of SoJIA, none of 12 patients who were in the arthritic phase (without systemic symptoms), and none of 12 healthy control patients.

The goal of a SoJIA expression signature is to diagnose patients with SoJIA as soon as they present to the hospital with fever (before they have arthritis) so that they can be treated with IL-1 blockers—and possibly IL-6 blockers—before they develop arthritis, Dr. Pascual said.

"We are going to apply this test now to a new cohort of patients who are going to be enrolled in a new trial with a different modality of IL-1 blockade [an IL-1 drug] in the United States," Dr. Pascual said. ■

DATA WATCH

**Children Aged 5-9 Years Accounted for the Highest Number Of New Lyme Disease Cases**




Source: 2003-2005 data, Centers for Disease Control and Prevention

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