Adolescents who are double-jointed at increased risk of joint pain

Adolescents who have joint hypermobility (commonly referred to as being double-jointed) are at an increased risk of developing musculoskeletal pain as they age. The shoulders, knees, ankles and feet are commonly affected. The prospective study performed by UK researchers is published in *Arthritis & Rheumatism* and shows that the likelihood of developing pain in the joints in those who are double-jointed is twice that of nonaffected children.

Having loose ligaments can result in joints extending beyond the normal range and studies have shown a possible genetic basis for the condition. When joint pain is present in the absence of a genetic cause, doctors may diagnose 'benign joint hypermobility syndrome'. A number of studies have found that joint pain is a frequent occurrence in children with hypermobility, with some studies suggesting that as many as 74% of children with hypermobility experience pain. However, it has been suggested by other studies that musculoskeletal pain is common in adolescence and does not occur more frequently in children who are double-jointed.

"With such conflicting evidence we set out to determine whether adolescents with joint hypermobility are at risk of developing musculoskeletal pain," explains lead author Professor Jon Tobias from the University of Bristol (UK).

In this investigation, participants were recruited from the ALSPAC, also known as the Children of the 90s study. A Beighton score of six out of a possible nine was used to establish those children who had hypermobile joints at approximately 14 years of age. Hypermobility in individual joints was diagnosed if, for instance, the knees bent backwards or the thumb could touch the wrist. A questionnaire was then used to evaluate joint pain when the participants were almost 18 years of age. Data from a total of 1267 boys and 1634 girls was analyzed. The percentage of adolescents who showed joint hypermobility at the age of 14 years was approximately 5%, and 45% of participants reported any pain lasting 1 or more days at the age of 18 years. A twofold increased risk of moderately severe pain at the shoulder, knee, ankle and foot was seen in those with hypermobile joints. It is of note that there was over a tenfold increased risk of knee pain.
in obese participants with hypermobility, suggesting that mechanical factors may be involved.

Professor Tobias added, “Our study provides the first prospective evidence that adolescents who display joint hypermobility are at increased risk of developing musculoskeletal pain as they get older, particularly in the shoulder, knee, ankle or feet. Further investigation of increased joint pain in teens is warranted to determine whether the long-term effects of joint hypermobility puts them at risk for developing osteoarthritis later in life.”

– Written by Sarah Jones

Innate immunity sensor enzyme discovered

New treatments for lupus and other autoimmune diseases could be possible thanks to two studies by researchers at the University of Texas Southwestern Medical Center (TX, USA). The research could also lead to better treatments for viral, bacterial and parasitic infections.

A new enzyme that acts as a sensor of innate immunity, which is the body’s first line of defense against pathogens, was identified by the research along with a novel cell signaling pathway. Foreign DNA and host DNA in the wrong part of a cell are detected by the pathway, which involves a naturally occurring compound that has been found in bacteria but, to date, not in humans, said Dr Zhijian ‘James’ Chen.

The research published in Science was lead by Dr Chen, professor of molecular biology and a Howard Hughes Medical Institute investigator at the University of Texas Southwestern Medical Center. He said that the response of the immune system to DNA has long been known, but not the mechanism behind this.

“In his 1908 Nobel acceptance speech, Ilya Mechnikov noted that surgeons in Europe treated patients with nucleic acids – the building blocks of DNA – to boost their patients’ immune responses. That observation came four decades before scientists showed that DNA was the carrier of genetic information,” Dr Chen said.

A novel biochemical approach was used to solve this mystery, which involved classical protein purification coupled with quantitative mass spectrometry. This unique methodology elucidated the protein at the centre of the newly discovered pathway.

DNA is normally contained with structures in the cell, such as the nucleus and in mitochondria. DNA outside of the membrane-bound structures and within the cytoplasm is a warning signal to the cell and results in an immune response, which includes the production of type I interferons.

“Foreign DNA in the cytoplasm is a sign of attack by a virus, bacteria or parasite,” Dr Chen said. “Host DNA that somehow leaks into the cytoplasm can trigger autoimmune conditions, such as lupus, Sjögren’s syndrome and Aicardi–Goutiere’s syndrome in humans.”

These studies identified cyclic GMP–AMP synthase as a new sensor of innate immunity, which alerts the cell when it encounters DNA in the cytoplasm. When the enzyme detects and binds to the DNA, it catalyzes the formation of the compound never before seen in humans – cyclic GMP–AMP (cGAMP).

cGAMP acts as a second messenger and binds to STING, an adaptor protein. This compound, in turn, initiates a signaling cascade that results in the production of interferons and cytokines – the agents of inflammation in the cell.

Dr Chen added, “Normally this pathway is important for immune defense against infections by microbial pathogens. However, when the immune system turns against host DNA, it can cause autoimmune diseases. Our discovery of cGAS as the DNA sensor provides an attractive target for the development of new drugs that might treat autoimmune diseases.”

– Written by Sarah Jones


Fibromyalgia drugs found just as likely to harm as to help

A new review in The Cochrane Library has shown that 22% of fibromyalgia patients taking either of two drugs commonly prescribed to reduce pain report substantial improvement whereas unpleasant side effects resulted in 21% quitting the regimen.

The symptoms of fibromyalgia include chronic widespread pain, sleep problems and fatigue. In total, 80% of the 5 million Americans affected by fibromyalgia are women. There is no cure for the disease and the cause is currently unknown.

This review used a quality of life scale to examine the impact of fibromyalgia on patients and revealed that quality of life ratings on a scale of 1 to 100 were lower than 15, even in patients taking medications.

The most commonly prescribed treatments for fibromyalgia are duloxetine (Cymbalta®) and milnacipran (Savella®).

“A frank discussion between the physician and patient about the potential benefits and harms of both drugs should...
occur,” noted the reviewers, led by Winfried Häuser, from Technische Universität München.

Ten high-quality studies involving over 6000 adults who had received duloxetine, milnacipran or placebo for up to 6 months were reviewed. The majority of those included in the analysis were middle-aged, white women.

“This is a very important study,” says Fred Wolfe, from the National Data Bank for Rheumatic Diseases. “There’s an enormous amount of advertising suggesting that these drugs really help, whereas the research data show that the improvement is really minimal.”

The reviewers added that drug treatment alone should be discouraged. By contrast, a multifaceted approach is recommended, which consists of medications, in those who find them efficacious, exercise to increase mobility and psychological counseling to strengthen coping skills.

“A frank discussion between the physician and patient about the potential benefits and harms of (fibromyalgia) drugs should occur.”

“The medical field does poorly with the treatment of fibromyalgia in general,” says Brian Walitt, a coauthor of the review and an expert in pain syndromes at Washington Hospital Center (Washington, DC, USA). “Chasing [a cure] with medicine doesn’t seem to work. The people who seem to me to do best sort of figure it out on their own by thinking about things, getting to know themselves and making changes in their lives to accommodate who they’ve become,” added Walitt.

The anticonvulsant pregabalin (Lyrica®) is also approved for fibromyalgia treatment in the USA and a review of the efficacy of this drug in fibromyalgia treatment will be carried out by the Cochrane Library later this year.

The researchers advised that more neuroscientific research to identify the underlying causes of fibromyalgia and other pain syndromes is required. Until more is known about the disease better symptom control may be achieved through the use of combinations of drug and nondrug treatments.

– Written by Sarah Jones

Sources: Häuser W, Urrútia G, Tort S, Üçeyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. Cochrane Database Syst. Rev. 1, CD010292 (2013); Drugs to Treat Fibromyalgia Just as Likely to Harm as Help, Review Finds: www.sciencedaily.com/releases/2013/02/130221104155.htm

---

IRHOM2 identified as a new target for rheumatoid arthritis therapy

Investigators from the Hospital for Special Surgery (NY, USA) have identified a protein that could serve as an alternative target for novel pharmacotherapy in the treatment of patients with rheumatoid arthritis (RA).

To a great extent, RA is triggered by TNF-α. This protein usually initiates a protective systemic inflammatory response. However, excess TNF-α production can cause tissue inflammation, as seen in RA. TNF-α blockers are the current standard treatment for RA. Nevertheless, their cost, toxicity profile and the fact that they are not effective in all patients has made the discovery of alternative targets for drug therapy a high priority.

TNF-α convertase (TACE) controls the shedding of TNF-α and its biological activity in vivo, making it an attractive target for RA drug therapy. As TACE also provides protection to the skin and intestinal barrier, there are some concerns about the possibility of side effects. IRHOM2 is a protein that regulates the maturation of TACE, leading researchers at the Hospital for Special Surgery to consider it as a potential target for RA therapy.

The activity of TACE has previously been shown to be regulated by IRHOM1 and IRHOM2. Earlier research demonstrated that mice lacking IRHOM2 do not have functional TACE on the surface of their immune cells, and therefore do not release TNF-α. Additionally, these mice did not develop intestinal or skin problems.

In this study, researchers were able to confirm their theories that IRHOM2 only appears to regulate TACE on immune cells, while IRHOM1 regulates TACE in other parts of the body, including in lung, brain and kidney cells. In a mouse model designed to mimic human RA, mice genetically modified to be deficient in IRHOM2 did not develop inflammatory arthritis associated with TNF-α blockers.

“When we tested mice that don’t have IRHOM2 in a model for inflammatory arthritis, we found they were protected and they were protected as well as mice that didn’t have any TNF,” commented Carl Blobel, program director of the Arthritis and Tissue Degeneration Program at the Hospital for Special Surgery. He added, “Because TNF is the driver of RA in human disease, as evidenced by how well anti-TNF drugs work, we feel that this provides a completely new angle on blocking TNF release. It would be wonderful to be able to inactivate TACE in a tissue-specific manner and IRHOM2 provides a unique mechanism for us to do so.”

The researchers hope to be able to identify pharmacological compounds or antibodies that would be able to block the function of IRHOM2, with the eventual aim of developing more specific and less toxic therapies for RA patients than those currently available.

– Written by Sophie Breeze