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ORTHOPAEDICS

Joint effort

The hunt is on for ways to diagnose and treat the joint problems that are now the main chronic problem in haemophilia.

BY KATHARINE GAMMON

As a physician who cares for adults with haemophilia, Annette von Drygalski sees patient after patient with bulging, painful knees and elbows caused by bleeding into the joint. The rise in cases of this crippling condition, which can lead to arthritis and disability, drives the work of von Drygalski and her team at the University of California's San Diego Medical Center — part of a growing body of researchers studying haemophilic joint disease and the pain that it causes.

Before clotting factor became widely available as a treatment (see page S8), people with haemophilia rarely reached adulthood, so haemophilic joint disease was not on the radar of most research programmes. But now that people with the disease have a life expectancy similar to that of the general population, arthritis caused by the disorder has emerged as a serious medical problem.

A bleed inside a joint leads quickly to stiffness and pain. The residual iron from pooled blood causes inflammation of the joint lining, a condition known as synovitis. Physicians can remove the inflamed tissue surgically (which, for people with haemophilia, comes with a high risk of bleeding) or by injecting radioisotopes into the joint. These emit radioactive particles that destroy the cells in the joint lining and prevent further bleeding. Such surgeries are delicate procedures, says Mauricio Silva, an orthopaedic surgeon at the University of California, Los Angeles, who specializes in haemophilic joint operations. "The deformities are much more severe than someone with arthritis," he says.

The basic remedy for bleeding into the joint has been for patients to self-administer more clotting factor when they believe they are having a bleeding episode. But this is expensive, and does not help everyone. "This field will require lots of new thoughts, beyond administering clotting factor for joint health, over the next decade to improve the life of those with haemophilia," says von Drygalski.

Researchers are tackling the problem from multiple directions: through better imaging, by using novel biomarkers that might be able to reveal even minor joint bleeds, and by applying knowledge from other types of arthritis. It will take research in all of these areas to work out new ways to diagnose and treat haemophilic joint disease and understand its causes.

JOINT INSPECTION

One problem is that there is no definitive way for physicians to distinguish between normal arthritic joint pain and that caused by a bleed. Von Drygalski's research shows that only one-third of painful episodes reported by people with haemophilia are associated with bleeding into the joint[1]. Similarly, physicians find it hard to determine the cause of joint pain: in one small study[1], von Drygalski and her colleagues found that physicians' assessments, based on patient interviews and physical examinations, were incorrect in 18 of 40 instances.

Imaging technologies can help. The highest-quality pictures come from magnetic resonance imaging (MRI), but these systems are slow, bulky and costly to run, and so are not commonly used in haemophilia clinics.

With an eye on those drawbacks, von Drygalski and her colleagues developed a clinical tool that uses ultrasound. The musculoskeletal ultrasound (MSKUS) system — featuring a hockey-stick-shaped ultrasound probe — can distinguish between bleeding and inflammation during painful episodes. As part of a large initiative in Europe sponsored by pharmaceutical giant Pfizer, staff at about 10–15 haemophilia treatment centres are currently being trained to use the technology. The same initiative is in the planning stages in the United States, where training will be given at 10 centres.

MSKUS checks the crevices of joints for inflammation or bleeding, and is less costly than MRI but just as accurate, says von Drygalski. In particular, she says, ultrasound provides greater detail on what is happening in acutely and chronically painful haemophilic joints, where bleeding has caused both synovitis and inflammatory changes to soft tissue.

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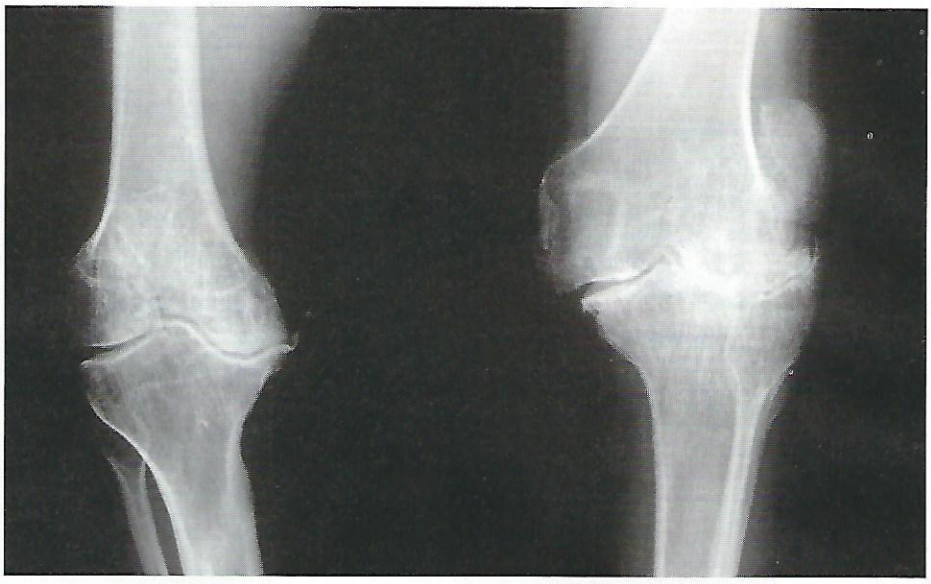

An X-ray of the knees of a person with haemophilia, both damaged from bleeding inside the joints.

MOLECULAR MARKERS

The molecular basis of how haemophilia results in joint pain is still not clear. One hypothesis is that the blood of patients with the disease is a poor activator of a key protein called thrombin activatable fibrinolysis inhibitor (TAFI), which controls clot stability and reduces inflammation. For example, administering additional TAFI relieves discomfort in non-haemophiliacs with inflammatory arthritis. Because the protein stops blood clots from breaking down, it helps people with haemophilia to form clots and maintain them. Von Drygalski, in collaboration with Laurent Mosnier, an assistant professor of molecular medicine at the Scripps Research Institute in La Jolla, California, is studying how treating patients with extra TAFI might help to relieve haemophilia joint problems.

Mosnier, for his part, is doing basic molecular studies to better understand the contribution of clot breakdown in bleeding, and to investigate whether TAFI can be genetically modified to make it more potent and diminish bleeding complications.

To tease out TAFI's clotting and anti-inflammatory roles — and to find out why TAFI may not be fully functional in people with haemophilia — both researchers are using haemophilic mouse models as well as mice that have been engineered to lack the gene that encodes TAFI. Von Drygalski hopes that this will lead to treatments beyond the standard infusions of clotting factor. If it is established that poor TAFI activation in haemophilia contributes to joint disease and inflammation, researchers could develop engineered versions of TAFI with high potency that persist for longer in the body. The researchers hope that such agents could eventually mitigate or even prevent haemophilic joint disease.

DRUG SEARCH

Ideally, physicians would like to have a test that determines which people with haemophilia have the highest risk of developing joint disease. At Rush University in Chicago, Illinois, molecular biologist Narine Hakobyan has found about half a dozen biomarkers in the blood of haemophilic mice[2] that could signal very minor bleeds before damage occurs in the joint.

She and her colleague Leonard Valentino (who now works at health-care company Baxter International in Deerfield, Illinois) set out to create animal models for haemophilic joint degradation in 2001. They made one mouse model that had joint bleeds after injury and another that bled into the joint even in the absence of trauma. They also created a scoring system to evaluate how well drugs stopped bleeding in the joints, which could be used to rank the effectiveness of new drugs.

Hakobyan's study[2] revealed biomarkers that could be detected after injecting just 25 microlitres of blood into the joints of mice that lack clotting factor — showing that even tiny bleeds have markers that could be used to predict joint deterioration. These could guide scientists' search for new drugs to treat haemophilic joint disease, and could point to the fundamental mechanisms underlying the illness. "It would be helpful to know at which point joint disease is reversible, and where we can act to use drugs as therapeutic agents," says Hakobyan. Other markers are likely to be found for different stages of the disease, Hakobyan says.

BEYOND CLOTTING FACTORS

To better understand the joint and its response to bleeding, researchers are studying changes to the bone around it. This may require creative thinking about mechanisms beyond clotting factors, says Paul Monahan, a haematologist at the University of North Carolina in Chapel Hill, who has studied whether rheumatoid arthritis drugs can improve mobility and reduce inflammation in haemophilic mice.

Monahan thinks that treatment with infusions of clotting factor, known as prophylaxis, is not a good way to treat all patients with haemophilia, especially those who have breakthrough bleeding — bleeds that happen in between their infusions of clotting factor. For instance, previous research[3] has shown that regularly giving extra doses of clotting agent beyond what is needed for primary prophylaxis adequately controls joint bleeding in less than 40% of people with haemophilia.

He likens this approach to giving only one therapy to patients with asthma. "You wouldn't treat an asthmatic with just a bronchodilator — you need to address both the acute spasm and the underlying inflammation," he says. Likewise, patients with haemophilia could potentially be treated with drugs that reduce inflammation as well as being given clotting factor.

Another potential therapy is the use of special radioisotopes to attack the inflamed joint lining. In July, Navidea Biopharmaceuticals of Dublin, Ohio, announced a partnership with the start-up firm Rheumco to develop a tin radioisotope technology that blasts out inflamed joint tissue. The idea is to inject a colloidal suspension of tin-117 particles into the joints of children with haemophilia. This radioisotope was selected because it has a small, focused area of radiative impact, so there is less chance of radiation damaging nearby tissue — an important consideration for children whose bones are still growing.

Navidea and Rheumco are completing animal testing for the tin-isotope project and are optimizing the technology for use in people. Being able to treat children with the method would be a boon because early treatment is key for these disorders, says Mark Pykett, formerly chief executive of Navidea and now chief executive of Agilis Biotherapeutics in New York. Physicians have identified joint microbleeds in patients as young as two years old. "If you can prevent that, 10 or 20 years down the road, they will be better off," he says.

The limited treatment options for haemophilic children and adults with joint pain strongly motivates researchers. Only a few decades ago, patients with haemophilia did not have the chance to grow old; now they are feeling the effects of living for longer with the disease. "Joints are so important," says von Drygalski, "because people are living to 60 or 70 years old — just trying to live normal lives." ■

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3. Greene, W. B., McMillan, C. W. & Warren, M. W. *Clin. Orthop. Relat. Res.* **343,** 19–24 (1997).