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Cricothyroid arthritis in a child with familial Mediterranean fever

Sir: We describe for the first time the occurrence of cricothyroid arthritis in a girl who first presented with migratory polyarticular arthritis but eventually developed the classical features of familial Mediterranean fever.

A 9 year old Palestinian Arab girl was admitted in January 1979 with fever and migratory polyarticular arthritis of the large joints. The heart was normal. The erythrocyte sedimentation rate was 110 mm/h and the antistreptolysin O titre was 400 Todd units. A diagnosis of acute rheumatic fever was made and treatment was started with secondary prophylaxis. During the following six years she had several episodes of arthritis, which were interpreted as recurrence of acute rheumatic fever due to irregular prophylaxis, and occasional fever and abdominal pain.

In January 1985 the girl was admitted with fever and arthritis of both elbows and the right wrist. Next morning she developed arthritis of the cricothyroid joint. The diagnosis was verified by indirect laryngoscopy. She also developed arthritis of the interphalangeal joints of both hands. She became better after five days of aspirin treatment. Two months later she had another similar episode of transient arthritis of the cricothyroid and interphalangeal joints. During the following three years the girl had several episodes of fever and abdominal pain, with the frequency progressively increasing to one to two attacks a week. She also developed arthritis of the ankles associated with erysipelas-like erythema. Family history disclosed that her mother, a maternal aunt, and two sisters had had similar recurrent episodes. Prophylaxis with colchicine was effective in decreasing the frequency of febrile and painful episodes; during the past 12 months the girl has had only three mild abdominal attacks and one episode of transient arthritis of the left ankle.

The synovial attack of familial Mediterranean fever typically appears as acute monoarthritis affecting a large joint of the lower extremity.[1–4] Involvement of the small joints, including the temporomandibular, sternoclavicular, and metatarsophalangeal joints, has been described in a minority of patients with familial Mediterranean fever,[1–4] whereas involvement of the interphalangeal joints has been reported to be most unusual.[1] Cricothyroid arthritis in the course of familial Mediterranean fever has not been previously described.

The presentation with migratory polyarticular arthritis, the involvement of the interphalangeal joints, and the long period before the appearance of the classical manifestations of familial Mediterranean fever are other unusual features in this case.

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Trauma and seronegative spondyloarthropathy

Sir: We would like to offer what we believe to be a necessary reply to Professor Panayi's letter published in the *Annals*.[1] Professor Panayi considers that in the two B27 positive patients we described, who developed peripheral arthritis immediately after trauma,[2] physical injury and the onset of peripheral arthritis were only coincidental. The first case represents, in his opinion, a reactive arthritis following gastroenteritis, and the second case, arthritis of the knees begun by chance after the trauma.

If other articles on this subject[3–6] are not taken into account this may seem to be the most logical conclusion, partly because no evidence of causality may be produced other than the immediate onset of peripheral arthritis after trauma, and the lack of an infective trigger. Wisnieski[3] and Masson *et al*[4] have reported other cases of peripheral arthritis in B27 positive subjects immediately after physical injury. In some of these, like our patient 1,[2] there was also urethritis with negative urethral smears and culture, in addition to arthritis. Our patient also had a diarrhoea with negative stool culture, which subsided in two days without any treatment. In 1982 Jacobs *et al* reported that five of their 58 patients with juvenile onset B27 positive spondyloarthropathy had a trauma severe enough for a doctor to be consulted before the onset of peripheral arthritis.[5] In 1988 we reported the cases of two B27 positive subjects who had never had pain to peripheral joints before, but developed an erosive peripheral arthritis of the right hip shortly after a severe physical injury to the same joint.[6] The rapid evolution of the destructive process, which is not usual in erosive arthritis of seronegative spondyloarthropathy, provides further evidence in favour of the triggering role of trauma.

In conclusion, the articles published on the subject suggest that as in psoriatic arthropathy,[7 8] physical injury may, in B27 positive subjects, trigger the onset of a peripheral arthritis predominantly affecting the injured joints. We hope that others will report similar cases and perform studies on the synovial fluid and blood of patients with B27 associated peripheral arthritis following trauma, in an attempt to understand the pathogenetic mechanisms. We appreciate the comments of Professor Panayi and thank him for drawing attention to this topic of seronegative spondyloarthropathy.

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Chondroprotective drugs and osteoarthritis

Sir: I read with interest the leader article by Doherty on 'Chondroprotection by non-steroidal anti-inflammatory drugs' published in the *Annals*.[1]

Although I am in general agreement with the views expressed by Dr Doherty, he raised some issues which I consider deserve further comment.

In his article Dr Doherty questions the relevance of certain laboratory derived data on non-steroidal anti-inflammatory drugs (NSAIDs) to their clinical use in osteoarthritis. He considers the standard for assessing these drugs is the long term symptomatic and functional improvement in patients 'rather than individual biochemical or structural characteristics'. It should be noted, however, that most NSAIDs are also powerful analgesics and may effectively relieve the symptoms of osteoarthritis without necessarily influencing its progression. Pain relief and improvement of joint mobility are thus inadequate criteria for distinguishing between an NSAID acting only as an analgesic and an NSAID which is also positively influencing the underlying osteoarthritic disease. More objective methods of clinical assessment of patient response to drug treatment are therefore required before this matter can be resolved. Such methods are presently under investigation, and promising findings have been reported with biochemical markers of cartilage breakdown in synovial fluid[2–4] and serum,[5 6] *x* ray microfocal (Buckland-Wright *et al*, unpublished data)

and magnetic resonance imaging techniques.[7] Eventually the accuracy and the methodology associated with these techniques will improve sufficiently to allow their routine clinical application, but in the short term we can only rely on data generated from animal studies to guide us in selecting the drugs of potential clinical interest.

Although we all agree that animal models of osteoarthritis are imperfect, they do permit a direct assessment of a drug's effect on a variety of joint features which are relevant to the human condition. These effects include not only changes in cartilage integrity but chondrocyte metabolic activity, subchondral blood circulation, osteophyte formation, synovial cell metabolism, and biosynthesis of hyaluronic acid, all of which should be included in any definition of chondroprotection.[8] Furthermore, most drugs used in clinical medicine today were selected from animal studies in which the drugs showed activity which may, or may not be directly applicable to human disease. If this practice is to be criticised the criticism should perhaps be directed at those pharmaceutical companies that have been reluctant to deviate from traditional methods of drug discovery, for there exists a plethora of 'super aspirins' and it is more by luck than design that some of these molecules seem to show chondroprotective activity.

For more than 80 years the medical community has been content to accept the products provided by the pharmaceutical industry for the treatment of musculoskeletal disorders. Today, as a result of the debate stimulated by laboratory studies, this attitude is changing and doctors are rightly questioning the long term efficacy of their NSAIDs, particularly the deleterious side effects which may accompany their use.

The influence of the advertising industry notwithstanding, the choice of an NSAID should be made by judicious evaluation of the laboratory and clinical data available at the time. Although these data may be imperfect they can provide the stimulus for further investigations and it is only by this means that we can hope to generate the ground swell of opinion necessary to change prevailing attitudes and promote new therapeutic advances in this much neglected field.

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Sir: I am sure that Dr Ghosh and I are in general agreement about the many issues relating to the effects of non-steroidal anti-inflammatory drugs on osteoarthritic and normal joints, and I welcome his comments on this subject.

As mentioned in the 1989 leader,[1] in vitro and animal work have given valuable insight into possible mechanisms of joint injury and repair, and stimulated interest in the effects, either detrimental or beneficial, of currently available drugs on the joints (not to mention the gut) of our patients. Nevertheless, I would reaffirm the need for caution in extrapolating too rigidly such laboratory derived data to the clinical situation of human osteoarthritis.

When considering the natural history or modification by health intervention of any disease process, it is important to distinguish *process* from *outcome* measures.[2] Process measures, clinical or investigative, primarily relate to mechanisms of disease causation and tissue response, reflecting such aspects as inflammation, immune reaction, tissue damage/synthesis/repair, and structural change. Outcome measures, by contrast, relate more to the meaningful effects of disease on the individual, reflecting such aspects as impaired function, suffering, morbidity, and mortality; such measures by their nature are predominantly clinical.

Although process and outcome measures may correlate positively, the former cannot be used to predict the latter.[2–4] In osteoarthritis, particularly, there is marked discordance between symptoms, signs, and radiographic or pathological abnormality: an association between any process markers that we have and outcome remains to be established. Although I share Dr Ghosh's enthusiasm for continuing work investigating biochemical markers of joint damage/repair and improved assessment of structure, we must remain aware of the limitations of such (predominantly process) measures. Again as previously discussed,[1] undue emphasis on cartilage (cf bone, capsule, ligament, muscle) may prove inappropriate. Although common sense dictates that cartilage loss is bad, this is not an isolated change within the joint and need not be the crucial factor determining outcome. For example, we know that despite gross cartilage loss most osteoarthritic joints, especially in the hand,[5] function normally with minimal or only periodic symptoms. In respect of intervention in osteoarthritis the whole joint (not just selected, individual biochemical or structural change) and whole patient need to be considered.

From a clinical standpoint, therefore, symptoms and functional status remain the standard by which to judge long term success or failure in osteoarthritis. Investigation of accompanying structural, physiological, and biochemical changes (in animals and man) may improve our understanding of its process, and perhaps suggest means of prevention. If found to equate with outcome, such process changes may additionally prove useful in monitoring effects of intervention.

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