INTRODUCTION

At a time when people with cystic fibrosis (CF) are living longer and receiving more drug treatment than ever before, symptoms arising from the joints and surrounding structures are both becoming more prevalent and assuming greater significance due to their adverse impact on quality of life. Joint diseases in CF are relatively common and can be both incapacitating and debilitating. Approximately 12-20% of individuals with CF will experience some form of joint disease, and many will require treatment. In general terms, joint symptoms in CF can be thought of as either being directly related to CF itself, a complication of its treatment or due to an unrelated joint disease.

The two main disorders related to CF are the episodic arthritis of CF and hypertrophic pulmonary osteoarthropathy (HPOA). These conditions may arise at any age, however they are both more common in adulthood. Drug induced joint dysfunction in CF is more common than in the general population as a direct result of repeated and/or prolonged exposure to drug therapy. It is also evident that people with CF will experience an array of musculoskeletal symptoms including mechanical back pain. The objective of this article is to discuss the range of joint disorders that affect people with CF and in doing so hopefully raise awareness of their potential effect on health in CF.

Episodic Arthritis
(also known as CF Arthritis and Episodic Arthropathy)
Despite being initially described in children, episodic arthritis typically has its onset in the early teenage years. This form of joint disease is directly due to CF and is probably the most common form afflicting individuals with CF. It affects around 2-8% of adults. Episodic arthritis can affect any individual with CF and it is not necessarily confined to those with more severe lung disease. This form of arthritis is characterized by short-term episodes of joint pain, redness and swelling. The onset is usually sudden but it can come on gradually over 12-24 hours. It is usually self-limiting and resolves within a one-week period. As a rule, all joint symptoms resolve completely between episodes and it can be many weeks to months before the symptoms return.

Large joints are usually affected, with the knee joints being the most common. Smaller joints (such as those of the hands and feet) are involved less frequently. Other joints involved include ankles, wrists, hips, shoulders and elbows (in decreasing order). Involvement is typically uneven through the joints of the body. Everyone will be different but it is likely that the pattern within a given individual will remain the same over time. Sometimes the affected joints have no signs of inflammation (a phenomenon termed arthralgia). Most reports describe this disorder as disabling or incapacitating. Fever or a skin rash may accompany the joint inflammation.

The cause of episodic arthritis is unclear. It tends to run a course of its own and active joint inflammation does not necessarily occur at the same time as an infective exacerbation of lung disease. There has been some suggestion that episodic arthritis may be associated with a worsening of lung disease, however this association has probably come about mainly as a result of sore joints limiting mobility and therefore leading to a reduction in physical activity and physiotherapy. This in turns adversely impacts on lung health and stability.

...related to the excessive activation of the immune system that occurs in CF...

There has been speculation that it may be related to the excessive activation of the immune system that occurs in CF as a result of repeated bacterial lung infections. This theory proposes that antibodies produced in response to infection combine with small components of the bacteria (antigens) to form immune complexes. These complexes in turn may be deposited in the joints and therefore lead to inflammation. Currently there is insufficient evidence to support a clear role for these circulating immune complexes in causing episodic arthropathy, however it is likely that an immune mechanism is involved in one way or another.

In the majority of cases there will be no lasting joint damage following the acute episode. Plain radiographs of the affected joints are usually normal. There is usually no need for
more invasive investigations such as joint aspiration, although this may occasionally be required if there is any concern about the possibility of infection within a joint.

Treatment typically consists of non-steroidal anti-inflammatory (NSAIDs) medications such as ibuprofen, which are only required whilst symptoms persist (i.e. usually less than a week). The majority of individuals will settle with this treatment alone. Sometimes however, NSAIDs are insufficient to control the inflammation, and oral steroids such as prednisone are necessary. Rarely episodic arthritis can progress to permanent joint damage. In the rare cases that involve permanent joint damage, more aggressive and potentially toxic drugs are required and require the direct involvement of a joint specialist (Rheumatologist), which is a service available in most specialist CF centers. In the minority of cases the joint disease parallels the activity of the associated lung disease. In these exceptional cases it is worthwhile aggressively treating the pulmonary exacerbation as this can often lead to an improvement in the joint symptoms.

**Hypertrophic Pulmonary Osteoarthropathy (HPOA)**

HPOA refers to the association of finger clubbing, chronic inflammation of the outer lining of long bones and joint inflammation. It is a condition associated with a variety of diseases, including lung cancer and lung fibrosis (cryptogenic fibrosing alveolitis). It has long been identified as an important and debilitating complication in CF and in fact it was the first reported joint complication of CF. It is likely that it is more common than is currently appreciated and this relates in part to some uncertainty regarding the exact criteria required for a diagnosis of HPOA. Between 2 and 7% of adults with CF are affected with HPOA based on x-ray confirmation. Other studies based on the mere presence of compatible symptoms suggest that it may affect up to 15% of individuals with CF. Adults are primarily affected, males more commonly than females and the average age of onset is approximately 20 years.

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The onset of HPOA is usually gradual and symptoms include joint pain, stiffness and swelling as well as tenderness of the distal ends of long bones such as the ankles and wrists. The joints typically involved are the wrists, knees and ankles and the small joints of the hands and feet are rarely involved. The pattern of involvement is characteristically symmetric (equivalent both sides of the body) and joints can become markedly swollen. There is a spectrum of disease varying from mild to very red and swollen joints. The pain arising from the distal ends of the long bones is related to inflammation and new bone formation developing on the outside of the original outer shell of bone at these sites (periostitis).

In severe cases this process may involve the ribs, collarbones, shoulder blades, pelvis and cheekbones. In men, HPOA may be associated with increased prominence and tenderness of breast tissue, and likewise females may become aware of breast tenderness. The joint and bone symptoms may uncommonly be associated with increased sweating and flushing.
Unlike episodic arthropathy, HPOA is clearly linked to the severity of underlying lung disease. Individuals with HPOA have more severe lung disease and the activity of their joint and bone symptoms typically will increase at the time of an exacerbation, in contrast to episodic arthropathy.

\[\text{Platelets are derived from bone marrow cells...}\]

The cause of HPOA is unclear. Various theories propose a role for the influence of certain nerves and hormones. Unlike episodic arthropathy, an immune basis is not suspected. Perhaps the theory that has received the most attention and seems most plausible is the one pertaining to platelets. Platelets are very small components of blood that play a key role in blood clotting. Platelets are derived from bone marrow cells called megakaryocytes. Megakaryocytes normally travel to the lungs where they are altered to release active platelets. In the process of releasing the platelets, other factors are also released (one in particular called platelet derived growth factor) which have an important affect to increase blood flow and new blood vessel formation. It is suggested that in the presence of the lung disease of CF (and other lung diseases), this process does not take place normally. Megakaryocytes accumulate in the very small blood vessels of the distal ends of the long bones and inappropriately release mediators at these sites, which is thought to lead to the inflammation and new bone formation.

The diagnosis can be made based on the typical clinical findings and the appearances on plain radiographs of the wrists and ankles. The classic radiological finding is of new bone formation. Sometimes plain radiographs may be normal, particularly if they are done early on in the course of the disease. In these circumstances a bone scan will be necessary.

The cornerstone of treatment is meticulous attention to the underlying lung disease. This involves intensive chest physiotherapy and appropriate antibiotic treatment of any infective exacerbation. Relief of symptoms can be achieved with NSAIDs such as aspirin or ibuprofen and in certain circumstances more powerful painkillers are required. Sometimes NSAIDs are either ineffective or contraindicated and a short course of corticosteroids is required. Failing this, there has been a recent report of successful control of symptoms with the bisphosphonate, pamidronate, which is also used for treatment of osteoporosis. This class of medication works to switch off the activity of a type of bone cell called osteoclasts. Symptoms completely resolve following lung or heart-lung transplantation in people with severe lung disease.

**Joint Disorders due to Co-Existent Conditions & Complications of Therapy**

This group of disorders is probably the most important to identify accurately because specific treatment is required for the co-existent joint diseases and drug induced arthropathies require the appropriate identification and then cessation of the responsible drug. Rheumatoid arthritis (juvenile and adult forms), the arthropathy of sarcoidosis and psoriatic arthritis have all been reported in the context of CF, however they are probably not directly caused by CF. Each of these different forms of joint disease has a characteristic pattern of joint involvement and various associated features, which are
beyond the scope of this article. Confirmation of their diagnosis and subsequent management requires specialist rheumatology involvement.

“A number of medications routinely used…can cause arthritis.”

A number of medications routinely used in the treatment of CF can cause arthritis. Ciprofloxacin, an antibiotic commonly used in the outpatient treatment of infective exacerbations, is probably the most common drug to produce joint symptoms. Ciprofloxacin can cause both joint aches as well as acute inflammation, and the onset of pain typically will occur after 3-8 weeks of treatment. The knee joints are usually affected and symptoms resolve within 2 weeks upon discontinuation of the drug. There is no evidence of permanent joint damage. Ciprofloxacin can also cause tendonitis especially in the achilles tendon. Cimetidine, which is an antacid used less frequently now than previously to treat symptoms of heartburn, can also cause joint inflammation. Again, as with almost all drug-induced arthropathies, the symptoms resolve with discontinuation of the drug.

SUMMARY

Joint disorders in CF can be debilitating and adversely impact on quality of life. Further, through their effect on limiting physical activity, joint symptoms can also compromise optimal treatment for the underlying lung disease. As such, an awareness of these disorders and their available treatments is important. There are two main disorders that are directly related to CF, episodic arthropathy and HPOA. Effective treatment is available for both of these. People with CF are also at an increased risk of drug-induced arthropathy owing to their repeated and often prolonged drug exposure, and early recognition of joint symptoms can lead to the appropriate withdrawal of the culprit medication. A number of other joint diseases are known to co-exist with CF, however CF probably does not cause them.

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Editor’s Note: Dr O’Carroll and Dr Bell have provided a list of recommended reading on this topic. For a copy of this list, please contact us: editor@cfww.org