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Ultrasound and magnetic resonance imaging assessment of joint disease in symptomatic patients with Cystic Fibrosis Arthropathy

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Abstract

Objectives:

Cystic Fibrosis Arthropathy (CFA) is a term commonly used for joint pain with and without swelling seen in some patients with CF. Early studies into CFA focused on presence of rheumatoid factor and immunological changes on synovial biopsy, with parallels drawn between respiratory and joint activity. Identification of anti-cyclic citrullinated peptide antibodies (anti-CCP) as a marker of rheumatoid arthritis (RA), along with increased access to sensitive imaging techniques including ultrasound (US) and magnetic resonance imaging (MRI), offer great potential to investigate and more accurately understand the type(s) of inflammatory arthritis that may underlie CFA. The

aim of this study was to phenotype an active CFA cohort using serology and imaging, as a basis for further work in this understudied area.

Methods:

This was a prospective observational cohort study of symptomatic CFA patients presenting with joint pain. Participants underwent serological testing, clinical and US joint and enthesal assessment, as well as MRI of the most symptomatic joint/joint area.

Results:

Ten symptomatic patients were studied with 9/10 having positive clinical findings. Inflammatory changes on US were seen in 8/10 cases. Five patients had positive findings on MRI (3 of whom had received IV gadolinium contrast). This included patients with significant erosive changes. One patient was anti-CCP positive suggestive of RA, and two were anti-nuclear antibody positive.

Conclusion:

Imaging, and to a lesser extent serology, identified inflammatory joint pathology in a proportion of cases, providing important data to explore in a large CFA cohort examining the clinical and imaging phenotype of this group.

Introduction

Cystic fibrosis arthropathy (CFA) is the most common form of joint pain in patients with cystic fibrosis (CF) and can be associated with significant morbidity (1, 2). The clinical picture may vary from a minimally swollen joint to a polyarthritis with swollen, tender joints resembling those seen in rheumatoid arthritis (RA). Joint disease in patients with CF may also be associated with adverse drug reactions and gout(3). CFA can follow a palindromic pattern with a remitting and relapsing course and symptoms mostly disappearing between attacks.

Cystic fibrosis arthropathy is usually described as a form of polyarthritis unique to CF that cannot be classified as any other rheumatological disorder(4). However, there is no formalised definition or diagnostic criteria for this condition and little understanding of its aetiology, pathogenesis or sequelae. CFA can affect any joint and while symptoms may be self limiting, they can also be severe, persistent and difficult to manage. Arthropathy may also be associated with joint effusions and in some cases a vasculitic rash(5).

Despite CFA becoming an increasing cause of morbidity in an ageing population, there is little data available about the spectrum of disease, underlying mechanism of the disease process, imaging and effectiveness of treatment (6-9).

There is no published literature describing the radiological ultrasound (US) and magnetic resonance imaging (MRI) features of symptomatic arthropathy in patients with CF.

The aims of this study were to describe the clinical phenotype of CFA, identify potential correlations between the history, examination and imaging and to assess the relative sensitivity of US and MRI as tools for assessing joint pathology in this group of patients.

Subjects and Method

Patients

This was a prospective observational cohort study of symptomatic adult patients with CF presenting with joint pain with or without joint swelling. All patients were attending the Leeds Adult CF Centre and had classical features of CF in conjunction with either two mutations or two abnormal sweat tests. Patients presenting with symptomatic joint pain were recruited to the study. Participants had serological testing followed by a clinical assessment, joint US and MRI on the same day. The study was approved by the Yorkshire and Humber Ethics committee 11/YH/0205.

Clinical assessment

Demographic, clinical and pathology data were collated from the CF unit's electronic patient record(10). Recorded parameters are summarised in table 1. A detailed symptom questionnaire covering respiratory, dermatological, gastrointestinal and joint symptoms as well as past medical history, drug, family and occupational history was undertaken with each subject prior to a quantitative joint assessment by an experienced physician (SD) who was blinded to the imaging results. As there is no validated joint assessment tool for CFA, a comprehensive 62 joint count was recorded, with joints assessed for pain, tenderness and swelling. The following areas were assessed (bilaterally where applicable): temporo-mandibular joint, acromio-clavicular joint, sterno-clavicular joint, shoulder, elbow, wrist, metacarpophalangeal joints 1-5, proximal inter-phalangeal joints 1-5, distal inter-phalangeal joints 1-5, cervical spine, lumbar spine,

sacro-iliac joints, hip, knee, ankle and metatarsophalangeal joints 1-5. Patients with 1-4 swollen joints were considered to have oligoarthritis, those with more than 4 were classified as polyarthritis.

Serology

Routine bloods were taken for full blood count, biochemistry (including CRP) and serology including rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP) antibody and anti-nuclear antibody.

Musculoskeletal Ultrasound (US)

At the time of clinical assessment, each patient underwent Ultrasound examination utilising grey scale (GS) and power Doppler (PD) assessment on a standard set of 34 joints and 14 peripheral entheses. Up to 10 additional joints were scanned if symptomatic. The US was performed by experienced ultrasonographers (JEF, LH) using a GE Logic E9 machine employing 12–5 MHz and 15–7 MHz linear transducers.

Ultrasound changes were scored semi-quantitatively using a grade 0-3 scale for both GS and PD, as previously described(11). Presence or absence of erosions at each site was also recorded. A core joint set of bilateral MCP 2-5, PIP 2-5, wrist, knees and MTP2-5 were scanned and other sites only if symptomatic (including shoulder, elbow, ankle and mid-tarsal joints). Each joint was scanned in both longitudinal and transverse planes. For the wrist, the radiocarpal, intercarpal, and ulnar-carpal joints were scanned and the highest GS and PD scores for any compartment were used as the overall score in this analysis. For the knee, the suprapatellar pouch and medial and lateral gutters

were scanned and the highest GS and PD scores for any compartment were used in this analysis as the overall score.

For entheses, bilateral medial and lateral elbow epicondyles, quadriceps tendon, superior and inferior patellar tendon, Achilles and plantar fascia insertions were scanned. GS and PD were scored on a 0-3 scale as previously described and maximum enthesal diameter in the longitudinal plane was noted(12). Presence or absence of erosion, bursa, bony spur, intra-tendinous calcification and tendon tear were also recorded.

Magnetic resonance imaging (MRI)

MRI of the most symptomatic joint/joint area was performed at the time of clinical and US assessment, with intravenous gadolinium contrast given where possible. Two MRI protocols were utilised, according to the patient's presentation, with the patient having either one knee or 1 hand and 2 feet imaged. Details of these MRI protocols are provided as supplementary material in table 5. MRI can visualize similar structures to US but often requires longer imaging times and reporting which limits the number of joint sites which can be assessed. Inflammatory arthritides such as rheumatoid frequently affect the feet (MTPs) first and have a predilection for the hands also, which is why the MRI protocol was devised. The knee protocol aims to capture those with a more 'sero-negative' large joint pattern of disease, as you may see in reactive arthritis. We are therefore trying to cover all potential aetiologies to maximise the information gained.

The MRI images were then read by an experienced musculoskeletal radiologist (AG) for synovitis (0-3 scale) and presence/absence of erosion. For the knee the following areas were assessed: supra-patellar pouch, medial and lateral recesses, medial and lateral joint spaces, quadriceps tendon, superior and inferior patellar tendon. For the hands and feet the following areas were assessed: unilateral MCP 2-5, PIP 2-5 and wrist (where overall highest score was used), bilateral MTP 2-5, Achilles tendon, plantar fascia. Presence/absence of hand and feet tenosynovitis was also recorded.

Statistical analysis

US and MRI scores and counts are presented as medians, inter-quartile ranges and ranges. Spearman's rank correlation was used to assess the extent of association between clinical, serological and imaging characteristics. Bias-corrected accelerated 90% confidence intervals for Spearman's rho were obtained from 1000 bootstrapped samples. A p value <0.05 was taken as significant.

Results

Ten subjects were recruited, mean (range) age 31 (23-41) years with 7/10 being female. Median duration of symptoms at the time of assessment was 48(12-204) months with half the patients having either constant or daily symptoms. None of the patients had a history of gout or hypermobility while one patient had a history of dactylitis. Clinical and serological data is summarised in table 1.

Three subjects reported symptoms affecting the large joints while the remaining seven had symptoms affecting both small and large joints. On clinical examination, 2/10 patients had no evidence of joint swelling whilst one subject had a single swollen joint.

However, all three subjects reported bilateral joint symptoms (Table 2). The majority of patients had a symmetrical pattern of disease affecting the wrists, knees and hands.

Axial joint assessment was unremarkable

Ultrasound

Joints

Median (range) total GS score was 10.5 (3 to 29) based on the 30 joints scanned (Table 3). Five patients had evidence of joint erosions on US.

Entheses

Two patients had erosions, one had bony spurs, 2 had tendon tears, 2 calcification and 4 bursae. The two patients with erosions had GS=0 & PD=2 and GS=2 & PD=3 in the eroded site respectively; the latter also had calcification in the same site. A summary of grey-scale (GS) US scores and location enthesal pathology is summarised in (Table 3).

Magnetic resonance imaging

Five patients had positive findings on MRI, 3 of whom had received IV gadolinium contrast. This included patients with erosive changes on US. There were no erosions on MRI in any of the sites scanned.

None of the 4 patients whose hands and feet were scanned had synovitis in their MCPs or PIPs. One patient scored 2 in their wrist and this same patient had a total score of 7

for synovitis across 4 of their MTPs, whilst the rest all scored 0. This patient's wrist was tender, swollen and painful clinically, but had no clinical issues in their MTPs. Another patient had plantar fasciitis, whilst another had 5th finger extensor tenosynovitis and peroneal tenosynovitis in the ankle.

Six patients had their knees scanned. In one, synovitis could not be scored due to lack of contrast. Of the 5 patients with synovitis scores, only 1 had detectable synovitis, scoring 11 in total across the 5 knee regions scanned (all 5 were involved). The knee of the patient with MRI synovitis was clinically tender, swollen and painful. However there were two more patients with clinical issues, one whose knee was tender and painful, another whose knee was swollen and painful, neither of whom had MRI synovitis. None of the patients had knee tendonitis on MRI.

Comparison between MRI and GS findings

In the hands and feet there was next to no correlation between GS and MRI. For example one patient with evidence of MRI synovitis in 4 MTPs and 1 wrist had an US GS score of 0 and 2 in their MTPs wrist respectively. None of these joints had evidence of synovial vascularisation according to PD (all scored 0). Meanwhile of the 71 joints deemed not to have synovitis on MRI, 15 scored GS=1, 6 scored GS=2 and 2 scored GS=3. Two scored PD=1, one scored PD=2 and another scored PD=3. Of the 76 joints in the hands and feet scanned on MRI, none of which were found to have erosions, 1 was identified as having an erosion on US.

In the knee, the patient with significant MRI synovitis scored GS=3 and PD=3. However, of the patients without MRI synovitis, two scored GS=2 and another scored GS=3 (none scored PD>0).

PD and GS scores association between with joint assessment

Total GS score was only very weakly correlated with joint counts [tender rho (90% CI)=0.25 (-0.46, 0.76); swollen rho=0.31 (-0.27, 0.70); painful joint count rho=0.21 (-0.49, 0.80)]. Correlation with total PD score was stronger for tenderness and much stronger for pain (tender rho=0.51 (-0.15, 0.91); swollen rho=0.19 (-0.36, 0.72); painful rho=0.82 (0.66, 0.91)]. The number of joints scoring >0 for PD was associated with both tender and painful counts (Table 4).

Serological markers

There were no clear correlations between clinical history, serological findings and joint assessments. One patient was anti-CCP positive suggestive of RA and two were anti-nuclear antibody positive. There were no features of systemic lupus erythematosus (SLE),

Conclusion

The results from this study confirm the inflammatory nature of CFA with the majority of patients having positive clinical features and inflammatory changes on US. Both large and small joints were involved, particularly knees and wrists in a symmetrical fashion. Such a pattern of joint involvement exhibits overlap between the RA pattern of

symmetrical disease and the large joint predilection of a sero-negative oligoarthritis.

This contrasts with reactive/post-infection sero-negative arthritis which often presents as an asymmetrical oligoarthritis.

Both US and MRI are extremely useful for assessing and monitoring joint disease.

Ultrasound is able to detect synovitis and effusion (13). It is very useful at assessing tendons, cartilage thickness and bony erosions. Views of certain joints such as the mid-carpal joint can be limited due to a lack of acoustic window. MRI can visualize similar structures to US but often requires longer imaging times and reporting which limits the number of joint sites which can be assessed. With MRI, the larger the area of interest, the more the trade-off occurs with respect to detail. To get the detail, a smaller focussed area of interest is identified, using an appropriate coil to achieve this. The MRI images were assessed for synovitis (active contrast uptake in areas of synovial hypertrophy), whereas the US images were scored in component parts (GS showing synovial hypertrophy), (which isn't necessarily active synovitis and power Doppler signal presence (an indicator of an inflammatory process)). This means that joints without synovitis on MRI can still have positive GS scores on US, indicating synovial thickening only. Differences exist between US and MRI features in different joint diseases.

In CF, MRI appeared to be a less sensitive tool for detecting joint pathology, and there was poor agreement between the two imaging modalities. There was a significant association between clinical joint assessments and ultrasound findings. Further large scale studies are required to characterise the differences between MRI and US in this population.

The advantage of US chiefly lies in its ability to image multiple joint areas at the same sitting, nor does it require the use of contrast. We used several different MRI imaging protocols based on the patient's symptoms, although the inability to give contrast because of a history of serious allergies was a frequent problem, perhaps over-represented in a such a group where allergy develops with repeated antibiotic use(14). Without using contrast, the ability to reliably differentiate synovitis on MRI is reduced.

Clarification of the diagnosis with a detailed history, joint examination and serology is essential when assessing individuals with CF and joint symptoms. CFA remains a diagnosis of exclusion and other arthritides such as drug induced arthropathy, crystal arthritis such as gout and specific inflammatory arthritides such as rheumatoid arthritis need to be considered in the differential diagnosis (3, 15). In the present study, one of the 10 patients proved to be positive for anti-CCP suggestive of RA, and two were anti-nuclear antibody positive. Anti-CCP is has been previously described in patients with CF and presumed RA (7). None of the patients were receiving quinolones and the three patients receiving intravenous antibiotics had developed symptoms prior to commencing treatment.

Cystic Fibrosis Arthropathy is a well-recognised complication of CF occurring in 9% of patients attending the Leeds Adult unit. There is presently little data on the pathophysiology of this condition. The most likely hypothesis is that CFA is a systemic reflection of the heightened and predominantly neutrophil driven immune-response seen in the CF lung (16). Early studies have focused on presence of rheumatoid factor and immunological changes on synovial biopsy, with parallels drawn between respiratory and joint activity. In this study only 3 patients were receiving intravenous antibiotics for a

pulmonary exacerbation with some patients having a normal CRP despite symptoms of arthropathy. Further larger cohort studies are needed to explore the association between CFA and lung disease. In one small study, high levels of circulating immune complexes and scanty lymphocytic infiltrates on synovial biopsies with positive immunofluorescent staining for deposits of IgM, IgG and components of complement C1q, C3, and C4 were demonstrated in patients with CFA(17).

Sensitive imaging techniques such as MRI and US are being used more frequently to assess the extent, variability, differences and distribution of inflammation in various rheumatological conditions such as RA and psoriatic arthritis (18). While the present study is limited by the sample size, these imaging techniques have proved helpful in characterising the inflammatory disease process in CFA. They may also provide biomarker and surrogate outcome measures for monitoring disease progression and response to future treatments. To date there have been no randomised controlled trials assessing the safety and efficacy of disease modifying anti-rheumatic drugs in CF-related arthritis, but small case series have reported the use of sulphasalazine, sodium aurothiomalate, methotrexate and leflunomide with variable success and tolerance.

In conclusion, US imaging, and to a lesser extent serology identifies inflammatory joint pathology in the majority of cases of CFA. US can be used as an adjunct in the diagnosing and as a tool for monitoring the response of modifying anti-rheumatic drugs and new therapies in CFA. Ultrasound is better placed for assess patients from a feasibility point of view. In terms of imaging phenotype, the possibility of a bilateral wrist/knee phenotype as defining typical CFA has been highlighted. Further studies in

larger cohort of patients are needed to explore the clinical and imaging phenotype of this group of patients.

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