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Imaging treatment in sacroiliitis and psoriatic arthritis & treatment of entheseal pathology in resistant spondyloarthropathy

Making Education Easy

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Professor McGonagle is internationally recognised for his work in imaging to elucidate the pathogenesis of musculoskeletal diseases and for his work in the biology of Mesenchymal Stem Cells in arthritis and their role in pathogenesis/repair in rheumatic diseases.

His major interests include imaging to understand pathogenic mechanisms of arthritis in man and using this imaging knowledge to define the cellular and molecular basis for disease initiation.

He is active in research across rheumatoid arthritis, the seronegative spondyloarthropathies and osteoarthritis, the latter being the major theme of the Wellcome-EPSRC Centre of Excellence in Medical Engineering.

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The history of psoriatic arthritis

Psoriatic arthritis (PsA) was discovered at the University of Leeds by Verna Wright, whose seminal 1956 paper in the Annals of Rheumatic Diseases described the common findings of nail disease in association with arthritis.[1] The spondyloarthritis (SpA) concept, including PsA, was also developed in Leeds by Moll and Wright.[2] This concept proposed that the aetiology of these arthropathies might be based on a unified concept, although subsequent research has failed to establish an anatomic or pathological basis for the "common thread".[3,4]

In 1998, Helliwell and colleagues in Leeds confirmed some of the radiological differences between PsA and ankylosing spondylitis (AS) described earlier by McEwan and colleagues, with the pattern of spinal disease and fusion in PsA more likely to be unilateral sacroiliitis, fewer syndesmophytes (chunky) and express lower levels of pain.[5,6] Another commonly reported finding is asymptomatic radiographic axial disease in psoriasis and PsA.[7-9]

Typically, the syndesmophytes in PsA tend to be sparse, chunky and asymmetrically distributed, whereas AS is more typically around the spine. This abnormality or pattern of spinal involvement is said to be present in about 40% of PsA patients. The advent of imaging with magnetic resonance imaging (MRI) and ultrasound has led to a unifying theme for this entheopathy; insertional site inflammation is now a well-recognised feature of PsA. The publication of the Mander Enthesitis Index (MEI; measures tenderness at 66 sites) followed by a subsequently modified MEI (measures tenderness at 22 sites) and also the Maastricht Ankylosing Spondylitis Enthesitis Score (measures tenderness at 13 sites), have helped researchers to recognise the primacy of enthesopathy.[10,11] A drawback of the measurement of enthesitis measurement is that it is very difficult to validate because it is impossible to take tissue for measurements, in contrast to the synovium.

In 1996, McGonagle hypothesised that enthesitis is ubiquitous in SpA. For instance, at least 32 entheses are present in a knee joint, with many insertions. Even the most skilled rheumatologist is not capable of palpating these structures, because they are intra-articular or deep-lying. Moreover, other closely juxtaposed factors including bursitis and synovitis cannot be discriminated from the enthesitis. Two previous papers on this subject that used conventional T1-weighted imaging MRI saw no difference between SpA and rheumatoid arthritis (RA).[12,13] In contrast, fat-suppressed MRI established that RA knee disease is typically a synovitis, with florid bone oedema (osteitis) reaction adjacent to the insertions in the posterior cruciate ligament, with inflammation extending beyond the actual tendon/ligament insertion to bone with extensive inflammation of the underlying bone marrow.[14] This pattern of abnormality is seen in about 30–40% of cases with knee disease. In 1999, a *Lancet* article by McGonagle and colleagues proposed that the difference between RA and SpA was that the spondyloarthropathies had a primary site of disease at the enthesis with cytokine diffusion leading to a secondary synovitis and diffusion into the extracapsular tissues leading to abnormalities such as dactylitis, whereas the synovitis of RA is primary (see Fig. 1).[15]

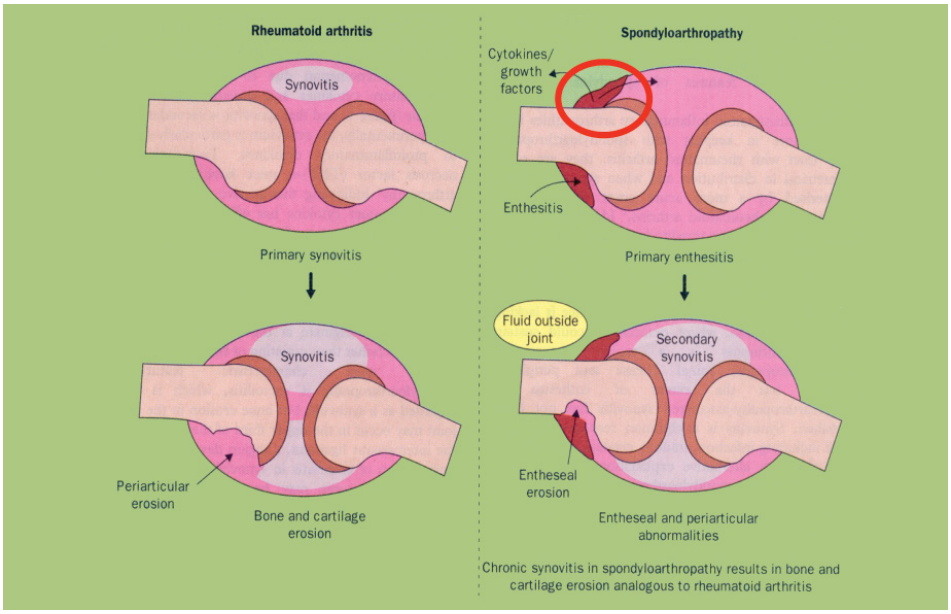

Figure 1. Synovial histology of RA vs SpA.[15]

This provocative proposal polarised opinions amongst researchers. It is impossible to prove in humans whether every manifestation equates to an enthesitis in every patient with PsA. Primary enthesitis models of PsA and SpA provide researchers with experimental systems for studying specific aspects of the disease process.

Psoriatic phenyotypes without T cells

The DBA/1 murine model of PsA clearly shows that the disease starts at the enthesis and subsequently spreads into the soft tissues, nail and bone.[16,17] Spontaneous arthritis in ageing male DBA/1 mice is accompanied by dactylitis with extensive subcutaneous oedema and tenosynovitis with disruption of muscle and tendon fibres, with inflammatory reaction adjacent to the enthesis.

In the tumour necrosis factor (TNF) transgenic model, evidence first published by Kontoyiannis and colleagues in 1999 showed that dysregulation of the TNF gene resulted in chronic inflammation of the joints and intestine; this murine model was accepted as a model of RA.[18] Prof. McGonagle noted that the evidence was actually representing prominent enthesitis. The same researchers later published the results of transplantation experiments in this TNF transgenic model.[19] Transplantation of wild-type normal bone marrow into an irradiated TNF transgenic mouse (in which the only cells producing TNF were non-immune cells or stromal cells, followed by reconstitution with normal TNF production) showed that disease starts at the enthesis in the stromal cells, with the local inflammation leading to recruitment of other pro-inflammatory mediators with immune cell ingression and activation. Thus the researchers clearly showed that a disease that was thought to be a surrogate for RA actually started at the enthesis and was due to intrinsic abnormalities in non-immune cells.

Another example of this non-immune phenotype is illustrated by a missense mutation in proline-serine-threonine phosphatase–interacting protein 2 (PSTPIP2) in a murine model of inflammatory bone disease.[20-22] Phosphatase is specifically expressed in osteoclasts and macrophages of the mice, which develop dactylitis, nail disease, skin hyperkeratosis and osteolysis. In these mice, disease arises at these sites independently of the synovium and of the immune system *per se*. Thus, very good animal model evidence documents the disease starting at the enthesis and spreading to the synovium and bone.

Understanding enthesitis in man

An enthesis is more than a focal attachment, rather, it is described as a group of related tissues designed to aid joint locomotion and be resistant high levels of mechanical stress.[23] The concept of the 'enthesis organ' was introduced by Benjamin and McGonagle, and consists of the following elements:

- The enthesis attachment site
- The adjacent bony tissue
- Bony tuberosities near insertions
- The adjacent fibrocartilages
- The adjacent synovium (SEC)
- Functional Enthesis – no insertion but identical anatomy, histology, mechanics and pathology

- Tendons

- Fibrocartilagenous synovial joints.

The enthesis attachment site: Murine studies have revealed that the fibrocartilage is shock-absorbent tissue with virtually identical function to articular cartilage, lining the adjacent bone and upper surface of the tendon (see Fig. 2).

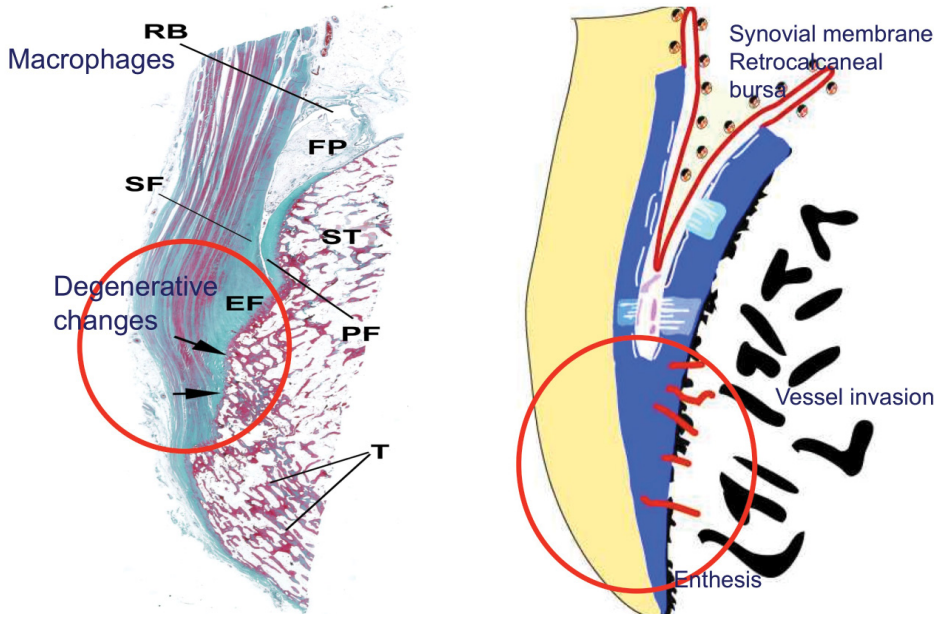

Figure 2. Tendon Enthesis Organ.

The adjacent bony tissue: High-resolution MRI studies and ultrasound-guided biopsy have shown that the epicentre of enthesis is not necessarily at the insertion but instead may be in the adjacent tissues, which are functioning as a unit.

When McGonagle and colleagues began to use ultra-short echo time (UTE) MRI and ultrasound scanning of enthesopathy, they noticed considerable bone oedema such as in cases of Achilles enthesitis and associated plantar fasciitis. The actual structure itself appeared to be relatively normal, because the tendon fibres are so closely intertwined that they restrict or minimise the amount of blood vessel infiltration. Biopsies of these lesions revealed vessel infiltration and inflammatory cells.[24]

Prof. McGonagle notes that osteitis or bone marrow with inflammation at insertion sites is only seen in ~40% of insertion sites. Thus, this osteitis is very important and characteristic, but not present in most cases.

The actual tendon is very difficult to see on conventional MRI, because of the intrinsically low blood vessel density and because it does not allow inflammatory cell accumulation. In contrast, the more recent technique of ultra-short echo time (UTE) MRI clearly delineates the inflammation relating to enthesopathy in the adjacent bursa and in the tendon.

Bony tuberosities near insertions: At entheseal points of insertion, Benjamin and McGonagle have shown that the normal caderveric enthesis at sites of insertion to the bone is characterised by substantial microdamage.[25]

The link between entities like the SAPHO syndrome and PsA has been queried, because of the lack of clear evidence for enthesitis-like features. Prof. McGonagle made the point that the entheses are so strongly anchored to bone, with substantial osteitis at the anchorage site and lots of microdamage at those sites, that the evidence supports the conceptualisation of this link between the enthesitis and the bone.

The adjacent fibrocartilages: A bone tuberosity is lined by fibrocartilage that minimises stress at the enthesis, so that when the Achilles or other insertions contract, they are also exerting pressure over this point. The load is therefore distributed over a wide area. This explains why some patients with PsA present with recalitrant bursitis and the enthesis proper is not tender or inflamed on clinical exam or imaging. Benjamin and McGonagle have shown that the entheseal fibrocartilage is riddled with microdamage with age: histological analyses of cadaveric entheses found a "synovio-entheseal complex" at 82% of entheses.[26] These findings suggest a novel mechanism by which synovitis could develop in both degenerative joint disease and spondyloarthritis.[26] Ultrasound imaging of the fibrocartilage at the enthesis has revealed similar microdamage also occurring in younger, healthy subjects; erosion at the normal fibrocartilage also reveals areas of destroyed fibrocartilage.[27]

The adjacent synovium: These cartilages require calcification and oxygenation; consequently, synovium is present – the synovio-entheseal complex. As well as microdamage in these structures, Benjamin and McGonagle have reported evidence of synovial hyperplasia adjacent to these insertions in fresh

cadaveric tissue from patients who had no clinical arthritis; up to 70% at some part of the enthesis had inflammatory cell infiltration and even evidence of pannus-type tissue eroding these cartilages in normal Achilles entheses.[26] In summary, there is much evidence that normal entheses in all the adjacent tissue are subject to much damage.

Initial criticisms of MRI in seronegative disease were that it does not always show obvious enthesitis. However, florid cartilage in the posterior cruciate ligament can articulate with the posterior cruciate ligament and thereby dissipate stress over a wide area, creating a dysfunctional problem in the structure manifests as synovitis. Conceptually, this is an entheseal pathology. Current imaging cannot prove this to be the case in humans, whereas it can be proven in animal models. MRI and histology of fresh cadaveric knee tissue has shown that in the anterior cruciate ligament the normal enthesis is a site of abundant microdamage, which undergoes repair responses in healthy conditions.

Functional Enthesis

Structures exist that are not insertions in the true sense, but behave like insertions. In SpA, a distinctive pathology exists independently of synovitis or insertion, with diffuse osteitis adjacent to an enthesis. The resulting structure encompasses both tension and compression of the bone, as with a normal enthesis.

Some have questioned whether a link exists between periostitis and enthesitis. However, in entities such as osteomyelitis or bone tumours, periosteal reactions are visible. Thus, wherever there is bone inflammation, there may be a subsequent periosteal reaction of bone growth that occurs related to these structures.

Similarly, MRI studies by Healy and Helliwell have shown abundant inflammation in PsA manifestations including dactylitis, although they did not highlight the presence of enthesitis.[28] Notably, the sacroiliac joint is a structure that functions like an enthesis. One of the earliest abnormalities in the sacroiliac joint is subchondral bone oedema that may not be related to an enthesis *per se*. The sacroiliac joint is a fibrocartilaginous joint and because it is vertical, it sustains both compression and shearing-type (tension) forces, which influence fibrocartilage development. Thus, a unifying biomechanical basis explains why disease occurs at this site.

Fat-suppressed imaging studies by Tan and McGonagle of unilateral sacroiliitis in a young man with a 3-month history of PsA revealed quite severe changes in the soft tissue along the muscle insertions.[29]

Mechanical and inflammatory enthesopathy bone changes

Bone oedema patterns in mechanical and SpA enthesitis look similar on MRI. Repeated MRI assessment of 21 elite-unit Finnish military recruits during their intensive physical training period and on completion of the 5-month training programme detected that asymptomatic grade I bone stress injuries were common.[30] Notably, these injuries healed or remained grade I asymptomatic, even when intensive physical activity continued. Thus, the abnormalities and changes seen in inflammatory SpA disease are also present in normal people.[31]

American College of Rheumatology Expert Panel recommendations for the diagnosis of SpA include back pain plus a positive MRI. However, McGonagle noted that there are degrees of positivity. In 2001, McGonagle and colleagues developed the Leeds MRI scoring system, grading lesions from 1 (mild) to 3 (severe).[31] Importantly, McGonagle cautions clinicians to be careful when interpreting Grade 1 lesions in SpA, which are seen in normals as well.

Bennett and colleagues at Leeds recently sought to determine what proportion of patients with MRI-evident sacroiliitis develop ankylosing spondylitis (AS) in the long-term and whether there are baseline predictors of outcome.[32] Forty patients were followed-up after a mean 7.7 years. At baseline, 33 of the 40 patients followed-up had MRI-evident sacroiliitis and 6 had unequivocal AS. At follow-up, despite significant improvements in clinical outcomes, another 7 had developed AS. The combination of severe sacroiliitis seen on MRI with HLA-B27 positivity was an excellent predictor of future AS (likelihood ratio [LR] 8.0, specificity 92%), while mild or no sacroiliitis, regardless of HLA-B27 status, was a predictor of not having AS (LR 0.4, specificity 38%). Basically, a baseline MRI and a sacroiliac joint can be used to predict who is going to develop radiographic sacroiliitis.

These researchers then undertook a study using the same protocol to investigate 185 patients with axial SpA.[33] Whole spine MRI scans were performed in these patients and also in patients with spinal metastatic cancer. Lesions detected by MRI were scored in a blinded manner. An imaging diagnosis was given based on MRI findings alone, and this was compared with the gold-standard treating physician's diagnosis. Diagnoses were mixed and included European Spondyloarthropathy Study Group (ESSG) criteria for axial SpA, degenerative spinal disease and spinal malignancy. Characteristic MRI lesions (graded 1–3) included Romanus lesions, posterior elements of the spine (facets and pedicles), ligament insertions on the spinous processes, and costovertebral joint lesions (as defined by Maksymowych and Lambert).[34]

Notably, when "characteristic" SpA RLs were imaged in different conditions (SpA, degenerative arthritis, malignancy), the malignant image was the only one to show an abnormality. Prof. McGonagle emphasised that this illustrates the fact that an MRI report cannot be taken as a definitive test. As shown in Figure 3, any Romanus lesion on its own has little predictive power (a likelihood ratio of 1.5), whereas the presence of >2 lesions in a patient aged ≤50 years is associated with a likelihood ratio of 12.4; in a patient with >5 lesions and age ≤50 years, an MRI on its own is diagnostic. In sum, when many lesions are present, an MRI is very useful for diagnosing the seronegative diseases.

SpA	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood ratio
Any Romanus lesion	0.67 (0.53 to 0.79)	0.56 (0.47 to 0.65)	1.5
>2 romanus lesions	0.45 (0.32 to 0.59)	0.82 (0.73 to 0.89)	2.5*
> 2 RLs & age ≤50yrs	0.33 (0.21-0.47)	0.97 (0.92-0.99)	12.4*
Grade 3 & age ≤50yrs	0.11 (0.05 to 0.23)	1.00 (0.96 to 1.00)	Infinite*

Figure 3. The diagnostic utility of Romanus lesions.

A recognised problem is that of normal MRIs in cases of clinical disease. In whole-spine MRI studies, as many as 23% of clinically active AS patients[35] and 38% of clinically active axial SpA patients[33] have no acute MRI sacroiliitis. Reasons include the fact that the osteitis may not be adjacent to the enthesis, the very low resolution of MRI of body coil in the spine, an intrinsically low-water content of entheses and ligaments, and well-enervated vessels. The patient can have inflammatory symptoms that are not visible radiographically. Reassuringly, the emerging evidence suggests that a negative scan means that the patient is less likely to have a progressive disease that is going to lead to fusion.

When evaluating the patients with virtually normal MRIs, Bennett and colleagues (2009) noticed that many patients with established SpA had "fatty Romanus" lesions (corner lesions in the same locations as inflammatory Romanus lesions, but fatty Romanus lesions are high-signal on T1 and suppressed on STIR [short TI inversion recovery] sequences as the lesion is fatty and fat is suppressed by STIR sequences).[33] In SpA, having >5 fatty Romanus lesions was highly suggestive (likelihood ratio of 12.56) of an axial SpA. This is a useful diagnostic test in the cases of axial SpA when there are no acute inflammatory lesions in pre-radiographic patients.

Prof. McGonagle noted that other research groups have since shown that these abnormalities occur after inflammation; i.e. after the inflammatory lesion has revolved. Still other researchers claim that a fatty abnormality is a harbinger or warning sign for AS at that segment, whereas others refute this.

Imaging MRI in axial disease in PsA: role of HLA-B27

Castillo-Gallego and colleagues recently examined whether any difference exists between PsA and AS on MRI and whether they are distinguishable entities.[36] Earlier radiographic data has demonstrated that AS differs radiologically from axial PsA, showing distinctive syndesmophytes in PsA.[5,6] The utility of MRI in the diagnosis and assessment of spinal disease in AS and axial SpA is now well proven. However, spine MRI data in axial PsA are sparse and it is unclear whether MRI appearances of spinal involvement differ between patients with axial SpA or AS and patients with PsA-related spondylitis.

This recent investigation by Castillo-Gallego and colleagues was inspired by an earlier paper showing that in plantar fasciitis, patients with HLA-B27+ status had a very diffuse osteitis or bone marrow oedema (BMO) compared to PsA patients or mechanically-driven disease.[37] This work appeared to indicate that HLA-B27 was a severity factor for the amount of osteitis in the skeleton.

Castillo-Gallego and colleagues then assessed the MRI prevalence of BMO lesions in symptomatic back pain in patients with PsA in comparison with axial SpA and AS.[36] They specifically asked whether HLA-B27 was a modifier of osteitis at insertions/fibrocartilages. A cross-sectional audit was performed on MRI scans of the lumbar spine (LS) and sacroiliac joints (SIJs) requested consecutively between 2007 and 2011 in the rheumatology service. MRI scans were scored with the semiquantitative Leeds Scoring System[31] for BMO lesions representative of inflammation in the spine and SIJs, whereby a lesion graded as moderate (grade ≥2) is considered clinically significant.

Data from 76 patients were categorised into 3 groups:

- PsA (CASPAR criteria)
- axSpA (patients fulfilled the ASAS criteria for axial SpA but not the modified New York criteria for AS)
- AS (if patients fulfilled the modified New York Criteria).

Age was comparable in all groups

- (median for PsA: 39 years; axSpA: 34.5 years; AS: 35.5 years).

Unusually, there were more females in the PsA group (75.76% vs 38.1% in SpA and 31.16% in AS groups), which might be important; as yet, research has not investigated the effect of sex on the pattern of these diffuse osteitis abnormalities.

- HLA-B27 positivity was similar in PsA (30.30%) and axSpA (41.67%) and higher in AS (94.75%).
- Total MRI scores (lumbar spine [LS] + sacroiliac joint [SIJ]) were higher in AS patients compared to PsA (p=0.025) and axSpA (p=0.007).
- Comparable amount of disease extent was shown by similar total number of BMO lesions both at the SIJ and LS in PsA, axSpA and AS patients….
- ….but the number of severe lesions at the SIJ (grade ≥2) was higher in AS (p=0.01) and in PsA (p=0.03) than axSpA.

When the groups were stratified by HLA-B27 status, a relationship was seen between the severity and extent of disease and HLA-B27 in the PsA group which was comparable to the AS group.

- HLA-B27- PsA patients had lower MRI scores than HLA-B27+ PsA (p=0.03) and AS patients (p=0.006) whereas HLA-B27+ PsA patients had similar scores to AS.
- Similarly, MRI scores of HLA-B27- axSpA patients were lower than AS (p=0.01) despite the similar MRI scores observed between HLA-B27+ axSpA and AS groups.

This is an important clinical implication. B27 results in immediately recognisable osteitis. However, it appears that osteitis is less common in PsA, which may explain why spinal MRI scans appear normal for these patients – because of this effect of B27. The characteristics of lumbar and SIJ involvement according to the groups are detailed in Table 1: LS grade ≥2 and grade ≥3 lesions were found in fewer HLA-B27- PsA patients than in the HLA-B27+ PsA and AS groups; a similar relationship was observed with SIJ involvement.

Table 1. Characteristics of lumbar and SIJ involvement in different patient cohorts and HLA-B27 status[36]

Lumbar spine	HLA-B27 neg PsA	HLA-B27 pos PsA	AS	HLA-B27 neg axSpA	HLA-B27 pos axSpA
number	22	10	19	13	10
At least grade 2 lesion n (%)	3 (13,6)	3 (30)	5 (26,3)	1 (7,1)	1 (9,1)
At least grade 3 lesion n (%)	1 (4,5)	1 (10)	2 (10,5)	1 (7,1)	1 (9,1)
SIJ	**HLA-B27 neg PsA**	**HLA-B27 pos PsA**	**AS**	**HLA-B27 neg axSpA**	**HLA-B27 pos axSpA**
number	23	9	19	14	11
Any lesion n (%)	5(21.7)	4 (44.4)	8 (42.1)	2 (14.3)	4 (36,4)
At least grade 2 lesion n (%)	2 (8.7)	3 (33.3)	6 (31.6)	1 (7.1)	2 (18,2)
bilateral n (%)	3 (13)	1 (11.1)	8 (42.1)	1 (7.1)	2 (18,2)

SIJ = sacroiliac joint; axSpA = axial spondyloarthritis.

The effect of B27 appears to be mediated adjacent to the enthesis in the bone. In this respect, B27+ PsA looks identical and probably has an identical pathophysiology to AS, but remains controversial.

Conclusions:

- HLA-B27-related active PsA spondylitis shows an extent of inflammation comparable to that of AS and greater than that seen in HLA-B27- PsA.
- Numbers are small in this study and ideally would need to be confirmed in larger cohorts.
- These results suggest that there are two axSpA phenotypes – one is linked to HLA-B27 with osteitis.

THERAPY LESSONS

Nails and enthesopathy

A significant proportion of psoriasis patients have undiagnosed PsA:

- 29% in the dermatology clinic setting (Haroon et al. 2012)[40]
- 14% in the GP practice setting (Ibrahim et al. 2009)[41]
- 18% in the dermatology clinic setting (Reich et al. 2009)[42]
- 5% in the dermatology clinic setting (Yang et al. 2011)[43]
- 30% of an Italian cohort attending a dermatology clinic were deemed to have PsA when seen by a rheumatologist (McGonagle et al. Rheumatology; in press).

Subclinical enthesitis is common in asymptomatic psoriasis patients (see Table 2); several papers have shown that as many as 50% of patients with psoriasis have evidence of subclinical enthesopathy. One of these papers documented entheseal abnormalities by ultrasonography in clinically asymptomatic patients with psoriasis.[45] These findings could be related to a subclinical entheseal psoriatic inflammation. There was also evidence of enthesophyte and retrocalcaneal bursa in this patient population.

Table 2. Subclinical enthesitis: common in asymptomatic psoriasis

Reference	Modality	No. of patients	Findings
Erdem et al. 2007[44]	MRI	26 psoriasis 10 healthy controls	92% patients with psoriasis had abnormal MRI of the foot. No abnormalities in control group.
Gisondi et al. 2008[45]	USS and x-ray	30 psoriasis 30 controls	Mean GUESS score significantly higher in patients with psoriasis than controls (<0.0001)
Namey & Rosenthal 1976[46]	Bone scintigraphy ^{99m}TcDP	12 psoriasis 12 controls	Psoriasis – 86% of 168 joints scanned were abnormal Controls – 12% of 168 joints scanned were abnormal
Offidani et al. 1998[47]	MRI and x-ray	25 psoriasis 12 healthy controls	MRI abnormal in 68% psoriasis patients and x-ray in 32%. Subchondral changes in 36% patients on MRI. Controls – one joint cyst only.
Ozcakar et al. 2005[48]	USS	30 psoriasis 20 controls	USS demonstrated enthesopathy in 53% of the psoriasis patients but in no controls
Raza et al. 2007[49]	Bone scintigraphy	50 psoriasis 25 controls	35 of 50 patients (70%) with no clinical evidence for arthritis had a positive bone scan. 16% controls had a positive bone scan.

Preliminary evidence suggests that subclinical enthesopathy may predict PsA in patients with psoriasis.[50] In a longitudinal cohort of 30 psoriasis patients, repeat clinical and ultrasound assessments were performed in 28 patients after 3.5 years. None had received systemic therapy. At follow-up, 7 of the 28 patients (23%) fulfilled the CASPAR criteria for PsA.[51] Four patients with enthesopathy also developed hand OA. Baseline GUESS (Glasgow Ultrasound Enthesitis Scoring System) scores were significantly higher in those patients who went on to develop PsA or OA.

Types of nail disease

The following features are found with nail bed involvement:

- Onycholysis
- Splinter haemorrhages
- Oil drop discolouration
- Nail bed hyperkeratosis

and with nail matrix involvement:

- Pitting
- Leuconychia
- Red spots in the lunula
- Nail bed crumbling

The CASPAR criteria, endorsed worldwide, list psoriatic nail dystrophy (including pitting, onycholysis and hyperkeratosis) as a feature that assists with the diagnosis of PsA.[51]

Pathology of nail disease in PsA

- An association has been reported between nail abnormalities and adjacent distal interphalangeal (DIP) arthritis[52,53]
- The nail is attached to DIP joint by fibres from the extensor tendon, collateral ligaments and flexor tendon[54,55]
- In DIP joint PsA, diffuse enhancement is seen both in the bone and the soft tissue.[56]

Recently published evidence has linked nail disease to underlying bone involvement.[57] Dalbeth and colleagues found that nails with onycholysis and hyperkeratosis at baseline were more likely to have corresponding distal phalanx (DP) bone erosion and proliferation on MRI. DP bone oedema on baseline MRI was associated with development of onycholysis and hyperkeratosis in corresponding nails.

The microanatomical basis for the inflammation and nail disease in PsA has been elucidated in MRI and histological studies.[54] The normal nail is functionally linked to the DP and several DIP joint structures, including extensor tendon fibres and the collateral ligaments.[58] In normal nails, the extensor tendon continues from its bony insertion to envelop the nail root, and the collateral ligaments form an integrated network on the sides of the joint, helping to anchor the nail margins. This virtual continuum of connective tissue structures merges with a thick periosteum on the distal phalanx and with the numerous cutaneous ligaments that anchor the fatty pads of the finger pulp to the skin. Thus, the nail is functionally integrated with the skeleton; pathology can manifest anywhere within this unit.

It is clinically difficult to differentiate DIP joint disease of PsA patients from OA DIP joint disease.[59] High-resolution MRI has identified similar anatomical changes in both diseases, but there are certain distinguishing features: diffuse bone oedema without cartilage damage was observed in the PsA joint, most prominently in the DP with contrast enhancement in the ligaments, and an associated erosion at the enthesis. Tan and colleagues observed extensor tendon enthesitis only in PsA.[59] Compared with normal controls, the OA cohort exhibited prominent ligament and entheseal changes, but with less contrast enhancement than in PsA and less bone involvement at the insertions.

McGonagle and colleagues are currently examining data from psoriasis patients with nail disease and psoriasis patients with normal nails. MRI shows abnormalities only at the tendon and enthesitis in the psoriatic group, whether or not they have nail disease. Occasionally, these researchers observe abnormalities in psoriasis patients with nail disease, with evidence of osteitis of the DIP joint. High-resolution ultrasound of the extensor tendon has revealed that entheseal thickening of the extensor tendon is more frequent in patients with nail abnormalities than in those with clinically normal nails:

- PsA 41% vs 19% (p<0.0001)
- Psoriasis 59% vs 14% (p<0.0001).

Extensor tendon enthesopathy has also been associated with thickening of the adjacent epidermis seen on ultrasound (p=0.006). Thus, these data demonstrate a link between nail disease in psoriasis patients and clinically occult enthesopathy in the same region. McGonagle and colleagues have queried whether nail involvement in psoriasis is associated with a much greater burden of remote systemic enthesopathy.[60] Forty-six patients with psoriasis (31 with nail disease) were recruited. In a comparison of median ultrasound scores, enthesitis, enthesopathy, and inflammation scores were all higher in patients with nail disease then in those without. GUESS scores were between 10 and 14 (low) in psoriasis without nail disease or healthy controls. There was a highly statistically significant greater burden of enthesopathy in the lower limbs in patients with nail disease. Thus, the presence of nail disease in a patient with psoriasis without clinical arthritis is linked to a remote enthesopathy. This investigation also showed that more severe nail disease is associated with a greater ultrasound enthesopathy score; i.e., the total amount of nail involvement was linked to the subclinical enthesopathy.

Recent research by McGonagle and colleagues investigated PsA patients, patients with psoriasis, and healthy controls.[61] Lower limb entheses were scanned by power Doppler ultrasonography. The scans showed that ~40% of PsA cases had power Doppler change in a symptomatic enthesis. This was present in 10% of psoriasis cases without arthropathy, but not present in any of the controls. This lack of power Doppler change in controls and its presence in psoriasis has already been reported by a Spanish research group in a cohort of several hundred Patients.[62] It appears that Doppler positivity could be a marker for progression of thickening and inflammation from vascularisation to clinical disease. The vascular changes observed at insertions in ~10% of psoriasis cases may offer a novel insight into the progression from skin to joint disease in psoriasis; the enthesis is marked by entheseal thickening and vascularity.

Take-home Messages

- Nail disease is a common feature in PsA and psoriasis
  - It appears to be associated with enthesitis around the DIP joint in both PsA and psoriasis
  - Nail disease may be a marker for more widespread enthesitis elsewhere in psoriasis patients
- Preliminary evidence suggests that subclinical enthesitis in psoriasis patients predicts the later development of PsA
- PsA and SpA are enthesitis/osteitis associated
- HLA-B27 plays a major role in enthesitis-related osteitis expression
- Anti-TNF therapy powerfully suppresses osteitis and may ultimately stop progression
- Imaging may play a role in predicting PsA.

Q&A session

Q: Does this biomechanical model put forward by McGonagle and colleagues explain some of the extra-articular features, such as the aortic diseases?

A: In the most recent model published in *Nature Medicine*, interleukin-23 overexpression results in spontaneous development of enthesitis in mice that subsequently spreads to the synovium and bone and they also develop a pustular-type skin rash that has psoriasiform features. Prior to therapies, even before steroids, the old-school pathologists such as Bywaters noticed enthesitis in the skeleton and stated it to be a common mechanical anchorage. Prof. McGonagle noted that much movement also occurs in the anterior uvea. A study from Spain that performed ultrasound of the lower limbs in patients with uveitis clearly showed that those with anterior uveitis had substantially more subclinical enthesopathy compared to patients with panuveitis or non-spondylo-uveitis. Thus, a subclinical enthesopathy is associated with uveitis. Furthermore, AS can typcially affect the long lipids and because the lung is elasticated, daily pneumothoraces are associated with more trauma, which is where the rupture and damage occurs. Thus, the principle holds for apical fibrosis. All aspects of the disease can be explained in terms of a mechanical basis.

Q: Frequently, radiographers diagnose patients with OA, when the physician suspects the disease to be in fact PsA, from the appearance of the syndesmophytes.

A: The spinal anatomy consists of the annulus fibrosis behind the anterior longitudinal ligament, which technically results in two different entheses. X-rays and CTs of AS do appear to indicate that the enthesis is at the anterior longitudinal ligament, where the new bone formation is occurring. Prof. McGonagle is of the opinion that all of the MRI data, whether in the hand or in the spine, look similar for OA and spondyloarthritis. Because young people with fusion in the spine in AS have normal disk spaces, syndesmophytes have to grow across and in a straight line, whereas PsA and OA involve more mechanical factors and there may be some degeneration reducing the disk space. The syndesmophytes may appear to be less rounded, more elongated and flatter-looking. However, it is virtually impossible to differentiate between the various types of syndesmophytes, due to so much inter-linking.

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