The Future of Rheumatoid Arthritis and Hand Surgery - Combining Evolutionary Pharmacology and Surgical Technique

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Abstract: Rheumatoid arthritis is a systemic autoimmune disease of uncertain aetiology, which is characterized primarily by synovial inflammation with secondary skeletal destructions.

Rheumatoid Arthritis is diagnosed by the presence of four of the seven diagnostic criteria, defined by The American College of Rheumatology.

Approximately half a million adults in the United Kingdom suffer from rheumatoid arthritis with an age prevalence between the second and fourth decades of life; annually approximately 20,000 new cases are diagnosed.

The management of Rheumatoid Arthritis is complex; in the initial phase of the disease it primarily depends on pharmacological management. With disease progression, surgical input to correct deformity comes to play an increasingly important role. The treatment of this condition is also intimately coupled with input from both the occupational therapists and physiotherapy.

Keywords: Rheumatoid arthritis, hand, arthropathy, sinovitis, inflammation.

Rheumatoid arthritis is a systemic, autoimmune disease of uncertain aetiology, which is characterized primarily by synovial inflammation with secondary skeletal destructions [1].

It is a chronic disease that challenges individuals psychosocially as well as physically, causing a great deal of stress to those living with this pathology [2, 3]. The stress resulting from the inability to perform simple day to day tasks independently, the associated discomfort and the insult to patient's aesthetic sensibilities result in high levels of depression in this group; at approximately 20% it is twice that of the general population [4]. It is well recognised that occupation, including paid employment has a large influence on personal well being and society as a whole [5-8].

Coming from the Greek rheuma- ("ρευμα-" meaning flux) and -toid ("-τοειδής" meaning form) [9] it describes a condition were synovial and articular tissues are focal target structures; the immunologic disorder frequently affects disparate visceral organs such as the heart, pericardium, and lungs [1].

This article aims to discuss and summarise the current perspective of Rheumatoid Arthritis in terms of epidemiology and pathophysiology as well as considering any new ideas in management of this condition.

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RHEUMATOID ARTHRITIS: DIAGNOSIS, CLASSIFICATION, EPIDEMIOLOGY AND GENETIC BACKGROUND

Diagnosis & Classification

Rheumatoid arthritis is a term that describes a condition were synovial and articular tissues are focal target structures. This immunologic disorder frequently affects various visceral organs such as the heart, pericardium, and lungs [1].

Numerous combinations of clinical findings exist and have been named after the person to first describe them. These eponymous forms of Rheumatoid arthritis include Adult Stills Syndrome, Feltey's, Sjogren's as well as Caplan's Syndrome [10] (Table **1**).

Juvenile Rheumatoid Arthritis (JRA) usually occurs before the age of sixteen; symptoms may start as early as six months old [11, 12].

Eponymous syndromes of JRA include: Polyarthritic-systemic Juvenile Chronic Arthritis (JCA), Polyarthritic-non-systemic seronegative JCA, Polyarthritic-non-systemic seropositive JCA, Oligoarthritis I and finally Oligoarthritis II [10] (Table **2**).

Clinically Rheumatoid Arthritis is diagnosed by the presence of four of the seven diagnostic criteria, defined by The American College of Rheumatology [13] (Table **3**).

Morning stiffness lasting over one hour, symmetrical arthritis, arthritis affecting three or more joint areas and arthritis of the hand joints must be present for at least six weeks before rheumatoid arthritis can be diagnosed [13].

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Table 1. The Different Types of Juvenile Syndromic Rheumatoid Arthritis and their Clinical Signs

Eponymous Juvenile Rheumatoid Arthritis	Associated Clinical Signs
Polyarthritic-systemic Juvenile Chronic Arthritis (JCA)	Early childhood with fever, sometimes severe organ manifestations
Polyarthritic-non-systemic seronegative JCA	Largest group
Polyarthritic-non-systemic seropositive JCA	Mainly girls in late childhood, Anti-nuclear antibodies positive in 77%
Oligoarthritis I ("early type")	Mainly girls, Chronic Iridocyclitis, ANA positive
Oligoarthritis II ("late type")	Mainly boys, fewer joints (esp. knee), Sacroiliitis, HLA-B27 positive, may develop Ankylosing Spondilitis

Table 2. The Different Types of Adult Syndromic Rheumatoid Arthritis and their Clinical Signs

Eponymous Rheumatoid Arthritis	Associated Clinical Signs
Adult Stills Syndrome	Chronic Polyarthritis, Hepatomegaly, Splenomegaly, Lymphadenopathy, Leucocytosis, Iridocyclitis, Polyserositis
Feltey's Syndrome	Seropositive RA, Splenomegaly, Lymphadenopathy, Leucopaenia, Granulocytopaenia, Thrombocytopaenia
Sjogren's Syndrome	Xerophthalmia, Xerostomia, Sicca Syndrome (1ry&2ry)
Caplan's Syndrome	Pneumoconiosis, RA

Table 3. The American College of Rheumatology Diagnostic Criteria for Rheumatoid Arthritis

	Diagnostic Criteria for Rheumatoid Arthritis
1	Morning stiffness
2	Symmetrical Arthritis
3	Arthritis of Hand Joints
4	Arthritis of tree or more joints
5	Rheumatoid nodules
6	Serum Rheumatoid Factor positive
7	Typical radiological changes in the hands and feet

Haematological investigation includes base line inflammatory markers, in addition to the rheumatoid factor. This however is only helpful in seropositive patients. Anticyclic citrullinated peptide antibody is highly specific for the disease and is particularly useful both in the diagnosis and prognosis of patients who are seronegative, for the rheumatoid factor [14].

Radiologically, Steinbroker published his findings of the radiographic stages of Rheumatoid Arthritis in a mixed, clinical-radiographic classification in 1949 [15]. This is based on the combination of radiological staging with clinical findings; it includes stage I where osteoporosis without erosions is seen, stage II where osteoporosis, slight narrowing of the joint space or subchondral bone destruction is evident; stage III with osteoporosis, destruction of the articular cartilage and extensive bone destruction is prevalent and finally stage IV which includes osseous ankylosis in existing osteoporosis and severe bone destruction.

In 1975 Larsen's grading of radiographic signs included six grades that ranged from Grade 0 with "Definitely no pathologic findings" to Grade V which denotes "Mutilating joint destruction" [16] (Table **4**).

Table 4. Radiological Grading System for Rheumatoid Arthritis

Grade	Radiographic Signs by Larsen
0	Definitely no pathologic findings
I	Unspecific pathological findings
II	Mild, but certain destructive lesions
III	Moderate destructive lesions
IV	Severe destructive lesions
V	Mutilating joint destruction

More recently Simmen and Huber (1994) differentiated three basic types of Rheumatoid Arthritis on a functional basis, reliant on a primarily surgical point of view. Type I is the Ankylosing subtype, type II is Rheumatoid Arthritis with secondary osteoarthritis and finally type III which is Rheumatoid Arthritis with disintegration [17].

Epidemiology

Currently there are almost half a million adults in the United Kingdom suffering from rheumatoid arthritis [18]. There is age prevalence between the second and fourth decades of life, in the adult variant of the disease [1].

Annually approximately 20,000 new cases are diagnosed [19]; women are affected three times more commonly than men [18].

One in seven patients will give up their employment within one year of diagnosis [20], and up to 25 percent of working people with rheumatoid arthritis lose their jobs within five years; three quarters of these are for reasons directly related to their condition [21].

The prevalence of Rheumatoid Arthritis in children is difficult to estimate because of differences in nomenclature and the heterogeneity of the diseases and the subtypes encompassed under this heading [22].

Genetic Background and Pathophysiology

The most well established genetic link is with HLA-DR4 [23]. However, this is not consistent across all studied cohorts and there are many other newly defined associations, including polymorphisms in PTPN22 and PADI4 [24].

IgM or IgG rheumatoid factors are present in more than 70% of affected patients, rendering them seropositive [25].

The exact aetiology of Rheumatoid Arthritis remains unknown but a model whereby repeated exposure to environmental agents is coupled with a genetic predisposition to autoimmune responses appears to be reasonable [26].

Of the numerous environmental factors proposed to contribute to Rheumatoid Arthritis, tobacco smoking is perhaps the best defined. Smoking exposure has a dose response relationship with Rheumatoid Arthritis risk [27-29].

Rheumatoid Arthritis usually begins with the proliferation of synovial macrophages and fibroblasts after a triggering incident, possibly autoimmune or infectious [30].

Matrix Metalloproteinases are produced by the rheumatoid synovium; these enzymes break down all components of connective tissue. This process is followed by the release of cytokines from macrophages; including tumour necrosis factor alpha, in addition to numerous Interleukins that degrade bone, cartilage, ligament and tendons [26]. Over time, bone erosion and irreversible joint damage can occur, leading to permanent disability [31].

RHEUMATOID ARTHRITIS: CONSERVATIVE AND SURGICAL MANAGEMENT

The management of Rheumatoid Arthritis is complex; in the initial phase of the disease it primarily depends on pharmacological management.

With disease progression, surgical input to correct deformity comes to play an increasingly important role, especially in women, who require significantly higher numbers of joint replacements than men [32]. The treatment of this condition is also intimately coupled with input from both the occupational therapists and physiotherapy.

The 'rheumatoid hand' is one of the earliest presentations of Rheumatoid Arthritis, and the progression of its pathology can be unpredictable [33].

It is this complexity of the disease and the resulting, devastating deformities that demand that such patients are management in a coordinated MDT setting [34]. The ultimate aim when dealing with Rheumatoid Arthritis is to induce complete remission. If remission is unable to be achieved, treatment is aimed at controlling disease activity and slowing the rate of joint damage [35].

Medical

Pharmacological treatment of patients with any inflammatory arthritis includes primarily the use of non-steroidal anti-inflammatory medication and cyclo-oxygenase-2 selective inhibitors. These drugs bring about both anti-inflammatory, as well as analgesic effects. There is however, no scientific proof that they prevent joint damage [36-38].

It is becoming increasingly evident that a 'critical period' may exist, during which - with aggressive medical intervention - the disease process of Rheumatoid Arthritis may be reversed [39]. This has resulted in disease modifying antirheumatic drugs being used much earlier in the fight against Rheumatoid Arthritis, rather than when the pathology has progressed further, as previously indicated [39].

Methotrexate treatment for example, has been shown to delay the diagnosis of Rheumatoid Arthritis and retarding radiographic joint damage [39].

Methotrexate remains the most commonly used, as well as most effective monotherapy; it is the recommended standard of comparison for new medications [40].

Biologic agents, such as TNF alpha-antagonists, have also been added to the resources available against Rheumatoid Arthritis. Individuals with no or poor response may be offered biologic agents, with a different mechanism of action: Most recently Tocilizumab. It is an IL-6 receptor inhibitor, which shows swift and significant efficacy in the battle against Rheumatoid Arthritis. This has been proven by satisfactory remission rates, in addition to a favourable safety profile [40].

It has been shown that patients started on disease modifying antirheumatic drug therapy early, exhibit reduced radiographic joint damage. They also experience greater preservation of function, when compared to patients whose treatment had been delayed [39-41].

Hence, current recommendations stipulate that patients who are most likely to develop disabling rheumatoid arthritis should start disease modifying antirheumatic drugs therapy the earliest possible [42].

Occupational Therapy

The aim of splinting in Rheumatoid Arthritis is to provide rest, anatomical and functional support for deformed joints [43, 45, 50-52]; to decrease inflammation, the subsequent swelling and resulting pain [43, 48, 53, 54] during flare ups of the condition [44-49, 54-56].

There is however little evidence to validate the effectiveness of resting splints. Therapists concur that resting splints have a place in the overall management of the Rheumatoid Arthritis patient, especially during exacerbations [44]. Resting periods of up to three weeks have been proven to be beneficial, longer periods on the other hand may result in joint stiffness [48].

Spoorenberg (1994) [57] concluded that resting splints were not popular with patients and that only 17% of his study cohort wore their splints regularly; mainly due to discomfort, size and difficulty with the application.

Occupational therapists are therefore encouraged to consider their patient's individual needs, in order to increase compliance and to provide the most comfortable and effective aids possible [46].

Physio Therapy

Van den Ende *et al.*, proved that dynamic exercise therapy is effective in increasing muscle strength, with out affecting pain levels or disease activity [58].

Two more recent studies [59, 60] show that exercise does not cause exacerbation of the disease in the short term; long term effects, however, are still unknown.

Weight reduction for Rheumatoid Arthritis patients, who are overweight or obese, limits impact on weight bearing joints and improves risk factors for cardiovascular disease. Weight control plays an important role in the general disease management [61].

Surgery

In 2001 Gordon *et al.,* concluded, in a study extending over a ten year period, that patients with Rheumatoid

Arthritis exhibited a deterioration of radiographs and function despite regular Disease Modifying Anti Rheumatoid Drug treatment and apparent clinical containment. There was a steady requirement for surgical intervention with time [62].

As mentioned previously, more effective and efficient medical options are utilised, earlier on in the treatment of the affected joint. This results in more restricted pathology and slower joint deterioration. Therefore, surgeons have observed that the rate of rheumatoid hand surgery has been decreasing in the developed world, where costly therapies are more readily available [63].

Surgical intervention is typically used when conservative therapy is unable to limit the disease evolution towards joint instability. Surgical intervention should be considered, especially when the instability is associated with uncontrollable pain and loss of function [64].

Rheumatoid hand interventions can be categorized into prophylactic and therapeutic surgical procedures:

Prophylactic procedures include the removal of inflammatory synovial tissue before synovial hypertrophy stretches the ligamentous support around joints, which can cause a tendon imbalance, or before synovial tissue invades into tendons, causing tendon rupture, or before it destroys the articular cartilage [64].

Once the joints are destroyed or the tendons are ruptured, surgical options may be considered:

Wrist

Rectifying wrist deformities is often vital to prevent and correct hand deformities [65]. Arthrodesis of the wrist offers an important possibility in the surgical management of rheumatoid disease. In patients with well-preserved midcarpal joints, a limited (radiolunate) fusion will preserve some wrist motion [66-68].

The Swanson Silastic wrist arthroplasty is an option that conserves movement, however careful case selection is vital. Arthroplasty is indicated only in patients with long term, dormant disease with a very low work demand and insufficient bone stock to allow a total wrist arthroplasty with a metal on plastic design [69-74].

Extensor Tendons

Tenosynovitis of the extensors is a relatively early finding in rheumatoid disease. Mechanical abrasion by dorsal wrist osteophytes may cause rupture of theses structures. Ischemia from pannus or direct invasion may also result in erosion of extensor tendons [75]. Dorsal tenosynovectomy is recommended for tenosynovitis that has resisted six months of medical management [76-78].

Flexor Tendons

'Mannerfelt lesion' is responsible for flexor pollicis longus rupture. This is the most common flexor tendon rupture in the rheumatoid hand and results from tendon erosion by direct friction against the scaphoid bone [79].

Flexor digitorum profundus and superficialis ruptures are usually due to direct synovial infiltration of the tendons [80] and attrition ruptures are unusual [81]. Flexor Digitorum Profundus tenosynovitis usually manifests as carpal tunnel syndrome or trigger digits. In such cases the carpal tunnel may be decompressed. For trigger fingers, the A 1 pulley should not be released, as it may be the only remaining supporting structure for the metacarpo-phalangeal joint. If synovectomy is not sufficient, then excising a slip of the Flexor Digitorum Superficialis could solve the restriction, by thinning the tendon.

MP Joints

Early disease of the MP joints can be addressed by synovectomy, which alleviates pain [82].

With extensive metacarpo phalangeal joint pathology, replacement arthroplasty may be indicated. Silicone arthroplasty of these joints is commonly performed, unlike with the wrist and in the thumb CMC joint where silicone arthroplasty has fallen out of favor [83-85].

Recurrent ulnar drift (31%), implant fracture (26%) and silicone synovitis represent possible complications of silicone joint replacements [86-90].

Finger Joints

Early synovectomy, to avoid the progressive synovitis that ultimately displaces and infiltrates the extensor mechanism is indicated. It is the preferred treatment, to conserve as much joint function as possible [91, 92].

Frozen PIP joints only respond to fusion or arthroplasty [93].

Thumb

Metacarpophalangeal joint synovectomy is indicated early on and may be combined with extensor mechanism modification such as Extensor Pollicis Longus rerouting or Extensor Pollicis Brevis advancement [94].

The recommended surgical treatment for mild to moderate swan-neck deformities is implant hemiarthroplasty. When there is advanced deformity, resection arthroplasty, combined with volar tenodesis of the joint may be performed. An alternative option to this is joint fusion, with release of the fascia of the first dorsal interosseous muscle [95].

Arthrodesis is recommended for moderate deformities, when the metacarpophalangeal joint is totally destroyed but the remainder of the thumb ray is only minimally involved. If destructive changes are evident at either the carpometacarpal or interphalangeal levels, metacarpophalangeal arthroplasty is preferred.

Allotransplant: The Future?

Iglesias *et al.* recently propose to perform an allotransplant of the osteomyotendinous structures in patients with Rheumatoid Arthritis, by comparing them to trauma patients, that receive allotransplants coupled with immunosuppressant medication, to ensure the graft's survival [96].

The basis for their hypothesis is that between 1998 and 2009, 42 hand and three arm allotransplants in 33 patients have been performed worldwide; after a follow-up from 17 to 120 months, 25 of these transplants are still viable [97].

Iglesias also drew on the similarity between the medication used by both the trauma patients on immunosuppressants and the rheumatoid patients.

Both groups of patients are often treated with non-steroidal drugs, corticosteroids, Methotrexate, Azathioprine, and monoclonal antibodies [98-101].

They set out to prove the feasibility of their hypothesis by operating on ten cadavers; the average operative time was approximately 20 hours.

Their approach specified the preservation of the recipient's skin flap and sensory nerves, to render the graft, psychologically more acceptable and functionally superior, for the patient [96].

DISCUSSION

A recent study, by Amy K Alderman, found that 70% of rheumatologists consider hand surgeons deficient in understanding the medical options available for Rheumatoid Arthritis, while 73.6% of surgeons believe rheumatologists have insufficient knowledge of the surgical options for the rheumatoid hand [102].

Mc Ewen and Chung KC had already confirmed with their preceding studies, that surgical outcomes research is limited for physicians managing RA hand deformities [103,104].

It is has therefore been proven, that both rheumatologists and hand surgeons have minimal interdisciplinary training, restricted interdisciplinary communication regarding clinical management and disagree significantly on the timing and indications for hand surgery [102].

Clinical pathways, with a multidisciplinary approach in mind, that include hand surgeons, rheumatologists and occupational therapists, are useful clinics that are more convenient for patients and more successful in targeted disease management [102,103].

CONCLUSION

The diagnosis and management of Rheumatoid Arthritis is a fast evolving field and it is important to keep up to date with the latest information.

One important step is to prevent a disarticulated approach, when managing a patient. Early involvement of all specialists and a coordinated treatment plan in an MDT setting is vital to successfully deal with the signs and symptoms of a Rheumatoid Arthritis patient.

As mentioned above, the current recommendations are that patients should start disease modifying antirheumatic treatment at the earliest possible opportunity to delay the degeneration of joint integrity.

The decision for surgical intervention must be based on its overall ability to address the patient's primary wishes and needs. Although there have been tremendous advances in the surgical armamentarium, the role of specific procedures has many areas of uncertainty and controversy.

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CONFLICT OF INTEREST

None declared.

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