IJBPAS, January, 2023, 12(1): 361-377

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

RHEUMATOID ARTHRITIS: A PAEDIATRICS DISEASE OR LEADING DISEASE OF ADULTS?

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Received 26th March. 2022; Revised 25th April 2022; Accepted 10th July 2022; Available online 1st Jan. 2023

https://doi.org/10.31032/IJBPAS/2023/12.1.6776

ABSTRACT

Rheumatoid arthritis (RA) is a disease of undetermined etiology and is defined as an inflammatory joint disease influencing almost 1% of the population worldwide. RA diagnosis is very difficult at early stages of disease as it is based on clinical symptoms. A serological marker that can be a disease specific autoantibody can prove useful in early diagnosis. The symptoms can be treated with the help of Non-steroidal anti-inflammatory drugs (NSAIDs), as drugs of 1st choice. The side effects associated with NSAIDs are limiting its use and switching to other alternative drugs such as corticosteroids, DMARDs and medicinal herbs. As per reports, 60-90% of the arthritis patients who are not satisfied with NSAIDs are switching towards complementary and alternative medicine (CAM). The alternative drugs were evaluated by using animal models of inflammation. The prevalence of RA in most

methodologies near to 1% among adults, 2% 5% in men and women, respectively, by the 65 years of age in Caucasian populations. The frequency of RA grows with age and reaches its peak around the 4th and 6th decades.

Keywords RA, NRAS, pathogenesis, etiology, inflammation

INTRODUCTION

Rheumatoid arthritis (RA), a prolonged, systemic, inflammatory autoimmune disease attacking flexible (synovial) joints and affecting many tissues and organs. If not treated adequately, it may lead substantial loss of functioning and mobility, a disabling and painful condition. The process includes an inflammatory cycle nearby the joints along with inflammation of synovial cells, increased amount of synovial fluid, and the growth of fibrous tissue. Rheumatoid arthritis (RA) is affecting around 1.3 million people in US **[1]**. RA is defined as a systemic disorder of unknown etiology involving synovial hyperplasia and invasion of bone and cartilage resulting in joint destruction **[2, 3]**.

1% of the youth is affected by including more women than men **[4, 5]**. The studies suggests that there are increased chances of CVS disorders in patients of RA **[6, 7]**. associated morbidity and mortality then person having no RA **(Figure1) [5, 8]**.

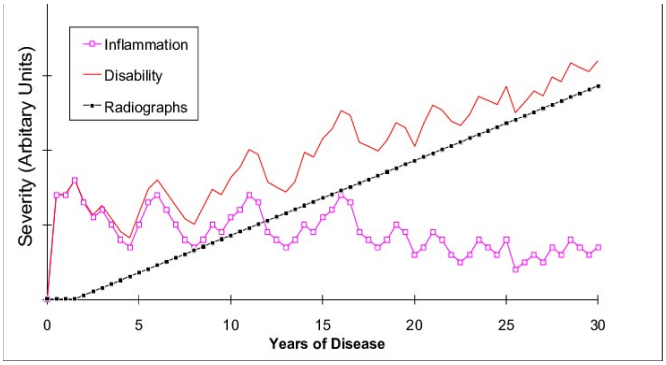

Figure 1: Severity of Disease with Years

ETIOLOGY

RA is a disease of unknown etiology but Davidson (1945) states that "suggestive features favour the view that infections play some etiologic role," other evidences favouring point" that it is due to the abnormal immunological reaction of the host to infection". Levinthal (1939) concluded that an abnormal immune response is the essential factor while both Angevine and Fraser (1942) do not support any specific infective etiology. Slater (1943) stated fatigue and crisis at emotional level are finding great importance. He

concluded 70% cases as of women with average age of onset around 40 years. Evidences suggest that environmental factors including infectious agents, oral contraceptives and smoking, also play a role **[9]**. The people can get affected with RA at any age but it is common after 40 years of age. Approx. 12K children around age of 16 years are suffering from juvenile form of this disease according to the National Rheumatoid Arthritis Society (UK) **[10]**.

Objectives

Pathogenesis

The RA pathogenesis consists of five phases as:

1. An immunogenic processed by antigen presenting cells is presented to T lymphocytes.
2. T cells proliferation induces proliferation of B cell. Angiogenesis is initiated as a scaffold for synovitis. Acute inflammation can be seen in synovial fluid.
3. There is production of cytokines, nodules and vacuities along with inflammation and synovial proliferation.
4. The sinusitis converts into macrophages and synovial cells start destruction of cartilage, ligaments and bone, irreversibly.
5. Articular cartilage loss, marrow invasion, subchondral bone loss, tendon rupture, ligamentous stretching followed by loss and joint deformity is manifest clinically as crippling deformity **[11]**.

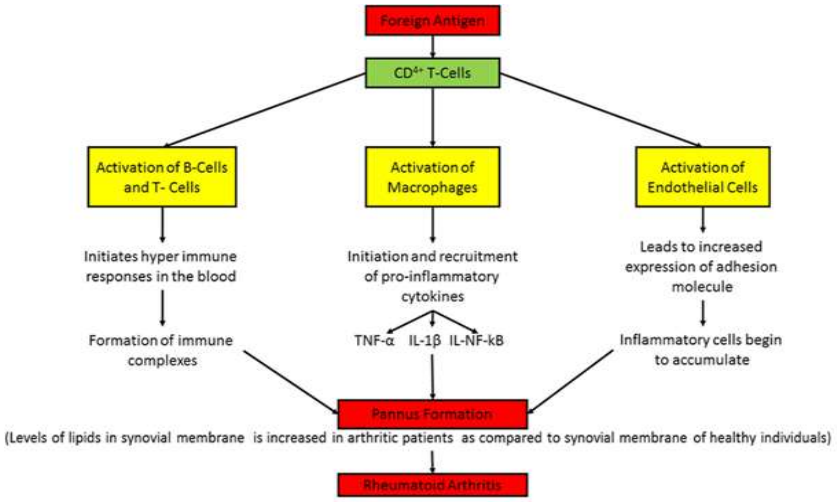

Figure 2: Pathogenesis of RA

Rheumatoid Arthritis: Causes

The RA cause is still unknown, exactly. This is assumed that certain factors and their combination triggers atypical autoimmune response, also genetic predisposition and infection by virus as biological trigger or environment changes. Rheumatoid arthritis, a type of autoimmune disorder in which the immune system of

body unknowingly destroy and attack health tissues and cells of own body **[12]**.

- **Inflammation and Immune Response**

The immune system determines the response of body against extraneous matter including toxins and viruses. The immune responses are responsible for the ability of the body to fight with infections and to heal injuries and wounds followed by inflammation. Process of inflammation is based on lymphocytes including B cells and T cells. The lymphocytes family constitutes white blood cells in which recognition is done by T cells. On recognition of foreign material as 'Antigen', there is release of chemicals known as cytokines which further initiate multiplication of B cells and releases antibodies (immune proteins). These antibodies get circulated in blood and identify antigen followed by initiation of inflammatory process so as to make the body free of invasion **[12]**.

- **Genetic Factors**

Factors related to genetic build up also impart their function in RA by worsening disease process due to increased susceptibility. The marker which is genetically linked with RA is Human leukocyte antigen. Its genetic forms do not develop or cause disease but they worsen the disease once developed. The variations in HLA region helps in predicting response of patient towards RA treatment **[12]**. The family history of RA does not increase risk of developing this disease but in some cases, people carry certain gene that increases their exposure towards RA development.

- **Environmental Triggers**

There is no direct relationship established between bacteria and viruses and RA but it is found that the level of Ab reacting with *E. coli* (intestinal bacteria) is higher in the synovial fluid of such patients. It is postulated that this *E. coli* associated antibodies may prolong RA by stimulating immune system after triggering of disease by some other infection. The triggers involve Parvovirus B19, mycoplasma, Epstein-Barr virus. Retroviruses and mycobacteria **[12]**.

- **Risk Factors**

According to the U.S. Arthritis Foundation, RA is affecting 1.3 million Americans. The usual onset of this disease begins around 30-50 years of age but this can arise at any age even from infancy. The higher risk of developing this disease is seen in women than men. The highest reported risk factor of RA is heavy long-term smoking even without family history. Evidences suggest that in women, RA can be protected by drinking moderate alcohol as 2 – 4 drinks per week **[13]**.

Autoantibodies in Rheumatoid Arthritis

RA is associated with two types of antibodies:

1. Antibodies associated with RA
2. Antibodies specific for RA

1. Autoantibodies associated with RA: These are observed in RA but can also be seen in other ailments. This includes:

- **Rheumatoid factor**

About 75 years ago, 'rheumatoid factor' (RF) was described first **[14]**. In nearly 75% of patients, RF antibodies are present with limited specificity in the patients of other autoimmune diseases including infectious diseases such as tuberculosis, hepatitis, Sjogren's syndrome and also among healthy population (3–5%) and healthy elderly persons (10–30%). RF acts as a diagnostic marker for RA even being of low specificity. RF is an antibody directed towards the crystallizable fragment of IgG molecules. IgG RF activates immune system due to its self-binding capacity **[15]**. According to some reports, the disease activity is considered by increased levels of IgA-RF levels **[16, 17]**.

- **Anti-RA33 antibodies**

A 33 kDa antigen was derived from the serum of RA patients by Hassfeld *et al.* **[18]**. This antigen, also known as RA33 was seen in 36% RA patients and only 1% in normal people. RA33 is being characterized as similar to A2 protein of the heterogeneous nuclear ribonucleoprotein complex **[19]**. RA33 is considered as an indicator for early arthritis[20]. These are also found in systemic lupus erythematosus (SLE) and in serum of some mixed connective tissue **[20, 21]**.

- **Anticalpastatin**

Calpains are defined as neutral cysteine proteinases dependent on Ca^{2+}. Calpains exist in two forms: μ-calpains or calpain I requiring μm concentration of Ca^{2+} for the activity and m-calpains requiring mm concentration of Ca^{2+} for activity. The substrates are diversified for these enzymes, consisting of proteins such as cytoskeletal, nuclear and some of extracellular matrix proteins such as proteoglycans and also cytokines **[22]**. The inflamed synovium contains elevated levels of extracellular calpain suggesting that calpains are potentially secreted by synovial cells which is responsible for cartilage degradation in RA **[23, 24]**. The Calpains are naturally inhibited by Calpastatin.

- **Other RA-associated autoantibodies**

The patients suffering from RA produce certain autoantibodies which are focussed on many auto antigens, but still all of them are particularly for RA. These vague antibodies are also focussed towards cartilage proteins including collagen and fibronectin. The autoantibodies are found

against several types of collagens but predominant one is against collagen type II (anti-CII). Anticollagen antibodies are usually seen in about 30% of patients with RA **[25]** but are not clear whether these antibodies are due to disease or play role in pathogenesis.

2. Autoantibodies specific for RA

- **Sa protein**

The antibody sera of around 40% RA patients reports the presence of autoantibodies for antigen Sa having high specificity **[26, 27]** and low sensitivity (23%) **[28]**. This antigen is a protein of around 48–50 kDa, usually present in extracts of human placenta **[29]** and can be seen in human spleen and the pannus tissues.

- **Heavy chain binding protein (p68)**

Around 64% of RA patients conatin the autoantibodies against heavy chain binding protein i.e., p68 protein (BiP) are found and are highly specific for this disease **[30-32]**. The immune response by T-cell and B-cell specific for RA, targets BiP antigen **[33]** in RA synovial tissues in comparison to control tissue. BiP, localised in endoplasmic reticulum, is a universally stated chaperone protein. The BiP protein shows non physiological localization and a change in glycosylation pattern resulting in an increased antigenicity of this protein in the pathogenesis of RA. The BiP protein is found in less abundance at cell surface but more in cytoplasm and endoplasmic reticulum of cultured cells. This antigen further relocalize to nucleus under stress conditions **[34]**.

- **Glucose-6-phosphate isomerase**

The novel autoantigen in RA is considered as the domestic enzyme glucose-6-phosphate isomerase (GPI) **[35]**. About 64% of RA patients were detected with the antibodies but not controls **[35]**.

- **Antiperinuclear factor**

The buccal mucosal cells cytoplasm was identified with a specific RA antibody system directed towards keratohyaline granules which is a protein component in 1964. The antigen was named Perinuclear Factor (PF) and antibody as antiperinuclear factor (APF) (Autoimmune rheumatic diseases: from clinic to the laboratory n.d.). APF antibodies are highly sensitive and has a strong specificity of 73–99% **[37]**. The antikeratine antibodies (AKA) described in 1979 is also a related group of RA-specific autoantibodies **[38]**. The filaggrin subunits converts arginine, basic amino acid to citrulline which is neutral by the enzyme peptidylarginine deiminase during distinction of epithelial cells and this is necessary for the autoantigenicity of filaggrin **[39, 40]**. Enzyme-linked immunosorbent assay (ELISA) and

Immunoblotting assays are used for the detection of antifilaggrin antibodies (AFA). The anti-CCP antibodies can be seen in early stages of RA bit with only 40-60% sensitivity.

2.4 Symptoms

Diarthroid joints are involved in RA where the inflammation of synovial membrane takes place. Indications of RA have been divided into early and late ones **[41]**.

- ✓ The early indications include: **[41]**
  - Morning stiffness
  - Swelling and pain in small joints including the interphalangeal and metacarpophalangeal joints.
- ✓ Late indications include **[41]**
  - Swelling and pain in the knee, elbow and ankle joints.
  - Systemic involvement i.e. anaemia, tiredness, low grade fever, pulmonary fibrosis pericarditis, vasculitis and myocarditis.
  - Depression is also a frequent disorder among persons with RA.

Hence, with the disease progression the patient suffers from substantial disability, poor quality of life, and the lost capacity to work. The onset of the disease is associated with work disability in 20% cases within 2 years and 50% cases in 10 years. The patients of severe RA are at a higher threat of early mortality when compared to the persons of same age without RA. Thus, RA has a significant impact on the patients that imparts a non-ignorable burden over health care systems **[41]**.

METHODS

Complications Associated with RA

The RA disease severity differs from person to person from less to more aggressive with time or may improve. Some develop severe form including complications which affect not only joints but other organs. The development of newer treatments proved helpful in decreasing disease progression and avoiding severe infirmity. The complications associated with rheumatoid arthritis are mainly due to chronic form of inflammation **[41]**.

- ❖ **Deterioration of joints and Pain**

The joints affected with RA lead to deformation. In some cases, the everyday performance effects badly making it difficult or impossible to move as they may experience muscle weakness in addition to pain.

- ❖ **Peripheral Neuropathy**

This type of condition is usually associated with the nerves of hands and feet resulting in tingling sensation, numbness, or burning **[42]**.

- ❖ **Anaemia**

The patients of RA disorder are usually at a risk of developing anaemia due to reduction in the red blood cell count **[42]**.

❖ **Eye Problem**

The ocular complications include the inflammation of blood vessels of eye i.e. scleritis and episcleritis which ultimately leads to the damage of cornea. The associated indications are redness seen in eyes and also a gritty type of sensation **[42]**.

❖ **Infections**

The patients of RA are at a border line of attaining other infections due to disease and also due to the use of drugs for RA such as immunosuppressant. The RA patients should take appropriate vaccinations depending upon their age e.g. varicella zoster virus, influenza, papillomavirus, hepatitis B, pneumococcus before starting treatment with biologics or disease modifying agents **[42]**.

❖ **Skin Problems**

Skin problems mostly on fingers and beneath nails are very common. A few of them show serious signs including ulcer, blister, nodules, lumps, rashes etc. Generally, more skin problems mean more severe RA **[43]**.

❖ **Osteoporosis**

Decreased density of bones is more prominent in women with RA who are postmenopausal, predominantly effecting hip. Danger of osteoporosis is more in men with RA having age more than 60 years **[43]**.

❖ **Lung Disease**

The patients of RA are more prone to attack of chronic lung infections such as pulmonary hypertension, emphysema and some other lung problems. RA and the drugs used in its treatment are the predominant factors for lung infections **[43]**.

❖ **Vasculitis**

Vasculitis usually means swelling of small blood vessels which ultimately affects others organs in the body. Complications associated with vasculitis includes ulcers of mouth, disorders associated with nerves, quick relapse of lungs, thickening of coronary arteries, and swelling of arteries supplying the intestine **[43]**.

❖ **Cardiovascular disorders**

The RA associated patients are at a higher threat of attaining CVS disorders such as coronary artery disease, auricular fibrillation, stroke and heart attack. Along with these they are more prone to develop emerging venous thromboembolism (VTE) **[44]**.

❖ **Lymphoma and Other Cancers**

The patients of RA are at developing danger for non-Hodgkin's lymphoma in comparison to healthy patients. RA associated chronic inflammation process with plays major part in developing such cancer. Drugs interfering with TNF used for treatment of RA too increases the danger associated with lymphoma, leukemia and other tumours **[44]**.

❖ **Periodontal Disease**

The gums and bones associated with teeth usually damages in patients with RA as RA is a risk factor for the development of periodontal diseases **[44]**.

❖ **Kidney and Liver Problems**

The drugs used for the treatment of RA can damage kidneys and the liver, although kidneys are rarely involved in RA **[44]**.

❖ **Emotional Complications**

RA is associated with the strain of allocating chronic illness resulting in severe pain and frustration. Patients usually face depression and anxiety **[44]**.

❖ **Pregnancy Complications**

The women with RA are at a severe danger of developing high blood pressure at 3rd trimester of pregnancy and have increased risk of premature delivery. In some women with RA, the disease decreases in pregnancy but as soon as after delivery, the signs rise severely **[45]**.

RESULT AND DISCUSSION

Diagnosis and Treatment

It has become apparent in last few years that as early the disease is identified and management is started with disease-modifying antirheumatic drugs (DMARDs), there is a "window of opportunity" in which treatment leads to better outcomes with prevention of entirely or utmost structural joint damage. So, it is significant to know the presentation of RA which is however not changed from past 23 years **[46]**. An early disease criterion does not specify early disease in fact emphasizes on utmost progressive disease such as rheumatoid nodules, radiographic changes, and extra articular manifestations. The American College of Rheumatology and the European League against Rheumatism released new classification criteria in 2010 which emphasizes more on initial analysis through identification of typical signs and exam findings, aided by laboratory tests.

Joint damage is usually seen in initial course of rheumatoid arthritis. The radiographic evidence of bones at time of analysis shows erosion in 30% of patients and this rises to 60% by 2 years **[47]**. These bony erosions and irregularities are largely irreparable. Prescribing DMARDs as initial treatment within three months after the analysis of RA is critical if there is any little delay in the introduction of these medications within 3 months, it results in considerably more radiographic damage at 5 years **[48-50]**. Thus initial identification even-though challenging **[51]**, but still critical **[52, 53]**. The diagnosis can't be based on a single laboratory blood test but is associated with the use of seven diagnostic criteria **[54]** and also by X-ray imaging. Stiffness of joints in the morning, arthritis in three or more joint locations, such as symmetric arthritis, hand joints, elevated serum rheumatoid factor, and radiographic abnormalities are among the

diagnostic criteria. Serum antibodies have been discovered to aid in the identification of patient subgroups **[55, 56]**. Other blood tests are performed to rule out other possible causes of arthritis, such as lupus erythematous. This phase includes testing for erythrocyte sedimentation rate (ESR), C-reactive protein, complete blood count, renal function, liver enzymes, and antinuclear antibody/ANA. RA treatment is usually associated with changes in life style and medicines **[57]**.

5. CONCLUSION

Patients with rheumatoid arthritis have several problems in their treatment. The lack of an accurate method for making an early diagnosis, which allows for early treatment; insufficient predictors of differential response to available therapy, as well as too few studies comparing effective therapies; and the high cost of new therapies, which has made them unaffordable for many patients, are three issues that stand out. The pathway for the future will be therapies that are aimed at inhibitory pathways involved early in RA, but with specificity sufficient not to induce immunodeficiency.

Acknowledgement

Authors are very grateful to Chandigarh University for their appropriate and constructive suggestions and also for providing necessary facilities.

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