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Role of infection in the pathogenesis of rheumatic diseases

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Abstract. Advanced immunological technology has revealed immunological abnormalities not only in some chronic and autoimmune connective tissue disorders but also in conditions like infective arthritis where infection apparently seems to play the only role. On the other hand role of infection in the pathogenesis of some connective tissue disorders has recently gained much importance from the observation of clinical, pathological and immunological similarities between these diseases and certain infectious diseases occurring in animal models. Meanwhile, knowledge gained into human leucocyte-A system and its association with certain diseases opens another angle in etiopathogenesis of certain rheumatic diseases. It has been postulated that adaptive mechanism of a microbe or the binding between the human leucocyte-A molecule and carbohydrate moiety of a microbe may set up an autoimmune reaction and in the presence of some triggering factors in the environment may lead on to disease manifestations. An attempt has been made to discuss the role of infection in the outcome of rheumatic diseases such as septic arthritis, polyarteritis nodosa, rheumatic fever, enteropathic arthritis, ankylosing spondylitis, rheumatoid arthritis and systemic lupus erythematoses in genetically susceptible individuals producing immunological abnormalities.

Keywords. Role of infection and arthritis; rheumatic diseases.

Introduction

While the role of microbial infection in causing acute septic arthritis has already been well established, infective etiology for most of the chronic rheumatic syndromes is recently gaining much importance, based on the fact that there are striking clinical, pathological and immunological similarities between these syndromes such as rheumatoid arthritis, systemic lupus erythematoses, diffuse vasculitis etc., and certain infectious diseases occurring in animal models.

Knowledge gained into the human leucocyte antigen (HLA) system and its relation to certain diseases opens a new angle in the etiopathogenesis of some chronic and autoimmune connective tissue disorders. The immunological profile in some of the diseases such as rheumatic fever, rheumatoid arthritis and systemic lupus erythematoses suggests the possibility of immunological abnormality in these patients. Thus it is possible that in the absence of definite evidence of a specific etiological factor, infection, along with genetic susceptibility may play an important role in the outcome of many

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Abbreviations used: HLA, Human leucocyte antigen; IRR, immuno regulatory ratio; PAN, polyarteritis nodosa; AS, ankylosing spondylitis; SLE, systemic lupus erythemetoses.

rheumatological disorders, producing immunological abnormalities.

Infection could be a prime factor as in the case of septic arthritis or it could be a triggering factor as in the case of reactive and post infective arthritis. Research is being carried out in many centres to understand the role of infection in some of the inflammatory arthropathies such as ankylosing spondylitis, rheumatoid arthritis and systemic lupus erythematoses. This article attempts to summarise the role of infection in the etiopathogenesis of some rheumatological disorders.

Role of infection in rheumatic diseases

General mechanism

In acute infections the infecting organism may invade the joints or they may produce toxins or enzymes and set up a inflammatory reaction. Phagocytosis, Opsonisation due to the coating of antigen with antibodies, complement activation and the various types of hypersensitivity reactions results in the release of acute and chronic inflammatory mediators such as histamine, serotonin, Kinins, prostaglandins and lysosomal enzymes which are responsible for triggering the inflammatory process leading to tissue injury.

When the immune mechanism fails to eliminate the infecting organisms from the body, the infection persists in some sites of prediliction (eg., in the reticuloendothelial cells in Brucellosis) and leads on to a chronic infective stage. Low doses of viral and other antigens have been found to induce a state of unresponsiveness of suppressor *T* lymphocyte function in experimental animals (Fudenberg and Wellis, 1976). Under normal conditions the suppressor *T* lymphocytes check the number of normally existing auto antibody producing *B* lymphocytes, just sufficient to remove damaged or aged tissues. If, these *T* cells function is defective, the system fails to control auto antibody producing clones. A similar mechanism may play a role in the development of auto immune disorders in human beings in the presence of chronic infections with microorganisms which establish in the body due to the deficient immune mechanism of the host, defective phagocytosis and inherent capacity of some microorganisms to multiply inside the phagocytosed cells. Such a mechanism in rheumatoid arthritis is evident from the study of subtyping of *T* cells using subset specific monoclonal antibodies which show that there is an imbalance in helper/suppressor *T* cell ratio. Veys introduced the concept of immuno regulatory ratio (IRR), helper/suppressor ratio which is normally about 1·5 in peripheral blood and which may be considerably higher (above 6·0) in active rheumatoid arthritis patients (Mackenzie and Williamson, 1983). Histological appearance of synovial membrane and immunological profile of rheumatoid arthritis patients imply the continued presence of an antigen and the identification of such an antigen may well be the key to the etiology of rheumatoid arthritis.

Role of infection: Types of arthritis

The organisms responsible for causing rheumatic diseases may play: (i) A direct role by invading the joints as in septic arthritis due to *Staphylococcus aureus,* Streptococci,

gram negative organisms etc., or (ii) An indirect role as in the case of post infective type of arthritis *eg.,* rubella arthritis and polyarteritis nodosa and reactive type of arthritis *eg.,* rheumatic fever, enteropathic arthritis due to salmonellosis, shigellosis, and yersiniosis, meningococcal infection, chickengunya infection and lyme arthritis due to tick borne spirochaetosis or the organism may play (iii) a hypothetical role in producing inflammatory poly arthropathies such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematoses etc.

Role of infection in septic arthritis—Pathogenesis

Although the involvement mostly of a single joint in septic arthritis is suggestive of a local rather than a systemic pathology, the likelihood of infectious or septic arthritis is greater, if host resistance is impaired by disease or by immune suppressive drugs or where there is previous damage of an apparently normal joint by trauma or by another arthritic illness.

Except for some rare instances in which the organisms are introduced into the joint by instrumentation or penetrating wounds, invasion of joint occurs by an extension of infection from adjacent bone or soft tissue or by haematogenous spread from a focus of infection elsewhere in the body. The organisms in order to set up an infection of joints must be able to elude an active reticulo-endothelial system, to colonise synovial tissue or juxta articular bone and to penetrate into the joint cavity. Once the penetration into the joint cavity occurs, a rapid series of events occur. The synovial vessels become engorged and dilated, the synovial tissue becomes oedematous and intra-articular pressure increases due to increased volume of synovial fluid. The phagocytes which migrate into the joint try to engulf and destroy the organisms resulting in accumulation of pus inside the joints.

As mostly the infections are due to haematogenous spread, antibodies would have already been formed against the organisms and antigen-antibody complexes can be found inside the joint cavity leading on to activation of complement mediated events such as histamine release, Chemotaxis and phagocytosis. Bacterial products alone even in the absence of antibody can trigger complement activation through the alternate path way (Schmid, 1979).

The impairment of host defence has been proved in instances of septic arthritis (*eg.,* diminished intracellular killing of *S. aureus* within macrophages in virus infected tissues and in subjects under cortisone therapy). Impairment of the function of polymorpho-nuclear cells, *viz.,* inadequate production of superoxide and hydrogenperoxide required for killing catalse negative bacteria, defects in chemotaxis and phagocytosis seen in chronic granulamatous disease have been associated with episodes of staphos-teomyelitis and suppurative arthritis (Schmid, 1979).

Role of infection—Polyarteritis nodosa (PAN)

PAN was described by Kussmaul and Maier over 100 years ago and was regarded for most of this period as a disease of unknown etiology. Presence of immune complexes of hepatitis *B* antigen has been demonstrated in affected tissues including kidney. Thirty

to forty per cent of patients formerly regarded as having unexplained generalised necrotising vasculitis are haepatitis *B* antigen carriers, a figure far greater than would be expected in general population. Immuno fluorescent observations led to the concept that polyarteritis may be due to the circulating antigen-antibody complexes causing lesions of vessel walls (Ziff, 1976).

Role of infection—Rheumatic fever

The arthritis of rheumatic fever has been included under reactive arthritis where the infecting microbial species is well known but where the infecting organisms or the products have not yet been found at the site of lesion. Till now, the particular type of *β*-haemolytic Streptococcus which can unquestionably cause rheumatic fever is not yet identified eventhough more than 63 Griffith type of organisms have been isolated. Moreover, it is not still clear whether the rheumatic fever subjects are more susceptable to group *A* streptococcal infections or whether susceptibility lies in the unusual features of immune response.

While no significant increase in any particular human leucocyte antigen has been found by many workers a study conducted by Caughey *et al.* (1975) showed an increase in the incidence of BW17 in subjects suffering from rheumatic fever.

According to Zabriskie (1976) subjects suffering from rheumatic fever show a hightened cellular and humoral response to group *A* antigens and cross reactive autoimmunity to various cardiovascular tissue and other antigens. Kingston and Glynn (1971) have reported cross reaction of rabbit antistreptococcal sera with a number of tissue antigens including fibroblasts of heart valves, skin and synovial membrane as well as astrocytes and endothelial cells. It can be postulated that the severity and the type of target organ damage may be related to the nature of cross reacting antibodies in susceptible individuals.

Role of infection—Enteropathic arthritis

Though the antecedent gut infection and the subsequent arthritis are very well known clinical entities, neither the organism nor the antigen could be demonstrated in the affected joints, but a raise in titre of antibodies against Salmonella, Shigella or Brucella and other such organisms could be demonstrated in serum and also in the joint fluid to a lesser extent. From the fact that the exacerbation of gut infection is closely associated with exacerbation of joint symptoms it has been postulated that the release of large quantities of antigen into the circulation from the gut predispose to the formation of soluble antigen-antibody complexes which enter the joint producing reactive synovitis by activating the classical and alternate complement pathways (Haslock, 1978).

Role of infection—Ankylosing spondylitis

Ankylosing spondylitis (AS) is one among the major inflammatory rheumatic diseases. Reports from Moll (1978) and Ford (1953) suggested association between AS and

genito urinary infection. Association between AS and certain bowel diseases are also well known (McBride *et al.,* 1963). While it is possible for the spread of pelvic infection *via* the lymphatics, it is unlikely, since mostly AS occurs even before the manifestation of genito-urinary or bowel disease. The other possibility is that the infection was already established in latent form.

Brewerton *et al.* (1975) and Schlosstein *et al.* (1973) have demonstrated the evidence of genetic factors in AS (HLA B27). A cross-tolerance hypothesis has been proposed to explain the association of HLA B27 with the AS. It is proposed that the HLA molecule itself stereo chemically resembles antigens found on some external agents such as micro-organism. Damian (1964) coined the term molecular mimicry for this adaptive mechanism shown by parasites which adapt antigens of the host in an attempt to avoid detection or immunological destruction. When such microorganisms reach a state of partial adaptation whereby antibodies produced against these organisms also have antiself or autoimmune action due to resemblence to self antigen, tissue damage results by complement activation (Ebringer and Ebringer 1981). Haemagglutination and lymphocytotoxicity studies lead to the implication of *Klebsiella pneumoniae* in the pathogenesis of AS due to cross reaction with HLA B27 (Orban *et al.,* 1983).

But Welsh and Black, (1983) contradict this molecular mimicry or antigenic cross reactivity between B27 and a particular micro organism based on the observation that a variety of microorganisms precipitate a class of rheumatic disorders *viz.,* AS, Reiter's disease and reactive arthropathies which are also closely associated with HLA B27. A more likely explanation could be that for reasons of charge, or because of a lectin like property, the B27 molecule binds to carbohydrates of the microorganism thus magnifying the response against the organism.

Role of infection—Rheumatoid arthritis

Though rheumatoid arthritis is one of the vastly studied diseases, conclusive evidence as to the etiology of this disease is still not forthcoming. Many etiological hypotheses for rheumatoid arthritis, namely, infective, metabolic, immunological etc., have been described and tested, but mostly with negative results. Genetic markers including histocompatibility antigens have not yet provided any clear evidence of an inherited genetic factor though Welsh and Black (1983) have shown a well documented association between DW4, DR4 and rheumatoid arthritis; DR4 being even more closely associated with rheumatoid arthritis than DW4.

The role of infection in causing rheumatoid arthritis is still hypothetical, although a number of workers have claimed to have isolated diphtheroids from infected synovial membrane and fluid (Duthie *et al.,* 1967). Some workers have demonstrated the presence of structures resembling the cells of *L* phase organisms in fluid cultures from rheumatoid arthritis patients (Bartholomew and Nelson, 1972).

There are persistent hints of the involvement of Rubella virus in juvenile rheumatoid arthritis (Martenis *et al.,* 1968). Elevation of para influenzae and Ebstein Bar virus antibody level in juvenile polyarthritis have also been reported (Phillips *et al.,* 1973) but conclusive evidence for implicating a specific virus is lacking.

Rheumatoid arthritis and animal model

Gastro intestinal abnormalities and rheumatoid arthritis like arthritis have been demonstrated experimentally in pigs which were fed on protein rich diet (Mansson and Nerberg, 1971). These animals developed joint deformities after some months and pathological changes similar to rheumatoid arthritis were demonstrable in the joints. No bacteria or mycoplasma were cultured from the joints but a delayed hypersensitivity to *Clostridium perfringens* was demonstrated along with a significant increase in the number of atypical *Clostridium perfringens* type *A* in intestine.

Rheumatoid arthritis and environment

Recently a disease very similar to rheumatoid arthritis has been described as naturally occurring in the dogs (Alexander *et al.,* 1976). This being a domestic animal which shares a very similar environment to man could be; important epidemiologically as suggested by Gottlieb *et al.* (1974) from the observation that ownership of pets can be associated with the development of rheumatoid arthritis in man. Soloman *et al.* (1975) after conducting an epidemiological survey on 964 African residence in an old established urban suburb came to the conclusion that rheumatoid arthritis is rare in rural Africans but the incidence rises with the adaptation of a more sophisticated life style.

Role of infection—Systemic lupus erythemetoses

Systemic lupus erythemetoses. (SLE) is one of the best studied examples of immune complex diseases. Despite considerable recent advances in the understanding of pathogenesis of SLE the etiology of the disease is still unknown. At the present time the disease is thought to result from a combination of genetic and infective factors.

Genetic factor

Siegel and Lee (1973) have shown from their epidemiological studies an increase in the prevelance of hyper γ-globulinaemia, antinuclear antibodies, biological false positive test for syphilis, clinical evidence of SLE and other connective tissue disorders in family members of patients with SLE. No definite relationship between any particular HLA group and SLE has yet been confirmed.

Infective factor

Results from animal studies have catalysed interest in possible viral etiology for SLE. *C* type virus particles have been associated with Canine SLE and Newzealand Mouse disease. The clinical and serological similarities between these and human SLE has stimulated a search for a viral etiology of SLE. Fresco (1970), using an electron microscope observed virus like structures in the kidney of a patient with SLE. Subsequently Gyorkey *et al.* (1972) have also described different types of inclusions in SLE glomerular epithelium. These are tubo-reticular structures found in the en-

dothelium of glomeruli. They resemble superficially the nucleocapsid of paramyxo viruses (Gyorkey *et al.,* 1972). But it is now felt that they represent cytoplasmic material, possibly altered as a result of viral injury (Graham and Houghes, 1978).

A few reported attempts at direct isolation of viruses from cell cultures of SLE tissue have yielded negative results (Feorino *et al.,* 1970). This may be due to the persistence of some viruses in joints in defective forms so that a systematic searcher for viruses in synovial membrane might have overlooked a critical population of such cells which are able to sustain a persistent infection (Denman, 1983).

Attempts to demonstrate a significant raise in any of the antiviral antibodies showed that many viral antibodies were high in SLE. Striking elevations in RNA viruses of the paramyxo, reo, corona and toga groups, and to DNA virus of the herpes simplex, group were often detected. This increased virus antibody in SLE can be interpreted in two ways, (i) Primary: SLE may be caused by more than one virus; (ii) Secondary: Depressed cellular immunity might allow abnormal persistance of multiple viruses or most frequent re-infection thus stimulating higher antibody levels (Phillips, 1976).

Epidemiological investigation of SLE and of drug activated SLE by Lee and Siegel (1976) suggest the concept that the SLE syndrome results from a complex interplay of factors, *viz.,* genetic, represented by familial, ethenic and sex predisposition, environmental represented by agents known to trigger activity of the disease *i.e.* ultra-violet exposure, trauma, and infection; and chemical represented by drugs capable of reacting within the body with DNA to form complexes which are more antigenic than native DNA and which more of less regularly elicit the formation of anti DNA complex antibody. Thus, the actual pathogenesis of SLE would depend on the development of anti DNA antibodies either because of alteration of DNA by means of virus, ultra-violet radiation, and drugs or marked enhancement of reactivity of immune system induced by viruses or genetic influence or a combination of any of these factors.

Conclusion

It is obvious that environmental and genetic factors may also be important in governing the immune response and cellular susceptability to an infection and in the clinical manifestation of the disease. Environmental agents such as drugs or sunlight may impaire a balanced host microbial relationship in favour of a disease. According to Fundenburg and Wells (1976), the genetic predisposition to the auto immune diseases merely reflects genetically determined selective immunologic deficiency for one or another micro organism.

Thus, a microbe sitting at a focal point may not be the prime cause but may be a part of a multifactorial etiopathogenic process.

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