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Etiopathogenesis of rheumatoid arthritis may be misunderstood of non-infectious-A review on infectious etiology of RA

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Abstract: Rheumatoid Arthritis (RA) the musculoskeletal disease of joints, mainly affects elderly people and some cases juvenile rathritis also reported. Until now no particular etiological reason put for initiation and development of the disease. The understanding rheumatoid arthritis has paramount importance, besides no particular mechanisms postulated for etiology have been well documented. In recent times many studies have given satisfactory explanation for infection and immunity for etiology. Many studies indicate soon after or during infection elsewhere in body play important role behind it. In this review some studies pertain to infectious arthritis were reviewed under rheumatoid manifestation for better understanding of etiopathogenesis of rheumatism.

Key words: Autoimmunity; arthritis, pathogens, microbes, virus, bacteria

INTRODUCTION

Rheumatoid arthritis is an autoimmune disease of unknown etiology, which mainly involves Joints. To etiology of rheumatoid arthritis, many different approaches have been taken over the past decade to understand the manifestation, led to many different strategies to rational development of arthritic etiopathologic hypothesis and anti-arthritic medications. Intensive research has been carried-out for a possible microbiological etiology of RA. Since no evidence has been found or postulated for the constant presence of an infectious agents and lack of epidemiological evidences pertains to triggering factor of the disease or as a persistent antigenic drive to inflammatory synoviocites, still involvement of infection to etiology has not been ruled-out. Robinson (1966) edited textbook for etiology of rheumatoid arthritis hypothesized that, it would be an infectious disease and possibly of other conditions as many as endocrine, psychosomatic, hereditary and recently apoptosis etc., Many suggested mechanisms to etiology of the disease is still believed relevant to manifestation for rheumatoid arthritis, even though no particular mechanism posted for etiopathology gives satisfactory explanation. The complex interactions between the triggering microbe and the defense mechanisms of the host in arthritis have been studied in several laboratories around the world, and interesting observations have been made. In addition, research also focused on the mediators in the inflammatory process in joints, and these results are helping to slowly build a comprehensive picture about the pathogenetic process in arthritis (Toivanen and Toivanen, 1997).

Regarding microbiological aspects of arthritis with arthritic microorganisms as causative agents responsible for the disease are Mycobacteria, Mycoplasma, Staphylococci, Streptococci, some gram- negative bacteria and viruses. The demonstration of antigens or nucleic acid of an infective agent at the site of disease, in association with specific local immune response suggests the pathogenetic importance of the agent. Recent studies of relationships between epitopes of infective agents, T and B-lymphocytes and MHC gene products suggest several ways in which infective agents can directly cause a disease such as rheumatoid arthritis without any requirement for autoimmune contributions.

In addition, several viral candidates induced abnormal immune cross-reactivity to host (Carty *et al*., 2004; Vita *et al*., 2008) and *Chlamydia trachomatis* in the hip joint of a woman with monoarticular synovitis is interesting (Jolly and Curran 2004; Rashid *et al*., 2004; Philippe *et al*., 2006) giving satisfactory explanation of infection connection to etiology. The disease rapidly progressed into seropositive oligoarthritis of large joints. Soderlin *et al*., (2003a) did a population based systematic survey of the infectious background of patients with early synovitis duration of symptoms less than 3 months showed patients had evidence of recent infection. Of the patients with early synovitis many experienced RA had serologic evidence of recent infection of either parvovirus B19 or *Chlamydia pneumoniae*. It suggests that patients with early RA have serologic evidence of recent infection.

MATERIALS AND METHODS

This present work is fully based on available data's on the research abstracts and full articles related to arthritic manifestation either with human subject and in animal models in www.pubmed.com and www.goolge.com. This manuscript is written on available

data's related to viral and bacterial infection connection to arthritis. The research articles were taken in this manuscript or based on the findings of viral and bacterial infection before or during or later to arthritic manifestation. This manuscript is written based on research findidng with animal models and human subject.

RESULTS

Table 1 and 2 illustrates the possible viral and bacterial infection to arthritis. Particularly the viral species like *Chlamydia pneumonia*, *Chlamydia trachomatic*, *Parvivirus B 19*, *Hepatitis B & C*, *Epstein-Barr Virus*, *Togaviridea*, *Ross River Virus*, *Rubella Virus* were identified before onset of arthritis manifestation or during the course of the disease or with exerbated disease state or viral epitopes were identified later stages of the arthritis manifestation. Like wise many bacterial species were also identified and isolated from blood and synovial fluid contents during arthritic manifestation especially Mycobacterium species infection is more prone do develop arthritis. The bacterial species were *Yersinia* sp., *Salmonella typhi*, *Shignella* sp., *Klebsiella pneumonia*, *Mycobacterium tuberculosis*, *Mycobacterium xenopi*, *Steptobacillus monisiforms*, *Staphylococcus* sp., *Streptococcus* sp., *Haemophilius* sp., *Enterobacteria* sp. The bacterial gram positive species cell membrane proteoglycan fragments and gram negative species cell membrane peptitoglycan fragments were identified by many laboratory methods from arthritis patients blood and synovial fluid samples and many immunological parameters like immunoglubulins against specific bacterial antigenic epitopes and PCR methodes for viral epitopes were identified.

Table.1: List of viral etiology for rheumatoid arthritis

Viral species
Chlamydia pneumonia
Chlamydia trachomatic
Parvivirus B 19
Hepatitis B & C
Epstein-Barr Virus
Togaviridea
Ross River Virus
Rubella Virus

Table 2: List of bacterial etiology for rheumatoid arthritis

Bacterial species
Yersinia sp.
Salmonella typhi
Shignella sp.
Klebsiella pneumonia
Mycobacterium tuberculosis
Mycobacterium xenopi
Steptobacillus monisiforms
Staphylococcus sp.
Streptococcus sp.
Haemophilius sp.
Enterobacteria sp.

DISCUSSION

Virus: The etiologic role of viruses in various rheumatic diseases is a subject of continued great interest. Viral infections can present with different patterns of joint and soft tissue involvement. Rheumatoid arthritis (RA) has been widely suspected to have viral infectious etiology. *Epstein-Barr virus, parvoviruses,* and *retroviruses, alpha viruses, rubella sp. Hepatitis C* are considered for primary candidates (Phillips., 1999) (Table.1). Cases of viral arthritis are frequent but instructive about pathophysiological mechanisms underlying acute and chronic arthropathies. Acute viral infection can cause disease by various means, including direct tissue damage, indirect damage via inflammation, or direct damage via an immune response (Kingsley 1997; Schumacher 1995; Hansen *et al*., 1998). Persistent infection can cause chronic pathology via any of these mechanisms by the fact that, many viral infections can induce autoantibodies (Kohler 1987). The *Epstein Barr Virus* (EBV) is of interest covering the question of distinct virus persistence in tissues (Kerr *et al*., 2004). Epstein–Barr virus (EBV) implicated in RA for several years. Balandraud *et al.* (2004) summarized the present knowledge of the poor control of EBV infection in patients with chronic RA. The patients having higher levels of anti-EBV antibodies than normal individuals. In addition, EBV-specific cytotoxic T cell function, which is needed for the control of the chronic infection, is defective in patients with RA; this probably causes the increased viral load observed in the patients. There is no good evidence in favor of the primary infection as a trigger of subsequent RA (Fox, 1988). In our study pertains to electorn microscopic identification of Cytotoxic T Lymphocytes invasion to arthritic knee joints of the rat model using complete adjuvant contains heat killed *Mtb* have advocated the possible involvement of infection to arthritic manifestation (Subramanian and Ramalingam, 2005b). The consequences of *Parvovirus B19* infection has broadened to include the variable clinical spectrum. Specific antibodies to nonstructural protein NS-1 in parvovirus B19-associated arthritis has been documented. Antibodies reactive with B19 epitopes can cross-react with some auto-antigens. *Parvovirus B19* DNA detected in the synovial tissue of patients with rheumatoid arthritis with raised levels of IL-4, IL-6, IL-8, TNF-alpha, IFN-gamma, MCP-1, GM-CSF, TGF-beta 1, and ET-1 giving satisfactory explanation for viral connection to production of proinflammatory cytokines. In addition cytokine levels following acute symptomatic infection with *Parvovirus B19* indicate a state of immune activation (Harrison *et al*., 1998; Tzang *et al*., 2007). In addition, increased frequency of IgM anti-B19 antibodies with juvenile chronic arthritis (JCA) (Kishore *et al*., 1998; Jobanputra *et al*., 1995; Lunardi *et al*., 2008). elevated IgM antibodies with arthritic patients (Jorgensen *et al*., 1993) and B19 DNA in synovial tissue and bone marrow specimens form patients with RA and Osteoarthritis (OA) (Takahashi *et al*., 1998) were also noticed. They also noticed *in situ* hybridization, B19 DNA and RNA, erythroid cells of lymphoid follicles, sublining

macrophages, and perivascular lymphocytes in synovium of RA patients. These data illustrate that, human parvovirus B19 may persist in bone marrow and synovial tissues of patients with arthritis of known origin might implicate upon viral infection in RA.

Concomitantly Lunardi *et al*., (1998) have demonstrated cross-reactivity of anti-B19 antibodies with several autoantigens in patients with chronic parvovirus infection resembling RA and had IgM antibodies to B19. Likewise patients with chronic B19 infection had IgM antibodies to the synthetic 24-aminoacid peptide and IgG. Those purified peptide reactive antibodies showed specificity to recognize keratin, type II collagen, ssDNA and cardiolipin. In another study, *Epstein-Barr virus* transformed cell clones generated from patients with chronic B19 infection were produced anti-B19 peptide. Similarly mice infected with the peptide developing anti-B19 response and also response to keratin, type II collagen, cardiolipin and ssDNA (Naides, 1998; Cassinotti *et al*, 1998). These findings suggest molecular mimicry. Further it suggests that human parvovirus B19 infection serve as a model for the study of virus-host interactions and the role of viruses in the pathogenesis of rheumatic diseases.

Furthermore alpha virus genus of the *Togaviridea* family caused arthritis also reported (Yterberg, 1997). Polyarthritis caused by *Ross River virus* affects the knees particularly the small joint of the hands and feet. Arthritis occurs with Rubella infection occurring more often in women than in man and in adults than in children. Those symptoms were also found for rubella vaccination (Ray *et al*., 1997). The *Rubella virus* can replicate in human joints tissue, synovial fluid and peripheral blood (Tingle *et al*., 1997). Zhang *et al*., (1997) identified mumps and measles virus in synovial fluid and peripheral blood of patients with RA. In addition Hepatitis C (HCV) also implicated for autoimmune disorders including cryoglobulinemia, autoimmune hepatitis, glomerulonephritis and sjogren's syndrome (Gorden 1996). Those patients feature resembling RA (Lovy *et al*., 1996). HIV infection, hepatitis B virus vaccination or measles and mumps vaccination are found associated with several rheumatic syndromes including polyarticular avascular necrosis resembled RA (Gerster and Rossetti (1998); Schnitzer and Penmetcha 1996). These data's illustrate more prone to viral infection particularly of who can develop auto-antibodies which can cross-react with self- molecules have possibility to show arthritic like symptoms. Those studies have giving more understanding on viral etiology for RA. Unfortunately, current PCR method used for detection of viral infection having some restriction because non-availability of specific primers. Hence possibility of viral etiology cannot be ruled out for presenting hypothesis for rheumatoid arthritis. Hence the above data's are contributory in understanding the viral etiology to RA.

Bacteria: Etiological diagnosis of arthritis based on the demonstration of recent infection with the causative bacterium may be done by serological demonstration of antibacterial antibodies and demonstration of the causative microorganism at an extra-articular site or by identification of bacterial nucleic acids or antigens in joint material from patients with arthritis. An increasing body of data appears to implicate bacteria and their products in the syndrome. Important evidences were surfaced in support of this view. Many bacterial species were identified during arthritis manifestation were listed in the Table 2. In addition continuous seeding of bacterial products from the gut or the synovial inflammation is followed by erosion or exposition of cartilage antigens imply upon their role in autoimmunity. A series of observations has led to a hypothesis that patients with rheumatoid arthritis might favour intestinal bacteria which are capable of inducing arthritis (Toivanen 2001; Simab and Schnitzler 2009). Since intestinal pathogens are important causes of reactive arthritis, and are responsible for transport of bacterial products from the gut to synovium (Bennett 1987).

The immunological relationships between host and bacterial peptidoglycans to arthritic manifestation is well documented, e.g., heat shock proteins (HSP), bacterial IgG Fc binding proteins, and rheumatoid factors. Concomitant to the above, HSPs in the immune complex of patients with juvenile chronic arthritis (Eden *et al*., 1991) and T cell clones recognized nine-amino acid sequence of HSP were also demonstrated (Gaston *et al*., 1989; Quayle *et al*., 1991; Celis *et al*., 1997). Likewise synovial fluid T cell response to the above amino acid sequence and pretreatment of the same induced resistance against adjuvant induced arthritis also elucidated (Moudgil *et al* 1997; Ragno *et al*., 1997; Schumacher, 1995). In addition *K. pneumonia* lippo-poly saccharide (LPS) molecules similarity with self-peptides and antibodies against those LPS and *Salmonella typhi* antigens elucidate cross reactivity mechanism and bacterial products in arthritis (Fielder *et al*., 1995; Rashid *et al*., 2004; Gracia *et al*., 1987; Wilder and crofford 1991). These data not only support the hypothesis that bacteria may play an important role in RA but also indicate that current concepts of infection and autoimmune disease are broadening and overlapping (Herman *et al*., 1995). Gram possitive bacteria membrane glycoprotein peptidoglycan in the immune complex formation widely discussed. Concomitantly study relate to determination of constituents of the immune complex (IC) on juvenile rheumatoid arthritis (JRA) large number of JRA patients immune complex analyzed with SDS-PAGE Western-blot showed four polypeptide bands with different molecular weight form anti-HiGM affinity column. Digestion with DNASE, RNASE and proteases failed to eliminate the bands, thus raising possibility of glycosaminoglycans, lippo-polysaccharides of entero-bacterial membrane or some other protein contains in the IC (Moore *et al*., 1995; McCulloch *et al*., 1993). The above experimental evidences providing importance of microbiological connection to arthritic etiology.

In differential diagnosis of bacterial infection-related arthritis, various laboratory methods are applied for the detection of the inciting antigen, specific antibodies or microbe-specific T-lymphocytes. In reactive arthritis following extra-articular infection with *Yersinia, Salmonella, Shigella, Campylobacter, or Chlamydia* bacterial products are determined by immunological methods and polymerase chain reaction (PCR) actually within the joint (Koehler at al., 1998' Braun *et al*., 1997; Siala *et al*., 2009). Even though in rheumatoid arthritis characterized with lack of culturable organisms in the joint, still demonstration of bacteria or bacterial macromolecules in the joints has elicited the idea that arthritis is a sterile process induced and maintained by antigenic material in the synovium. However it may be hypothesized that continued synthesis of antigens to maintain synovial inflammation probably requires establishment of persistent bacterial infection in the joint, or at the primary site of infection.

In addition, screening for DNA sequences of bacterial species in synovial fluid (SF) of patients with inflammatory joint disease found bacterial DNA in peripheral joint of patients with juvenile chronic arthritis (JCA). Such findings as bacterial DNA in patients with JCA with longstanding disease, suggests that in later stages autoimmune mechanisms may operate (Salliot *et al*., 2006). Synovial lymphocytes, from the site of disease, by their response to microbiological antigen stimulation as measured by the [3H]thymidine uptake method, indicated microbiological cause for arthritis.

Furthermore *Mycobacterial* species are widely deled in understanding their role in autoimmune manifestation. The *Mycobacterium xenopi* is a nontuberculous mycobacterium responsible for opportunistic and nosocomial infections, chiefly of the lung; few cases of bone and joint infection have been reported (Soderlin *et al*., 2003b). Concomitantly, population-based study of the patients presenting with new-onset arthritis had a prior infection. Remission during the first 6 months was especially frequent in those groups of patients with a prior infection, but the remission rate was relatively high even for arthritis without prior infection (Legout *et al*., 2005). Further it suggests that infection no longer need at the site for maintenance of inflammatory reactions. Hence infection in other sites implicate upon their relation to such mechanism. For example sub-clinical Proteus urinary tract infection the main triggering factors for RA. It suggest that molecular mimicry and cross-reactivity between these bacteria and RA-targeted tissue antigens assists in the disease process through production of cytopathic auto-antibodies (Ebringer and Rashid 2006). Likewise both *Mycoplasma fermentans* (Mf) DNA and specific antibodies to Mf were noticed in the SF of RA patients (Horowitz *et al*., 2000; Heijden *et al*., 1999; Leal *et al*., 2007). From the above, it may be conferred that the bacterial connection most obvious reason in triggering immune response beside to eliminate invaded microbial components is often importantly more necessary to protect host environment. Further it could be suggested that continues seeding of bacterial products form gut or infection elsewhere in the body could be of contributory for etiology of rheumatoid arthritis.

Immunoglobulin: Polyclonally raised serum immunoglobulins are seen in association with many infective and inflammatory conditions. Non-specific polyclonal B cell activation which can result from an inherent abnormality of B and T lymphocytes or lymphokines or other signals such as bacterial lippo-polysaccharides and similar bacterial products found source for the production. In addition elevated titre of bacteria-specific IgG- and IgA-class antibodies indicates recent or persistent infection (Wollenhaupt *et al* 1998). IgM antibodies to B19 appear 10 to 12 days after inoculation and last for 1 to 3 months but IgG antibodies appear several days after IgM antibodies and presumably last throughout the life (Lorber *et al*., 1978). The onset of polyarthritis is associated with the development of the anti-B19 IgM antibody, which clears virus infection. Therefore patients present at the time to the rheumatoilogist with polyarthritis are no longer infectious but they would have symptoms of polyarthritis and antibody titre. Concomitantly IgM antibody may last up to 2 to 3 months following an acute infection but the level usually falls off. However reappearance of IgM antibody may indicate recrudescence of the infection. The presence of IgM antibody will confirm a recent infection or exacerbation of infection (Nesher *et al*., 1995). Thus the increased immunoglobulins concentration obviously reflect in one-way or another the underlying immunological process of rheumatoid arthritis. Patients evaluated for acute inflammatory polyarthritis up to 6 years by screening of B-19 DNA by PCR. 12 of the patients exhibited IgM anti-B19 DNA by PCR and by the Sothern Blot analysis. Initially the rheumatoid factor was negative in all B19 cases except one, but become positive in 4 patients after 2 to 4 months after the infection (Murai et al., (1999); Lehmann *et al*., 2008). B19 DNA was no longer detected in blood samples but continued to remain positive in bone marrow and synovial tissue. Patients with recent onset RA produced increased quantities of immunoglobulins when their peripheral blood lymphocytes were stimulated by EBV in vitro (Jokinen *et al*., 1994). The enhanced response to EBV predicted the development of joint destruction (erosions) in the patients during the subsequent 2-year follow-up. This evidence of an abnormal response to EBV, and in the case of EBV infection in a patient during the incubation phase of RA, this would be an indicator of a more persistent and destructive form of arthritis. Specific immune stimulation and production of antibodies certainly needs specific microbial connection thus provides such intrigue.

Primary Immune Deficiencies (PIDs): Primary immune deficiencies (PIDs) are characterized by functional and quantitative abnormalities of one or more immune system components. Several bone and joint abnormalities can

occur in patients with PID, arthritis being the most common. Intrinsic defect either in T or B-lymphocytes arm of immune system has been demonstrated in many studies (Mageed *et al*., 1994; Goronzy and Weyand 1995; Said 2007). Arthritis in patients with PID is usually infectious in nature, the most common causative organism being Mycoplasma, followed by *Staphylococcus, Streptococcus, and Haemophilus*. These bacteria can induce not only synovial infections, but also arthritogenic inflammatory responses. Hence arthritis having demonstrable relation to chronic infection ascribed to effective immunity-driven mechanisms that exhibit a number of specific features. Familiarity with PID syndromes provides insight into the pathophysiology of bone and joint abnormalities associated with immune dysfunction (Cuomo *et al*., 1995). In addition it has been proposed that several infectious agents leads to recognition of self-antigens and consequently to be disordered immune response and dysregulation of cytokines production that initiate and maintains the disease (Sordet *et al*., 2005; Peters *et al*., 1996; Ozcan *et al*., 2008). Patients persistently infected with B19 with prolonged disease course manifested by polyarthritis showed prolonged period of elevated IgM antibodies as well as the lack of specificity for the minor capsid species suggested a class switch defect (Bijlsma *et al*., 1999). Further it suggests that patients do not produce B19 antibodies and patients with congenital acquired immunodeficiency produce antibodies that fail to react with viral capsid protein epitope known as quantitative defect. The fact behind this might be of defective immune response especially in specific immunoglobulin synthesis, because defective antigenic drive either in identification of microbial epitope or with its presentation to B cell for maturation to plasma cell or with greater memory loss against earlier infection was found contributory to the arthritic mechanism. Concomitantly *Epstein-Barr virus* infections of B cells causes the cell to display increased binding sites on the cell surface for human Herpesvirus-6, thereby increasing susceptibility to super-infection with human herpesvirus-6 shows another defect in autoimmunity in certain viral infection (Fish *et al*., 1989). However so, immune deficiency might have contributory role in autoimmune phenomena, but only with causative organism gives much satisfactory explanation. Because age related syndrome like memory loss in immune system especially of memory B cell activity is more importantly necessary to maintain avoiding cross-reactivity with self-molecules. Re-infection of same old infectious agents is more frequently deled by memory B cells. Likewise memory B cells elicited very weak primary response to antigen on transfer into immuno-deficient mice also noticed (Inman 2006). In addition maintenance of memory B cell population by exposure to environmental antigens including viruses, bacteria and other parasites could provide intermittent immune stimulation through cross-reactivity epitopes such as highly conserved heat hock proteins. Those data implicate upon further need of constructive research in PID connection to arthritic etiology.

Anaerobic Bacteria Infection: Infections attributed to anaerobic bacteria are common in children and may be serious and life-threatening. The recent increased recovery of these organisms from children has led to greater appreciation of the role anaerobes play in paediatric infections at all body sites, including the joints and bones. The etiologic importance of anaerobic microorganisms in bone and joint infections has recently been emphasized for RA. Anaerobic bacterial infection are common and may be serious and life threatening. Anaerobes are the predominant components of the normal human skin and mucous membranes bacterial flora (Liu *et al*., 1997) and, therefore, are a common cause of bacterial infections of endogenous origin. Because of their fastidious nature, these organisms are difficult to isolate from infectious sites and are often overlooked. Their exact frequency is difficult to ascertain because of the inconsistent use of methods for isolation and identification. Their isolation requires appropriate methods of collection transportation and cultivation of specimens. The recent increased recovery of these organisms from children has led to greater appreciation of the role anaerobes play in pediatric infections at all body sites, including in the joints and bones. Feigin *et al*., (1975) reported two children with septic arthritis caused by clostridia. Nelson and Koontz (1966) reported patients with septic arthritis caused by some common anaerobes showed effusion in the joint cavity, which rapidly becomes purulent. At later stage cartilage destruction occurs (Ament and Gall 1967).

Lactic acid measurements of joint fluid may clearly differentiate between septic arthritis and other sterile inflammatory and non-inflammatory conditions in the joints. Lactic acid levels higher should be considered highly suggestive of the presence of a bacterial infection. In our study of adjuvant arthritis induced by using Complete Adjuvant which contains heat killed *Mycobacterium tuberculosis*, we found the lactic acid content increased significantly in the adjuvant treated rats. Bacterial infections and granulocyte activities are associated with permeability response and leukocytes activation (Stetson and Good 1951). Our study also revealed the free lactate anions in addition to proteases act as a moderately potent permeability factor. By attributing such role to the lactic acid, the phenomena of angiogenesis and the release of phagocytic cells are made possible with in the reactive region in vivo in the adjuvant arthritic tissues. Hence, it may be concluded that the lactate concentration in the inflammatory region play important role for entry of bacteria, release of phagocytic cells and other proteins. Thus it could be inferred that inflammation induced by bacterial agents and the migration of phagocytic cells need preparative reactions such as lactate synthesis (Subramanian and Ramalingam 2004a,b,; 2005a). Concomitantly synovial fluid studied

for bacterial antigens by immunoelectrophoresis or gas liquid chromatography revealed leukocytosis, elevated sedimentation rate (ESR) and C reactive protein (CRP). Frequently mixed aerobic-anaerobic bone or joint infection develops as a consequence of infection in adjacent areas. The incidence with which anaerobes are present in these settings is undoubtedly underestimated and may often be unappreciated in regard to the selection of therapeutic agents. Therefore, a practical approach to the treatment of infections involving anaerobes that is based on our current knowledge is necessary. Animal models are now available for study in conjunction with prospective human studies utilizing careful microbiologic techniques; it should be possible to determine the significance of anaerobic bacteria when a polymicrobial flora is present in bone and joint infections (Nakata and Lewis 1984). Many patients with osteomyelitis due to anaerobic bacteria have evidence of anaerobic infection elsewhere in the body, which is the source of the organisms involved in osteomyelitis (Brook 2002; Fenollar *et al*., 2008; Brook 2008). In anaerobic infection caused arthritis destruction of cartilage occurs at areas of joint contact. Bone is not affected in the early stages, but the femoral and humeral heads, may have to undergo necrosis and subsequent fragmentation and pathologic dislocation. Epiphyses with synchondroses located within the joint capsule are at particularly high risk for infection and necrosis. During the chronic phase of the disease and the phase of repair, organization of the exudates is present in the joint, and granulation tissue appears and becomes fibrous. This may bind the joint surfaces together, causing fibrous ankylosis. When motion is present, the synovial fluid tends to regenerate, but limitation of motion and associated pain generally remain, as a result of the production of residual strong intrasynovial adhesions. Most of the cases of anaerobic arthritis are secondary to hematogenous spread. Almost all of the isolates of anaerobic Gram-negative rods, including the fusobacteria and the Gram-postive anaerobic cocci that were reported, were also involved in a concomitant anaerobic sepsis. Predisposing conditions to joint infection are trauma, prior surgery, presence of a prosthetic joint and contiguous infection. *P. acnes* isolates were associated with prosthetic joints, members of the *B. fragilis* group with hematogenous spread, and *Clostridium* spp. with trauma. The presence of multiple septic joints was common in cases of spread of the organisms from a primary site through the blood stream or in cases of endocarditis (Mcvay and Sprunt 1952). The ability of anaerobes to cause tissue destruction may be seen in the amount of damage they can inflict on the joints, cartilage, capsule and adjacent periosteum. Thus anaerobic organism might have been proved in accordance to its involvement of arthritogenesis. Current culture techniques are not very much appreciable for detection of anaerobic organisms. Hence data's presented from above studies should be given more importance in accordance to elucidate a relationship between anaerobes and arthritic manifestation.

CONCLUSION

Studies seeking epidemiological evidences for etiology of arthritic manifestation thaw infectious connection to RA. For obvious reason, triggering immune response against antigenic determinant is a preparative cascaded reaction in order to eliminate invaders. There are two principal difficulties with the hypothesis that infection triggers rheumatoid arthritis: first proving a causal relation and second the limitation of the methods of detection of recent or past infection. Past or recent infection develops onset of polyarthritis persistently associated with the development of antibody response, giving satisfactory explanation for infection triggering immune response in rheumatoid phenomena. No particular studies documented persistence of infectious agents in joint inflammatory site, even though availability of bacterial products at the site of inflammation and triggered immune response to earlier infection and its related antibody activities and particularly of cross-reactivity might be given attention in order to facilitate hypothesis to etiology of rheumatic diseases. And also from clinical concern, patients with earlier infection before develops rheumatological criteria may be no longer infectious giving opportunity to understand its connection and involvement of such infectious connection to etiopathology. Hence it could be strengthening the suggestion that rheumatoid arthritic etiology has satisfactory explanation for infection, and joint inflammation might have develops soon after or during an infection elsewhere in the body. Current anti-rheumatic therapies like biologics also can be taken supportive explanation for microbial etiology basis on the current strategy that targeting particular immune arm for remission. In addition besides to different region of inflammation different names for clear understanding of etiopathology, but not for different manifestation.

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