

FREQUENCY OF PROTEUS MIRABILIS INFECTION IN RHEUMATOID ARTHRITIS

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ABSTRACT

Objective: To assess the frequency of proteus mirabilis infections in patients of rheumatoid arthritis.

Study Design: Cross-sectional study.

Place and Duration of Study: Combined Military Hospital, Rawalpindi Pakistan, from Jul 2018 to Jan 2019.

Methodology: A total of 100 cases of rheumatoid arthritis with urinary tract infection were enrolled. Freshly voided urine samples were obtained and sent to the pathology lab. The serotypes of proteus mirabilis were evaluated by enzyme-linked immunosorbent assay (ELISA) and immunoblotting and presence of proteus mirabilis was noted.

Results: A total of 100 cases of rheumatoid arthritis with urinary tract infection were recruited. The mean age of patients was 61.22 ± 10.18 years. There were total 67 (67%) females and 33 (33%) were males. About 79 (79%) patients had sedentary lifestyle while 21 (21%) had active lifestyle. There were 41 (41%) patients had positive urine culture with proteus mirabilis while 59 (59%) had other organism involved in urine infection.

Conclusion: The high frequency of proteus mirabilis infection has been detected and the frequency was of females with complaint of urinary tract infection was high.

Keywords: Proteus mirabilis, Rheumatoid arthritis, Rheumatoid factors, Urinary tract infection.

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INTRODUCTION

Microorganisms residing inside the human body develop a complex eco-system. The conjoint impact of microbes and immune system of the human body or host establish the beginning of several diseases like inflammatory bowel disease, obesity, pseudomembranous colitis, atopic diseases, type 1 diabetes or reactive arthritis¹. New molecular diagnostic techniques and multi-center trials may support to understand the role of microbiota in health & disease. Rheumatoid arthritis (RA) has multi-faceted cause and is under debate^{2,3}.

Indications showed the significant impact of microbiomes residing in oral cavity, lungs, intestines and urinary tract on initiation of rheumatoid arthritis. Contacts between microbiomes and human immunity, is important in pathogenesis of rheumatoid arthritis⁴.

Proteus-mirabilis (*P.mirabilis*) got great fascination of micro-biologists for >100 years with its distinctive flooded diversity, dienes line construction and powerful urease activity. Transcriptome outlining during both; host infection & swarming motility, coupled with availability of comprehensive genome sequence for *P. mirabilis*, has exposed the existence of interbacterial struggle and killing via type VI secretion system, and

joint regulation of bond and motility, along with close links between metabolism, swarming and virulence⁵. Patients with RA are reported to have in their sera raised levels of antibody specific to *P.mirabilis*. Infection of *P.mirabilis* bacteriuria in RA patients was 52%⁶.

In recent methods for the management of RA normally do not consider the early stages of development of the disease and as a substitute only symptoms have been treated. At the same time as, this method might help to relieve the pain considerably as well as the discomfort related to the RA. But this method could not avert the progression of the disease and further destruction of joints tissues happens as a sequel. Additionally, several number of severe adverse effects occur due to prolonged intake of the current available treatment methods. One of the well improved approach might be applied to get rid of the source of the RA, thus evading the events of later phase. Still in routine, it has not been probable because of the lack of understanding of the causes of the RA^{7,8}.

Rationale of this study was to assess the frequency of *P.mirabilis* infections in patients of RA belong to local community. *P.mirabilis* is the major bacterium involved in RA. But there was a lack of evidence regarding the extent of *P.mirabilis* infections in local community. So we conducted this study to find the commonness of the *P. mirabilis* in patients of RA.

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METHODOLOGY

This cross-sectional study was conducted at department of Medicine, Combined Military Hospital, Rawalpindi, from July 2018 to January 2019 after taking permission from Institutional Ethics Review Board (IERB no. 24855291). Cases aged 35-85 years, either gender of RA (positive RA factor) presenting with complaint of urinary tract infection (on urine examination) were included in the study by using non-probability, consecutive sampling technique. Patients having renal failure or disease (creatinine >1.5 mg/dl), renal carcinoma, patients with recurrent infection within 3 months of treatment were excluded. Sample size of 100 cases were calculated with 95% confidence level, 10% absolute precision and percentage of *P. mirabilis* i.e. 52% in patients with RA presenting with complaint of urinary tract infection. Informed consent and demographics were noted. Freshly voided urine samples were obtained by using a sterile container under aseptic measures. All samples were sent to the laboratory of the hospital to assess bacterium present in *P.mirabilis*. The entire drawn blood samples were centrifuged and stored in ice room. The serotypes of *P.mirabilis* were evaluated by enzyme-linked immunosorbent assay (ELISA) and immunoblotting and presence or absence of *P.mirabilis* was confirmed.

Analysis plan: All the information was entered electronically to Ms Excel Sheets and analyzed by using SPSS-21. Descriptive statistics was calculated i.e. mean ± SD for quantitative variables and frequency & percentage for qualitative variables.

RESULTS

The mean age of the patients was 61.22 ± 10.18 years. There was a total of 67 (67%) females and 33 (33%) were males. About 79 (79%) patients had sedentary lifestyle while 21 (21%) had active lifestyle. The duration of RA diagnosis was 21.36 ± 8.91 years. The mean duration of urinary tract infection symptoms was 25.67 ± 9.14 days (table-I).

The most common symptom of urinary tract infection was cloudy urine 89, followed by burning sensation during urination (82%), lower abdominal pain 77%, persistent urge to urinate in 71%, pink or cola color urine in 69% while 59 had passing frequent urine (table-II).

There were 41 patients had positive urine culture with *P.mirabilis* while 59 had other organism involved in urine infection (figure).

In all the urine samples, other than *P. mirabilis*, *E. coli* was detected in 21 cases, acinobacter species in 14 cases, *klebsiella species* in 10 cases, *streptococcus species* in 8 cases, *enterococcus spp.* In 5 cases while *pseudomonas aeruginosa* in 1 cases (table-III).

Table-I: Summary of demographic and diagnostic characteristics (n=100).

Parameters	Values
Age (mean ± SD)	61.22 ± 10.18 years
Gender	
Male	33
Female	67
Lifestyle	
Sedentary	79
Active	21
Duration of rheumatoid arthritis	21-0.36 ± 8.91 years
Duration of urinary tract infection symptoms	25.67-9.14 days

Table-II: Common symptoms of urinary tract infection.

Parameter	Frequency
Lower abdominal pain	77
Persistent urge to urinate	71
Burning sensation when urinating	82
Passing frequent, small amounts of urine	59
Cloudy urine	89
Pink or cola color urine	69

Table-III: Bacteria isolated from urinary samples.

Bacteria	Frequency
<i>P. mirabilis</i>	41
<i>Escherichia coli</i>	21
<i>Acinobater species</i>	14
<i>Klebsiella species</i>	10
<i>Streptococcus spp.</i>	8
<i>Enterococcus spp.</i>	5
<i>Pseudomonas aeruginosa</i>	1

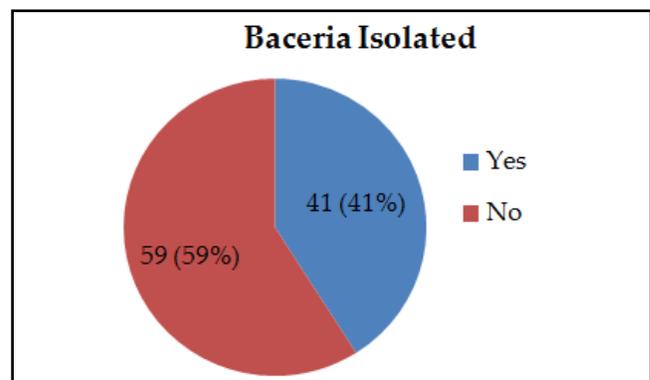


Figure: Distribution of urinary tract infection due to proteus mirabilis.

DISCUSSION

RA is the prolonged inflammatory auto-immune disorder of human beings, which mainly causes pain and swelling in the joints⁹. RA is a complex auto-immune disorder which affects about 1-2% of general population all over the world. The etiopathogenesis of RA includes the inter-play of several hereditary risk factors and environmental causes^{10,11}.

The numerous phenomena are involved in growth of the rheumatoid arthritis, which are not entirely understood and are under debate. It has been suggested that several diverse environmental factors, for example smoking cigarettes, atmospheric and occupational agents can act as triggering stimuli for development of RA in candidates who are inherently exposed to the disease, leading to the synovial hyperplasia and the bone damage. The early stage of RA is related to the variation of native and adaptive immune system, which has consequential production of auto-antibodies, pursuing several molecules together with amended self-epitopes⁹.

A better consideration of how the pathological phenomena initiate the corrosion of RA growth in patients is immediately necessary with the intention of developing the therapies that would successfully manage the patients at every stage of RA progression¹². Therapies and medications for management of RA are continued to increase promptly¹³.

Urinary tract infection is one of a very common type of infections in local community and vulnerability of uropathogens to commonly applied antibiotics has been decreased during recent years. So it is very important to check to susceptibility patterns of these uropathogens occasionally, with the intention that empirical therapy can be planned by using recent evidence to manage urinary tract infection properly and timely. This may also help to improve the outcome of patients having urinary tract infection, particularly in patients complicated with rheumatoid arthritis. This may also help to minimize the failure of empirical therapies and also help to prevent the misuse of antibiotics¹⁴.

In a very recently conducted multi-centre trial, which involved nine Spanish hospitals, 784 females with uncomplicated cystitis were examined for the occurrence of isolated uro-pathogens and their susceptibility to several antibiotics. Out of 650 isolated pathogens, the most frequent bacterial agents detected were *Escherichia coli* (79.2%), which was followed by *staphylococcus saprophyticus* (4.4%), *P.mirabilis* (4.3%), *enterococcus faecalis* (3.3%), and *klebsiella pneumoniae* (2.3%)¹⁵.

In our study, the mean age of patients was 61.22 ± 10.18 years. There were 67 (67%) females and 33 (33%) males. About 79 (79%) patients had sedentary lifestyle due to RA and feeling pain during some work. The mean duration of RA diagnosis was 21.36 ± 8.91 years and patients were already taking treatment for RA. They presented with symptoms of urinary tract infection for about 25.67 ± 9.14 days duration.

In our study, we observed the most common symptom of urinary tract infection was cloudy urine 89 (89%), followed by burning sensation during urination (82%), lower abdominal pain 77%, persistent urge to urinate in 71%, pink or cola color urine in 69% while 59 had passing frequent urine. On urine culture, there were 41 (41%) patients had positive urine culture with *P. mirabilis*, which is a high percentage and cannot be ignored.

Senior *et al*, done one study on 76 patients who had RA. Those patients had history of having high antibody levels in their serum, explicit to *P.mirabilis*. Infection of *P.mirabilis* bacteriuria in patients of RA was observed in 52% cases⁶.

RA is still one of the chronic inflammatory disease with unidentified etiologies. The associated risk factors are: tyrosine phosphatase gene, HLA-DR genes, genes of cytokine coding, peptidylarginine deiminase gene¹⁶. There are several types of herbal treatments which can be used in local Australian traditional medicinal systems to manage RA and inflammation¹⁷.

RA is a systemic and arthritic autoimmune disease affecting millions of people throughout the world. During the last 4 decades extensive data indicate that subclinical urinary tract infection by *P.mirabilis* has a role in the aetiopathogenesis of RA based on cross-reactivity or molecular mimicry between Proteus haemolysin and RA-associated HLA-DRB1 alleles as well as between Proteus urease and type XI collagen¹⁸. In another study, conducted by Cock *et al* found that with herbal preparations are applied in customary African medicines to manage RA and inflammation, 85.3% extracts avert the growth of *P.mirabilis* and 67.7% of them tested rectified the growth of *P.vulgaris*¹⁹.

Raised levels of antibodies against *P.mirabilis* have been discovered in patients with RA in many inhabitants of fourteen countries²⁰. Moreover, in patients with rheumatoid arthritis, there were significant raised concentration of antibodies to *P.mirabilis* but not against >20 other microbes, including *E. coli*²¹. These antibodies will attach to the joint tissue and will be cytopathic to the joint tissues, which transport the proteus

cross-reactive antigens and this immune system in reaction will release the more self-tissue antigens with following secretion of further auto-antibodies, proliferation of pathological progression and development of classical rheumatoid arthritis, like *Streptococcus* causes rheumatic fever & valvular complications in cardiac muscles^{22,23}.

Raised concentrations of anti-bodies to the *P.mirabilis* have been identified in the patients having RA in different populations from fourteen different countries including United Kingdom, United states of America, England & Netherlands²⁰. The specificity of the proteus anti-bodies in the patients of RA has been reported in several studies. Deighton *et al*, observed that anti-bodies against *P.mirabilis*, other than the pathogens involved in urinary sample were significantly high in RA patients²⁴. Furthermore, in one review analysis, it has been reported that in patients of rheumatoid arthritis, there were significant high concentrations of anti-bodies against *P.mirabilis*, but those were not against >20 other entero-bacterial or uro-pathogenic microorganisms, like *E. coli*²¹.

As a consequence of molecular mimicry or resemblance in proteus and self-antigens, patients having infection due to proteus species would yield not only the antibodies against this microorganism, but also contrary to the self-tissue molecules transporting the cross-reactive antigens¹¹. These antibodies would bind to and be cytopathic to the tissue of the joint which transport the proteus cross-reactive antigens. Also, this protected response may lead to the secretion of more self-tissue antigens with the consequential production of further auto-antibodies, proliferation of the pathological procedure and the growth of the classical RA. Similarly, *Streptococcus* causing the rheumatic fever and valvular lesions inside the cardiac muscles^{22,23}.

Urinary tract infection is deliberated to be the most common type of infection in human beings and disturbing either; upper kidney or bladder in many ways. RA is most possibly initiated or caused infection in upper urinary tract cause of bacteria known as proteus bacteria²⁰.

In another study, Chandrashekar *et al*, it was observed that whether medical therapy can raise the concentration of anti-Proteus antibodies in patients who had rheumatoid arthritis. The blood samples of 32 patients who had RA were obtained after one year, who were recruited in one of the previous studies and were continued to contribute in the follow-up study. All the patients were prescribed to take methotrexate

along with hydroxychloroquine with sufficient dose of non-steroidal anti-inflammatory drug. After one year, 11 cases were in clinical lessening, while remaining 21 patients were still in state of vigorous disease. Anti-proteus anti-bodies titres were considerably high in cases of RA after one year of continuous treatment. However, this rise was not significantly different in patients who had clinical remission and those who were in state of vigorous disease²⁵.

CONCLUSION

The high frequency of *P.mirabilis* infection has been detected in this study and the frequency was of females with complaint of urinary tract infection was high. So there is a need to screen the RA patients of urinary tract infection regularly and suggest them some preventive measures to avoid urinary tract infection in order to avoid *P.mirabilis* infection.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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