

Evaluation of Auto-antibody Profiles in Patients with Tuberculosis

Mohammad Hadi Faris (D.R-M.R)¹, Ahmed Methab Athab (FICMS)²
and Rokan M Fadhil (H D RM)³

Abstract

Background: Tuberculosis remains a major public health problem internationally, causing 9.6 million new cases and 1.5 million deaths worldwide, Tuberculosis (TB) has become one of the most important diseases in the past two decades. It leads to organ dysfunction, mortality and various clinical manifestations. Previous studies have shown that sera from patients with active TB may contain autoantibodies that are unique in autoimmune diseases.

Objective: To detect the prevalence of wide array of autoantibodies in sera of patients with tuberculosis compared with healthy control subject.

Patients and Methods: A consecutive patients with recently diagnosed pulmonary and extra pulmonary {axial & peripheral joints TB}, mean age 36.2 years . 41 males and 21 females . the autoantibodies are R.F IgM, ANA , anti ds DNA. P-ANCA , ACL, ENA,SSA, SSB . RNP SM SCL70}.

Results: Mean duration of symptoms 15.69 & 15.70(SD) months . 82% had fever , 39.3% had cough and hemoptysis . 27% had arthralgia and myalgia , 31.1% are diabetic and 24% are smoker serum level above the upper normal limits were found in 25.7% of patients with RF ,ANA was 8.8% , 20% , 6.3% in pulmonary , peripheral , axial TB respectively , P-ANCA 10% , 6.3% & for anti DNA was 5% , 10% , 6.3% for pulmonary , peripheral & axial :ACL was 33.3 , 12.5 pulmonary , axial TB,ENA was {SCL70 3.2% , SM 3.2% , RNP3.2%, SSA 8.1% SSB 6.5% }.

Conclusion: R F: Rheumatoid Factor--Anti ds DNA: Anti-deoxyribonucleic acid (double strand).-ACL: Anti cardiolipin Antibody.-ANCA: Anti neutrophil cytoplasmic Antibody.-ANA: Anti nuclear Antibody.-ENA: Extractable Nuclear Antigen. S: Significant. N-S: Not Significant.Pul: Pulmonary.TB: Tuberculosis .AFB:Acidfastbacilli.

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Corresponding Author: athab69@yahoo.com

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^{1,3}Baquba Teaching Hospital - Diyala -Iraq.

² College of Medicine- Diyala University - Diyala -Iraq.

Introduction

Mycobacterium tuberculosis (M TB) is the cause of pulmonary TB and the clinical manifestation of infection can be either acute or latent and a symptomatic, depending on the immune response set up by the infected patient after being exposed [1]. Since one third of the world's population carries M. TB

in its latent form, and that 5% develop active disease during the first years of infection, its estimated that [8] million new cases of TB and three million deaths occur each year [2]. furthermore the risk of reactivation increases as a consequence of associated pathology, Immunosuppressive therapy, malnutrition

and co-infection with human immunodeficiency virus (HIV) – [3]. The standard diagnosis is still made by clinical examination, direct sputum microscopy and by bacterial culture. The heterogeneous immune response observed, together with the absence of reactivity to single antigen or to specific group of antigens, suggest the existence of variations among individuals as well as an influence of disease stage[4]. Secretory proteins of M TB are found to be the major targets of immune recognition [5], and the humeral response against antigen of 6- 16 KDa associated reactivity to these antigens is mainly present in individual with active disease [6]. Also it's found that antibodies to 88KDa,amalate synthase (GICB) and (MPT5 1) were present in serum obtained during incipient sub clinical TB. [7]. In other study observed that the antigens of M TB from 6 to 45KDa was found to be immunologically important in patients with TB[6].

The articular manifestations of TB include TB arthritis and TB spine.

Tuberculous Arthritis

TB arthritis is caused by infection of a joint with tubercle bacilli human or rarely bovine type. No joint is immune, but the joints most often affected are the large joints such as hip and knee, the formation of "cold" abscess is a common feature, children and young adults are most commonly affected [8].

Tuberculosis of the spine

Spinal TB has been known since antiquity, Elliot smith described a typical case of TB of

the spine with severe curvature and loin abscess dating from around 3700 BC.

Dalechamps (1510) was the first to have described the classical paraplegia and kyphotic deformity.

Sir percival pott (1 779), whose name is still associated with paraplegia due to TB of the spine.

Delpech (1828) and Rokitansky (1842) established that TB bacilli caused spinal caries. The lower thoracic and upper lumbar spine is the commonest involved site. About a fifth of newly diagnosed cases of TB are extra pulmonary, and the spine is involved in 50% of cases of bone and joint TB. The M.R.C trials from India and Korea reported 38% involvement of adults over 40 years and most of reports suggest an incidence of 30-40% of children of both sexes being involved. Radiographs remain inconclusive in 3% of cases; computerized tomography revolutionized the diagnostic results of TB of the abscesses[9].

Autoimmunity And TB

Autoimmune diseases are defined as pathologic squeal of immune response, It must be noted that presence of natural auto antibody is normal feature in sera of healthy individuals and their presence may only be circumstantial or transitory, such natural auto antibodies are usually present at low titer and have poor affinity for their corresponding antigen and usually belong to IgM class [10] the idea that infectious agents may represent one of major environmental factors initiating autoimmune responses is now generally accepted [1 1,12].

Links between autoimmune diseases and infection have been described in several studies, as in cases of myocarditis following Coxsackie's virus and trypanosomal infections [13,14], Rheumatic fever in relation to streptococci [15]. Ankylosing spondylitis and klebsiella [16]. Reactive arthropathy and Epstein Barr viruses [17, 18], and recently heart disease and chlamydia [19]. Patient with TB were important to be studied because of earlier reports have established between M. TB and autoimmunity for example auto antibodies such as ANA IgM RF have been detected in chronic pulmonary TB [20]. BCG immunization has been shown to induce autoantibody production [21]. Clones of T lymphocytes derived from rats with an adjuvant arthritis induced by injections of M. TB in oil may be arthritogenic[22].

Recently a human monoclonal anti-DNA antibody was found to bind three glycolipids derived from M. TB and a mouse monoclonal antibody to M. TB was found to bind to DNA and synthetic polynucleotides and to share a common idiotype (16/6) with human monoclonal anti-DNA antibodies [23]. The range of autoantibodies induced in response to common infections and their significance needs further studies to establish the real relationship between them.

Autoantibodies

Rheumatoid Factor (RF)

RF is a heterogeneous group of high molecular weight IgM molecules directed against the antigenic sites on the FC portion of the body own immunoglobulins [24].

Antinuclear Antibody

An unusual antibody that is directed against structures within the nucleus of the cell. ANAs are found in patients whose immune system is predisposed to react against their own body tissues and result in production of antibodies [25].

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

ANCA are autoantibodies directed against antigens found in cytoplasmic granules of neutrophils and monocytes. There is multitude of antigens recognized by ANCAs. Although only two (i.e. proteinase 3 {PR3} and myeloperoxidase {MPO}) have proven to be of clinical significance [26].

Anticardiolipin (ACL) Antibodies

An antibody directed against cardiolipin. ACL antibodies are one of the antiphospholipid groups of antibodies that associated with antiphospholipid syndrome; they are strongly associated with venous and arterial thrombosis [27].

To detect the prevalence of a wide array of autoantibodies in sera of patients with different groups of TB (pulmonary ,axial & peripheral TB) compared with healthy control. The autoantibodies are {anticardiolipin, Anti-Neutrophil cytoplasmic Antibody (ANCA)& Anti-dsDNA, Extractable nuclear antigen (ENA), Rheumatoid factor, Anti nuclear antibody (ANA).

Patients and Methods

A prospective study was conducted in diyala province in the period between 2015-2017 on the following groups.

1-patient study group :this group includes sixty one [61] patients affected by TB[pulmonary ,axial ,peripheral joints, forty one[41] are males and [21] are females all patients are subjected to questionnaire.

2- healthy control group :this includes [20] healthy persons [10] males and [10] are females.

From each individual 10 ml of blood was harvested centrifuged and serum divided into aliquots and stored at [-20],for further processing all sera was thawed once . KIT & CHEMICALS 1.Kit of enzyme immunoassay for the quantitative [IgA 'IgM' IgG] anticardiolipin determination of Kit of enzyme immunoassay for quantitative of ANA antibodies.

3- Kit of enzyme immunoassay for quantitative determination of IgM, IgA autoantibodies to double stranded DNA.

4- Kit of enzyme immunoassay for quantitative determination of MPO auto antibodies.

5- Kit of latex agglutination slide test for quantitative determination of IgM RF

Enzyme —linked immune sorbent assay for the quantitative determination of ACL.(IgG , IgM ,igA) inhuman serum .

In a normal range study with serum samples from healthy blood donors, the following ranges have been established with ACL tests ACL screen {u/ml} Cut off=10.

The results were interpreted as follows, patients samples with optical density value greater than or equal to cut off value was considered positive for aCL, where as optical density values less than this cut off was considered negative for ACL.

ANA Antibodies

ANA screen by enzyme-linked immunosorbent assay (ELISA). It is designed for the qualitative screenings on IgG class auto antibodies directed against SS-A (Ro), SS-B (La), sm, RNP-70Kd, RNP/Sm, Sci-70, centromere-b, jo- I.

Interpretation of Results

ANA screen

Index value

Negative	< 1.0
Positive	1.0- 1.2
Strong positive	>or=1.2

Index value =OD sample/OD cut off
Enzyme-linked immuno sorbent assay for the quantitative determination of IgG, IgM, IgA, Autoantibodies to (Is DNA in human serum: Patient results may be classified interims of negative, positive or strong positive.

Alternatively the concentrations of the control may be used to calculate a calibration

curve for semi-quantitative results. The following ranges have been established with Anti cls DNA {IU/ML} Cut off=25.

Enzyme-linked immuno sorbent assay for the quantitative determination of MPO Auto antibodies in human serum.

Anti-MPO is a indirect solid phases enzyme-linked immuno sorbent

assay ELISA), it is designed for the quantitative measurement of IgG class auto antibodies directed against myeloperoxidase (MPO).

Interpretation of results

In a normal range study with serum samples from healthy blood donors, the following ranges have been established with the Anti-MPO A.b. [U/MLI]

Normal < 5

Elevated > 5

Latex test

Clearly visible aggregates of latex particles with a clear background indicates RF concentration Above 8.0 iu/ml.

Fine aggregates indicate a RF concentration close to 8.0 iu/ml. A smooth homogenous milky suspension indicates a RF concentration below 8.0 iu/ml.

Reagent Composition

1- Latex reagent

An aqueous suspension of latex particles coated with human gamma globulin.

2- Diluent

Glycine buffered saline pH 8.2.

3- Positive Control

A stabilized liquid containing RF at concentration greater than 8.0 iu/ml.

4- Negative control

A stabilized liquid containing RF at a concentration less than 8.0 iu/ml.

Statistical Analysis

Statistical analysis was done using simple data arrangement with number, percentage & standard deviation, association between variables measured by chi-square & fisher's

test. p value less than 0.05 considered as significant

Results

Sixty one [61] patients from them [41] [67.1%] males and 20 [32.8] females with mean age of [36.21] years, range of [18-76] years twenty healthy control group 10 [50%] males and 10 [50%] females with a mean age of [36.8] years with range of [26-60] years.

The study shows in table 1 & table-A the TB is more prevalent in the age group of [18-35] years of them 18 (29.5%) with pulmonary TB & 11 patient (18.3%) with extra pulmonary TB.

Male gender [22] compared to [9] female patients in the same age group. There is no statistically significant difference [p value = 0.8] between all age groups in pulmonary and extra pulmonary.

The duration of the disease ranged between one month — sixty months with a mean duration of symptoms [15.961] months.

Table (2) shows symptomatic presentation of patients with TB, 35 patients [57.3%] diagnosed as pulmonary TB, 26 patients [42.6%] proved to have extra pulmonary TB patients [82%] had fever and sweating [42] patients [70%] had loss of appetite and malaise 39 patients [65%] had loss of weight, 24 patients [39.3%] had cough, 19 patients [31.1%] are diabetic, 17 patients [27.9%] had arthralgia and myalgia and 17 patients [27.9%] had contact with TB patients.

16 patients [26.7%] had hemoptysis with sputum.

15 patients [24.6%] are smokers.

Radiological Parameters & Laboratory

[13.1 0/0] had positive culture for AFB. 10 patient 16.4% had positive pleural fluid culture ESR ranged between 40-100mm/hr PT and PTT tests are within normal range in comparison with control .

Table (3) shows chest X-ray manifestation. Chest X-ray findings was:

16 patients [26.2%] present with infiltrations and hilar lymph adenopathy.

12 patients [19.7%] present with apical density.

7 patients [11.5%] present with pneumonitis.

4 patients [6.6%] present with cavitations.

2 patients [3.3%] present with miliary TB.

MRI was suggestive in 22 patients [36.1%].

Lupus anticoagulant was not available, also the test for anti-jo-1, antiHiston and c-ANCA.

Table (1): Shows age and gender comparison between pulmonary and extra pulmonary TB groups).

Age	M	F	Pulm TB N	%	Extra Pulm TB N	%	Healthy cont. N	%
18-35	22	9	18	29.5	11	18.3	6	30
36-45	3	4	3	4.5	4	6.6	4	20
46-55	8	5	7	11.5	6	9.8	7	35
56-65	4	2	4	6.6	4	6.5	3	15
66-75	3	0	2	3.3	1	1.6	0	0
76-85	1	0	1	1.6	0	0	0	0
Total	41	20	35	100	26	100	20	100

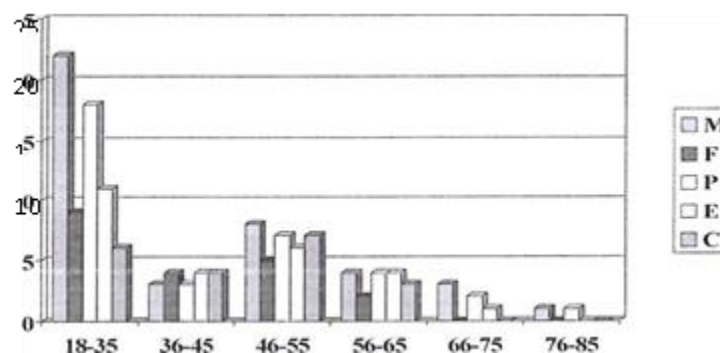


Figure (1): Figure 1- Shows age and gender comparison between pulmonary and extra pulmonary TB groups.

Table (2): Show seroprevalence of anti cardiolipin anti bodies [ACL] total (IgG, IgM, IgA).

SITE	NO.	%
Pulm	11	33.3
Periph	0	0
Axial	2	12.5
P-value	0.047	S

Shows there was statistically significant differences between each group separately

Table (3): Seroprevalence of P-ANCA anti bodies among different groups.

SITE	No.	%
PULM	0	0
PERIPH	1	10
AXIAL	1	6.3
P value	0.27	NS

There were no statistically significant differences between each group.

Table (4): Seroprevalence of rheumatoid factor (IgM).

SITE	No.	%
PULM	9	25.7
PERIPH	0	0
AXIAL	0	0
P value	0.018	S

While in healthy control only one is positive

Table (5): Seroprevalence of ANA antibodies among the different group.

SITE	No.	%
PULM	3	8.8
PERIPH	2	20
AXIAL	1	6.3
P value	0.43	NS

shows, no statistically significant differences.

Table (6): Seroprevalence of anti-DNA antibodies among different groups.

SITE	No.	%
PULM	2	5
PERIPH	1	10
AXIAL	1	6.3
P value	0.89	NS

also Show no statistically significant differences.

Table (7): Seroprevalence of extractable nuclear antigen (ENA).

Antibody	Pulm N	%	Axial N	%	Periph N	%	P value
SSA	1	2.9	3	18.8	1	10	0.145 NS
SSB	4	11.4	0	0	0	0	0.205 NS
SM	2	5.7	0	0	0	0	0.46 NS
RNP	2	5.7	0	0	2	20	0.128 NS
SCL-70	2	5.7	0	0	0	0	0.46 NS

Antibodies among different groups show no statistically significant differences.

Discussion

RF IgM

A total of [68.8%] of the [61] patients with TB (pulmonary & extra pulmonary) had demonstrable antibodies of them [9] patients [25.7%] had RF IgM isotype of more than 8.0 IU /ml in our study table (6), exclusively in pulmonary group which correlate with other studies which state:

RF was prevalent in [13%] of TB patients [28].

RF was prevalent in [20%] of TB patients [16].

RF was prevalent in [62%] of TB patients [29], and was [46.5 0 0] and [40%] in other studies [31,21] respectively.

RF test showed statistically significant differences in relation to patient's age group and site of TB. (Pulmonary & extra pulmonary). (P value 0.018).

RF is prevalent in one patient (5%) of control healthy group table [7].

ACL is detected in a total of 13 patients [2 1 .3%], 1 I (33.3%) with pulmonary TB and 2, (12.5% with axial TB) in our study table (4), which correlate with the other study in which ACL was prevalent in [30.3%] of TB patients [31]. And in other studies was [59% IgG, 46 0 0 IGM isotype][29] and (53% IgM) in patients living in tropical areas [32].

ACL test showed statistically significant difference in relation to patient age group and site of TB (pulmonary and extra pulmonary TB). (PV 0047) ACL is not detected in healthy control group.

ANA were detected in a total of 6 (9.8 0/0). patients {38.8% with pulmonary TB,

2[20%] peripheral TB and one [6.3%] with axial T B in our study table 8), which relatively correlate with other studies finding, which state ANA was prevalent in [20%] and [14%] [42 %] of TB patients [29,31,16].respectively . The low level of serum ANA in our study could be explained by it's high level in pleural fluid (titer of 1 : 1280) for ANA IgG in other study finding [33].

ANA dose not showed statistically significant difference (P value 0.43) in comparison with groups of TB, ANA is not detected in healthy control group.

Anti- ds DNA were detected in a total of 4(6.5 0 0) patients [2]. [5%] with pulmonary TB and one [10%] peripheral, and one [6.3%] axial TB in our study table (9). Which is in between with other two studies that state: Anti -ds DNA was prevalent in [32%] of TB [29], and it's not increased above normal serum level [31]. Anti-ds DNA dose not showed statistically significant difference (P value 0.89) in comparison with groups of T B. Anti-ds DNA is not detected in healthy control group.

ENA were detected in a total of 17[27.8%] patients in our study table (10).

SS A is prevalent in axial TB (3, 18.8%).

SS B is prevalent in pulmonary TB [4, 1 1.4%]. RNP is prevalent in peripheral TB (2, 20%).

The study is relatively correlate with other studies, which state that SSA is found in 64 0/0 of TB [29]; also RNP is detected in 15% and 4% of TB patients (29. 16 respectively).

SM was detected in 38%; in our study it is 5.7%. In our ENA'S studies P values dose not showed statistically significant difference in TB groups. ENA is not detected in healthy control group. and could be explained by the small number of our patient sample.

P -ANCA were detected in 2[3.7%] patients, one peripheral [10%] and other one is axial (6.3%) in our study. No data available confirm prevalence of ANCA in TB.

P-ANCA dose not showed statistically significant difference (Pvalue 0.27) in groups of TB.

P-ANCA is not detected in healthy control group. The low level of detectable anti bodies possibly due to removal of the anti bodies from circulation by immune complex formation as confirmed by it's elevated levels in sputum (AFB+++) positive [34].

Conclusion

These results taken overall point to several conclusions: Serum level. RF, ACL could be considered significant among different groups of TB. Almost all other antibodies in our study are elevated above their normal Some autoantibodies are easily induced. The presence of some autoantibodies is insufficient to induce autoimmune disease. More specific antibodies might be produced by molecular mimicry or idiotypic cross-reactions.

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