World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

UNDERSTANDING HUMAN AUTOIMMUNE DISEASES AND IT'S SEROLOGY TESTS USING ELISA TECHNIQUE: A REVIEW

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Article Received on 21/12/2022 **Article Revised on 11/01/2023** **Article Accepted on 01/02/2023**

ABSTRACT

The human immune system defend the body against infectious and certain other diseases, it's made up of different organs, cells, chemicals and proteins which are known as antibodies. It fights against the foreign substances, sometimes our immune system unidentify the foreign materials and attacks the own body tissues and organs. This process is called as autoimmunity. Autoimmunity is the most common factor for autoimmune diseases. Nowadays researchers have found various techniques to test autoimmune diseases. ELISA is a one of the fabulous and excellent technique for immunology, it's an easy way to find out the antigen- antibody interaction and easily interpret the results. The aim of this review is to focus Rheumatoid arthritis, Systemic lupus erythematosus (SLE), Celiac disease (CD), antiphospholipid antibody syndrome (APS) autoimmune diseases and diagnosis using ELISA technique.

KEYWORDS: Autoimmune, antigen, antibody, antiphospholipid antibody syndrome, Rheumatoid arthritis, Celiac disease.

INTRODUCTION

The word 'immunity' usually refers to the resistance exhibited by host toward injury caused by microorganisms and their products. There are different types of innate (native) or acquired (adaptive) immunity is obtained. Immunity is extremely broad scientific discipline involving concept mechanisms are involved in the protection of the body against infectious agent but they can also hurt host organism called as autoimmunity.[1] A general aspect of all autoimmune diseases is the presence of autoantibodies and inflammation, including mononuclear phagocytes, plasma cells (autoantibody producing B cells) and autoreactive T lymphocytes. Autoimmune diseases should be classified as organ-specific or non organ-specific depending on whether the autoimmune response is directed against a particular tissue.[2] Although the role autoantibodies play in the aetiology of autoimmune disease is unclear, their detection is considered important in the diagnosis of most AID.' Different techniques are used to detect these antibodies. The most techniques are rely on immunofluorescence; sometimes Ouchterlony immunodiffusion also used. These techniques compulsory needed considerable knowledge and experience to interpret the results. Therefore, these techniques are being replaced more and more by ELISA (Enzyme-linked immunosorbent assay). The ELISA technique is trouble-free to perform and can be automated. Moreover, its results can be quantified and its interpretation is thus simple and straightforward[3] ELISA (enzyme-linked immunosorbent assays) technique was first described by Engvall and Perlmann at 1971[4] ELISA is a fundamental immunology concept of an antigen binding to its specific antibody, which should be used to identify very miniature quantities of antigens such as peptides, hormones, proteins, or antibody in a fluid sample.[5] Alkaline phosphatase and glucose oxidase enzymes are most commonly used. The antigen in fluid phase is immobilized, generally in 96-well microtiter plates. The antigen is allowed to bind to a particular antibody, which is itself later on detected by a secondary, enzyme-coupled antibody. A chromogenic substrate for the enzyme yields a visible color change or fluorescence, signify the being there of antigen. Quantitative or qualitative measures can be assessed based on such colorimetric evaluation. Fluorogenic substrates have higher sensitivity and can perfectly measure levels of antigen concentrations in the sample.[6] In the present review was focused to some important autoimmune diseases and their estimation using enzyme-linked immunosorbent assays.

Autoimmune Diseases

Autoimmunity is the mechanism where an organism fails to recognize its own self constituent parts, which results in an immune response against its own cells and tissues.[7] Any disease that results caught from such an aberrant immune response is called an autoimmune disease. Autoimmunity is categorized by the reaction of cells (auto reactive T-lymphocytes) or products (autoantibodies) of the immune system against the organism's own antigens (autoantigen). It may be part of the physiological immune response (natural autoimmunity) or pathologically induced, which may finally lead to growth of clinical abnormalities (autoimmune disease).[1] The autoimmune diseases appear to be either *organ-specific* (e.g. Type 1 diabetes mellitus) or *systemic* (e.g. systemic lupus erythematosus). This classification, although clinically helpful, does not necessarily correspond to a difference in causation.[8] A more useful division distinguishes between diseases in which there is a common alteration in the selection, regulation or death of T cells or B cells and those in which an aberrant response to a specific antigen, foreign or self, causes autoimmunity. An example of a common defect is the absence of the Fas protein or its receptor- proteins involved in cell death- and a representative antigen specific disorder is the demyelination syndrome that follows enteric infection *Campylobacterjejuni*.[9] Autoimmune disorders are a group of conditions in which functional or structural damage to cells/tissues/organs/organ systems is produced by the correlation of immunologically competent cells or antibodies against the usual component of the body. This occurs as a outcome of interaction between several genetic, environmental and endocrine factors on our immune system by the following mechanisms:- 1. Discharge of tissue exact auto antibodies via the initiation of complements lead to cytolysis of the target cells; 2. Auto antibody binding to soluble mediators causing in immune complex deposition; 3.Auto antibody mediated attack on the normal immune system causing in phagocytosis, cytotoxicity & antibody mediated cellular immunity; 4. Auto antibody focused against foreign antigen and epitopes of auto antigen that mimic the foreign antigen (cross reactive antigen) resulting in hurt of the tissue –*"Molecular mimicry*" and 5. Action of auto antibodies on cell surface structures resulting in either stimulation/ obstruction of the target structure.[10]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease mostly characterized by synovitis. It usually affects women in their age 30 to 50, with an incidence out of 1 in 150. It is accompanied by multi-organ disorders, in addition to swelling, pain and stiffness of multiple joints. Thus, correct diagnosis and treatment are required in the early stages of the disease.[11] Rheumatoid arthritis is associated with several auto antibodies i.e. anti-cyclic citrul-linated peptide antibodies (CCP), rheumatoid factor (RF), anti-perinuclear factor (APF), ANCA, anti-flaggerin anti-bodies, anti-keratin antibodies (AKA), etc.[12]

Clinical Diagnosis

Regular viral screening by serologic testing does not significantly facilitate the analysis of rheumatoid arthritis in patients with early RA, nor is it useful as a potential identifier of disease progression. The laboratory studies in suspected RA fall into 3 categories markers of inflammation, hematologic parameters, and immunologic parameters. Erythrocyte sedimentation rate (ESR), Complete blood count (CBC), C-reactive protein (CRP) level, Rheumatoid factor (RF) assay, Antinuclear antibody (ANA) assay Anti−cyclic citrullinated peptide (anti-CCP), anti−mutated citrullinated vimentin (anti-MCV) assays and Anti filaggrin antibodies (AFA) Micro RNA (miRNA).[13]

Anti-CCP test

In June, 2010 the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) revised the 1987 ACR classification criteria for rheumatoid arthritis and introduced anti-CCP antibody estimation in an effort to progress early diagnosis of RA [14]. Anti-CCP antibody has been establish in sera up to 10 years before the onset of joint symptoms in patients who later develop RA and may appear somewhat earlier than rheumatoid factor. From 10% to 15% of RA patients remain seronegative for rheumatoid factor throughout the disease course. Rheumatoid factor, first described in 1940, is an antibody against the Fc portion of immunoglobulin G. The cutoff value for positivity varies by laboratory but is generally greater than 45 IU/mL by enzyme-linked immunosorbent assay or laser nephelometry, or greater than 1:80 by latex fixation [15]. Various studies have shown between 41–80% sensitivity and an 89–99% specificity of anti-CCP for RA diagnosis. In some studies, anti-CCP predicts a less favourable course and a greater radiological progression in patients with RA. Other studies have shown that anti-CCP is found earlier in the course of RA than RF and is, thus, a better marker of early RA.[11]

Treatment strategy for rheumatoid arthritis

There is no specific treatment for RA, but the treatment can improve symptoms and slow the movement of the disease. Disease-modifying anti-rheumatic drugs considered the mainstay of RA therapy. While DMARDs are started early, they give suitable results in many cases. The goals of treatment are to decrease incidence of symptoms such as pain and swelling, to avoid bone deformation and to maintain day-to-day activities.[16]

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a severe autoimmune disease that produces different antibodies and involves several organs. Among patients with SLE, 60% develop lupus nephritis (LN), which is also a fundamental reason for the increased mortality of SLE.[17] The disease predominantly affects women of

childbearing age, with a female to male ratio of 9 to 1.[18] Systemic lupus erythematosus is a disease that affects multiple systems and its symptoms differ widely. The various organ damage in SLE is due to the production of auto-antibodies against different organ systems including the brain, renal and vascular tissues, ribosomes, nuclear antigens and phospholipids. Intracranial vascular lesions (vasculitis and thrombosis) and inflammation have been related to the local release of cytokines.[19]

Clinical Diagnosis

The diagnosis is based on classification criteria established by the American College of Rheumatology (ACR). A minimum of 4 of the 11 ACR criteria should be met in order to qualify as SLE for clinical trials.[20] ANA's are included in the diagnostic criteria and are seen in more than 95% of SLE patients.[21] Other antibodies have been identified that are recognized based on their targeted autoantigens and are collectively known as anti-extractable nuclear antigens (ENA). Anti-double stranded DNA antibody (anti-dsDNA) is highly specific (95% specific) for SLE, especially with renal disease. Anti-Sm antibodies (antibodies against Sm core particles) are unique and highly specific for SLE with renal disease, although seen in only about 20-30% of SLE patients overall. Other antibodies may be seen in SLE, but are not specific for the disease and can be seen in other autoimmune conditions.[22]

ANA test

Anti-nuclear antibody (ANA) is a general name for the antibodies against the contents of the cell nucleus. The detection of ANA is used as screening test for the diagnosis of autoimmune diseases especially for rheumatologic disorders. Around 25% of the community has ANA positivity but the prevalence of significantly elevated levels is about 2.5% which indicates an autoimmune disease [23]. Nowadays, estimation of ANA has been widely used to provide supporting proof of a diagnosis of autoimmune disease such as systemic lupus erythematosus (SLE).[24] SLE is a multisystem disorder that is considered as a prototype immune complex (IC)-mediated disease. This autoimmune disease related to central or peripheral nervous system; about 17% to 75% of patients respectively.[25] In 1941, Klemperer, Pollack and Baehr first described systemic lupus erythromatosis (SLE) as one of the CTD.[26] Observations of the "LE cell" by Hargraves et al in 1948 led to the first laboratory test for ANA. This was an important discovery, as it provided the clinicians with a test that could be used to support the diagnosis of SLE. These include antibodies against single and double stranded DNA (dsDNA) discovered way back in 1957. The anti-dsDNA antibodies are considered to be confirmatory in diagnosis of SLE.[27] The prevalence of positive ANA tests in various autoimmune rheumatic diseases varies greatly, e.g., 90-100% in systemic lupus erythematosus (SLE), 60-80% in systemic sclerosis (SSc), 40-70% in Sjogren's syndrome, 30-80% in polymyositis/dermatomyositis, and 30-50% in rheumatoid arthritis (RA) and the prevalence of autoantibodies has been shown to differ between different races.[28]

Anti-dsDNA assays

A number of factors may contribute to discrepant anti dsDNA antibody detection abilities of laboratory assays. First, variation exists in the types of anti-dsDNA antibodies that may be detected. Anti-dsDNA antibodies may differ according to properties that influence their pathogenicity, including isotype (IgG, IgM), charge, complement-fixing ability, and avidity.[29] Anti-dsDNA antibodies are generally detected and quantified by commercially available kits for enzyme-linked immunosorbant assay (ELISA, also automated versions), *Crithidia luciliae* immunofluorescence assay (CLIFT), and radioimmunoassay methods developed according to Farr technique (FARR-RIA).[30] The cut off values was determined through a constantly running internal quality assessment programme. Lot to lot variation of analytical ELISA based kits, relevant to determination of cut off values, were examined and adjusted when essential by internal and external reference antibodies. Through our participation in national and international quality assessment programmes, our selected cuts off values were similar to those of other laboratories participating in these quality programmes. A result was regarded positive at >55 units for both the anti-ssDNA and anti-dsDNA ELISAs.[31]

Treatment strategy

Systemic lupus erythematosus (SLE) represents a challenge for the treating physician in terms of diagnosis and treatment. Immunosuppressive therapy (for induction and maintenance of remission) is indicating in organ-threatening lupus. Hydroxychloroquine, Glucocorticoids, and Immunosuppressive (IS) drugs are recommended for SLE.[32]

Celiac Disease

Approximately 1% of the worldwide population affecting Celiac disease (CD), it is an immune-mediated enteropathy. The gold standard for the diagnosis of Celiac disease has been measured to be a small intestinal biopsy since the histological lesions of CD were discovered in 1954 [33]. In clinical practice, serological tests for CD are helpful in identifying patients who require intestinal biopsy. Although anti-reticulin antibodies have historically has been used in the estimation of CD.[34] Tissue transglutaminase was newly identified as the autoantigen recognized by EMA, and a number of enzyme-linked immunosorbent assay (ELISA) commercial kits were developed to find out the serum anti-tTG antibodies. Anti- tTG antibodies were found to have 90±100% sensitivity and 94± 100% specificity for celiac disease, and an excellent correlation with EMA.[35] Celiac disease has a diverse clinical picture ranging from tangible symptoms such as malabsorption, diarrhea, weight loss, iron and folic acid deficiency, arthralgia, fatigue, and abdominal discomfort. Serological tests are key instruments for detection of celiac disease.[36]

Diagnosis

Several serologic tests have been introduced and validated against biopsy specimens for the diagnosis of celiac disease. The availability of non-invasive serological tests has dramatically changed the diagnosis of celiac disease. Over the past few decades, Immunoglobulin (Ig) G and IgA gliadin antibody tests have been replaced by more sensitive and specific IgA endomysial antibodies (EMA) and IgA anti-tissue transglutaminase test (IgA anti-tTG).[37] Presently, most celiac serology test is performed with commercial ELISA kits in worldwide. Starting with anti-gliadin (AGA) testing, which antibodies are produced in response to gliadin, a prolamin found in wheat, then passing by anti-tissue transglutaminase (anti-tTG) and anti-endomysium (EMA) determination, up to anti-deamidated gliadin peptides (anti-DGP) antibodies.[38]

Anti-tissue transglutaminase (anti-tTG IgA)

The research on anti-tTG IgA is very sensitive to celiac disease diagnosis and for the follow up of CD patients under gluten free diet.[39] Anti-tissue transglutaminase (tTG) antibodies are the most effective strategy for serologic diagnosing of CD patients' serum by enzyme-linked immunosorbent assays. These antibodies show sensitivity higher than 97%, specificity around 96%, and an accuracy of 98%, while IgA anti- endomysial (IgA EMA) antibodies are used as a supportive check in tTGA positive cases thanks to their high specificity (approximately 100% vs 91% of tTGA).[40] The upper limit of a normal range of serum TTG-IgA for healthy control group was presumably adapted from the manufacturer's guideline, at the cut-off value of 10.0 U/ml. The lower finding limit for TTG-IgA was 1.0 U/ml. A previous review about diagnostic accuracy of serologic tests using human recombinant TTG-IgA revealed 98.1% of sensitivity and 98.0% of specificity among Caucasian adult population.[41]

Antigliadin antibodies (AGA IgA)

This is one of the oldest marker and it's determined by the ELISA method. Reference values are not constant among laboratories. Its efficacy is challenging to define, for available records in literature are heterogeneous and do not permit comparison. Its specificity is around 90%, and the sensitivity is approximately 85-90%, presenting low positive predictive value. There are other tests with higher diagnostic performance.[39] Recently, testing for antibodies against DGP has become clinically presented. This is based on the change of certain gluten peptides to deamidated peptides by the action of intestinal tTG. These peptides bind with high affinity to human leukocyte antigen DQ2 or DQ8 on celiac patients' antigen-presenting cells to potently stimulate the inflammatory T-cell response detected in the intestinal mucosa of patients with Celiac disease. The outcome is an antibody response to these deamidated gliadin peptides that shows a higher specificity for CD than antibodies to native gluten (AGAs).[42]

Treatment

Potential approaches to drug treatment include: 1. "glutenases" for the degradation of the immunedominant gluten peptides that would otherwise not undergo proteolytic degradation in the intestinal lumen, 2. Drugs to lower intestinal permeability, 3. Gluten vaccination to induce oral tolerance, 4. Inhibit intestinal TG2 with specific TG2 blockers. 5. Blockade of antigen-presenting HLA-DQ2 (-DQ8).[43] The National Institutes of Health (NIH) Consensus Statement on Celiac Disease recommends the following five key elements to celiac disease management: Consultation with a skilled dietitian, Education about the disease, Lifelong adherence to a gluten-free diet, Identification and treatment of nutritional deficiencies, Access to an advocacy group, Continuous long-term follow-up by a multidisciplinary team.[44]

Phospholipid Syndrome

The antiphospholipid antibody syndrome is defined by thrombotic events or obstetric complications and the occurrence of antiphospholipid antibodies (APAs) identified in patient plasma. Presently recognized laboratory criteria for APS include lupus anticoagulant (LA), immunoglobulin (Ig) G or IgM anticardiolipin (aCL) antibodies, or IgG or IgM anti–beta-2 glycoprotein I antibodies (anti-B2GPI). Lupus anticoagulants are identified by clot-based coagulation tests, whereas aCL and anti-B2GPI antibodies are identified by enzyme-linked immunosorbent assay (ELISA).[45] The first aPL, a complement fixing antibody that reacted with extracts from bovine hearts, was find out in patients with syphilis in 1906.

The relevant antigen was later detected as cardiolipin, a mitochondrial phospholipid. This observation became the basis for the Venereal Disease Research Laboratory (VDRL) test for syphilis, which is presently used. It was later established that many patients with SLE had positive test for VDRL without any other evidence for syphilis.[46] In 1983, Harris and co-workers described a radioimmunoassay for the estimation of anticardiolipin antibodies (aCL), and two years later they established the first enzyme-linked immunosorbent assay (ELISA) for the quantitative detection of anticardiolipin antibodies. These progresses led to a renewed interest in aPL, which in turn led to the description, by Hughes and his co-workers in 1986, of the anticardiolipin syndrome. A year later, Harris *et al.* coined the term "antiphospholipid syndrome".[47]

Diagnosis

Laboratory diagnosis of APS requires documentation of aPL which are directed against serum proteins bound to anionic phospholipids. These can be detected by: Lupus anticoagulant tests, Anticardiolipin antibody (ELISA), Anti-β2 glycoprotein-1. As APS can occur in the setting of underlying disease such as systemic lupus erythematosus (SLE), tests to document SLE or allied collagen vascular disorders are equally important.[48]

APL test

ELISA is the excellent technology for aPLs detection. The bond of the aPL antibodies in analysed plasma/serum to the surface of a 96 well microtiter plate coated with a fixed phase is the principle of this sandwich method, when a complex antigen/antibody is formed. Peroxidase conjugate and Human Ig is bound to this complex. Peroxidase enzyme cleaves a exact chromogenic substrate, generating a color change, the intensity of which is examined through photometry by a reader at a wavelength of 450 nm. The aPL results are obtained by reading the measured optic density from the calibration curve and they are commonly indicated in arbitrary units IU/mL or in GPL/MPL units. The cut-off differs for the individual aPLs. Serrano et al. determined a cut-off >20 units in anti-_2GPI IgA using ELISA (99th percentile) by measuring 321 healthy volunteers. The test results of several kits in various laboratories show quite large variability. Due to this reason, the outcomes of aPL tests often do not provide a sufficient advantage for the clinical use; the method needs to be more standardized.[49]

Treatment and Management

Overall, treatment of both primary and secondary APS is same. It includes: Antiplatelet drugs (Aspirin and Clopidogrel), Anticoagulants (Heparin, Warfarin and Hydroxychloroquine). Regarding management, there is consensus that patients of APS with first venous thrombosis should be treated with anticoagulation with a target international normalized ratio (INR) of 2.0 to 3.0. A woman with obstetric manifestations of APS is best treated with aspirin and heparin.[48]

CONCLUSION

In autoimmune diseases, this inflammation becomes chronic, causing pain and permanent changes or damages the specific tissues. There is no exact cause for autoimmune disorders; they show patterns of remission and recurrence and they are challenging to diagnose because the specific disorders have different probable symptoms and individual symptoms varies. ELISA technique play very significant part in immunology, it's a good technique for easily identify the particular substances. So many autoimmune diseases are conformed by ELISA tests. Following days, ELISA related tests are increase and various products also introduce, it's a well-known fact about ELISA technique.

ACKNOWLEDGEMENT

We thank to the host institution Dr.N.G.P. Arts and Science College, Management, Principal, Deans, Head of the Department, Guide, and all other staffs of Department of Biochemistry for rendering all the facilities and support. Communication no: DrNGPASC 2022-23 BS014

Disclosure of Conflict of Interest

The Authors have declared that, no conflict of interest.

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