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DIAGNOSIS OF RHEUMATOID ARTHRITIS USING LABORATORY AND INSTRUMENTAL METHODS

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Abstract:

This article reviews the recent advances in the diagnosis of rheumatoid arthritis (RA) with a focus on immunological methods that enhance diagnostic accuracy and disease activity assessment. The role of various markers, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACCP), in disease detection and prognosis is discussed. The importance of laboratory indicators such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) for evaluating inflammation and disease activity is also highlighted. Furthermore, the role of imaging methods, such as ultrasound and magnetic resonance imaging (MRI), in early diagnosis and treatment monitoring is examined. The article emphasizes the need for further development of diagnostic methods to ensure timely RA diagnosis and effective treatment monitoring.

Keywords: Rheumatoid arthritis, diagnosis, rheumatoid factor, anti-citrullinated protein antibodies, C-reactive protein, erythrocyte sedimentation rate, ultrasound, magnetic resonance imaging, laboratory diagnostics.

INTRODUCTION

In recent years, significant advancements in modern experimental and clinical immunology have enabled more effective diagnosis of rheumatoid arthritis (RA). Immunological tests, including circulating autoantibodies and acute-phase inflammation markers, play a crucial role in disease detection, activity assessment, and treatment monitoring.

Rheumatoid factor (RF) has long been used as a standard immunological marker, but its specificity is relatively low, as it can also be detected in other diseases. Therefore, new markers, such as anti-citrullinated protein antibodies (ACCP), have gained increasing importance in RA diagnosis.

Additionally, laboratory tests such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are valuable tools for evaluating disease activity and treatment efficacy. Advanced imaging techniques, including ultrasound and MRI, are also essential in early diagnosis and monitoring treatment outcomes.

The relevance of this study lies in improving the accuracy of RA diagnostics, ensuring early disease detection, and enhancing treatment effectiveness.

The primary objective of this article is to study precise diagnostic methods for rheumatoid arthritis using modern laboratory and instrumental approaches.

MATERIALS AND METHODS

In conducting this study and preparing this article, we utilized various scientific literature and electronic sources, including research articles, books, journals, reviews, and official documents. The data were obtained from databases such as PubMed, Web of Science, and Google Scholar, as well as from periodicals in the field of neuroimmunology.

To ensure the accuracy and reliability of the information presented in our study, we used modern and verified sources.

DISCUSSION

In recent years, advancements in modern experimental and clinical immunology have enabled the effective laboratory diagnosis of rheumatoid arthritis (RA). These diagnostic methods allow for a precise characterization of immunopathological changes, which is essential for identifying the disease, assessing its activity, predicting its course, selecting treatment strategies, and monitoring therapeutic effectiveness.

Modern RA diagnostics are based on evidence-based medicine principles, optimizing the selection and application of immunological methods. Among the most informative tests are circulating autoantibody detection and acute-phase inflammation markers.

For over 70 years, rheumatoid factor (RF) has been used as a standard immunological marker for RA. While RF is a sensitive indicator, its specificity is limited. RF can also be detected in other rheumatic diseases, chronic infections, lung diseases, malignancies, primary biliary cirrhosis, and in elderly individuals.

RF consists of autoantibodies that react with the Fc fragment of immunoglobulin G (IgG). These autoantibodies are locally produced by B-lymphocytes in synovial membrane follicles and germinal centers. The most common type is IgM-RF, which is found in 60–80% of RA patients.

The diagnostic sensitivity of IgM-RF ranges from 50% to 90%, while its specificity varies between 80% and 93%. The positive predictive value of RF ranges from

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24% to 84%, while the negative predictive value is between 75.2% and 89%.

When interpreting RF results, it is important to consider the presence of seronegative RA variants. Seronegative RA is more common in women and elderly patients compared to men and middle-aged individuals.

IgA-RF and Its Prognostic Value

High levels of IgA-RF are associated with rapid joint erosion, extra-articular manifestations, and poor prognosis. Elevated IgA-RF levels may also predict poor response to TNF-α inhibitors.

IgG-RF and Other RF Subtypes

IgG-RF can be detected in various diseases, but its clinical significance remains uncertain.

The standard methods for detecting RF include:

Latex agglutination test (using IgG-coated particles)

Sheep erythrocyte agglutination test (Waaler-Rose reaction)

Nephelometry

Enzyme-linked immunosorbent assay (ELISA)

Among these, ELISA provides the highest diagnostic sensitivity and specificity, as it simultaneously detects IgM, IgA, and IgG-RF.

RF and Long-Term RA Risk

Recent studies show that individuals with high RF levels have a 26-fold increased long-term risk of developing RA. The absolute risk of RA clinical manifestation within 10 years increases by 32% in these patients.

Anti-Citrullinated Protein Antibodies (ACCP) in RA Diagnosis

In addition to RF, anti-citrullinated protein antibodies (ACCP) play a critical role in RA diagnosis. These include:

Anti-perinuclear factor

Anti-keratin antibodies

Anti-filaggrin antibodies

Anti-citrullinated cyclic peptide (ACCP)

Sa-antigen/citrullinated vimentin antibodies

Anti-citrullinated fibrinogen antibodies

In RA patients, ACCP concentration in synovial fluid is 1.5 times higher than in serum, indicating that these antibodies are locally produced by synovial membrane cells.

Diagnostic Value of ACCP

ACCP detection specificity ranges from 90% to 99%, while its sensitivity is 41% to 68%.

Second-generation ACCP assays (using synthetic citrullinated peptides) have improved sensitivity to 49–91%, while specificity remains above 98%.

Studies confirm that 34–69.3% of RF-negative RA patients test positive for ACCP, making it an essential diagnostic marker.

Combining RF and ACCP for Better Diagnosis

A study by E. V. Efremova on 230 RA patients demonstrated that combining RF and ACCP testing significantly improves diagnostic accuracy. Early identification of seropositive patients allows for timely treatment initiation.

In cases where both RF and ACCP are negative, additional immunological markers should be explored to confirm RA diagnosis.

In assessing RA activity, clinicians commonly rely on acute-phase reactants, including:

Erythrocyte sedimentation rate (ESR)

C-reactive protein (CRP)

Serum amyloid A (SAA)

Fibrinogen

Matrix metalloproteinase-3 (MMP-3)

Erythrocyte Sedimentation Rate (ESR)

ESR depends on two main factors:

1. The aggregation level of erythrocytes
2. The physicochemical properties of erythrocytes

ESR is a highly sensitive but non-specific indicator of systemic inflammation. While it is useful for monitoring RA progression, ESR levels do not always correlate with disease activity and should not be the sole criterion for adjusting treatment.

C-Reactive Protein (CRP)

CRP is a traditional acute-phase protein and one of the most sensitive biomarkers for inflammation and tissue damage.

CRP measurement is essential for assessing disease activity and predicting joint destruction.

Studies show that CRP is more accurate than ESR in evaluating 28-joint disease activity scores (DAS28).

Baseline CRP levels are also useful in predicting cardiovascular risk in RA patients.

Serum Amyloid A (SAA)

SAA is a precursor to amyloid protein A, which is the primary component of secondary amyloidosis deposits.

Some studies suggest that SAA is more sensitive than CRP for detecting RA activity.

Elevated SAA levels may indicate an increased risk of secondary amyloidosis.

Fibrinogen in RA

Fibrinogen (Factor I) is a protein primarily synthesized by the liver.

In RA, fibrinogen levels are elevated and correlate with disease activity.

Increased fibrinogen deposition in synovial fluid is associated with joint damage and inflammation.

Matrix Metalloproteinase-3 (MMP-3)

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MMP-3 is an enzyme that degrades extracellular matrix components and is involved in joint tissue destruction.
High MMP-3 levels are found in both synovial fluid and peripheral blood of RA patients.
MMP-3 correlates with disease activity, radiographic changes, ESR, and CRP levels.
However, MMP-3 elevation is not specific to RA, as it is also observed in other rheumatic diseases.
Genetic engineering-based biologic therapies target MMP-3 expression, and measuring MMP-3 levels during treatment helps in predicting remission or maintaining low disease activity.
Radiographic and Imaging Techniques in RA Diagnosis
Assessing disease progression and treatment response requires regular imaging studies.
X-ray Examination of Joints
Joint X-rays are widely used, but their sensitivity for early RA detection is low.
Osteoporosis around joints is an early non-specific sign, but significant joint erosion requires weeks or months to become visible on X-rays.
Erosions first appear in the lateral aspect of the fifth metatarsal bone, followed by the medial surfaces of the second to fourth metatarsal bones.
In the hands, erosions are first seen in the styloid process of the ulna and middle joints, later progressing to proximal interphalangeal and metacarpophalangeal joints.
X-rays of large joints are less useful for RA diagnosis, as erosions may not appear at any disease stage. However, they are helpful for determining treatment strategies.
Steinbrocker's Classification of RA Stages
O. Steinbrocker's 1949 classification system is widely used for radiographic staging of RA:
1. Stage 1 – Narrowing of the joint space and periarticular osteoporosis.
2. Stage 2 – Appearance of cyst-like lesions and possible early erosions.
3. Stage 3 – Multiple erosions become apparent.
4. Stage 4 – Joint ankylosis (fusion of bones) occurs.
Each subsequent stage includes all features of the previous stages.
Synovial Biopsy and Joint Fluid Analysis
Synovial biopsy and fluid analysis were once considered essential for RA diagnosis, but they have lost their diagnostic value.
RF-negative synovial fluid findings may indicate RA, but the results are not highly specific.
Scintigraphy in RA Diagnosis
Scintigraphy is primarily used to confirm inflammatory processes in RA.
This technique detects increased blood flow in inflamed areas, but lacks specificity.
Ultrasound and MRI for Early RA Diagnosis
Early RA detection relies heavily on ultrasound and MRI.
Musculoskeletal ultrasound (MSUS) helps detect synovitis, with sensitivity comparable to MRI.
Power Doppler ultrasound (PDUS) improves detection of inflammatory activity.
Combining synovial membrane thickness and joint erosions on ultrasound increases diagnostic accuracy to 77% specificity and 99% sensitivity.
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CONCLUSION

The significance of modern approaches to rheumatoid arthritis (RA) diagnosis is continuously increasing. Immunological markers, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACCP), play a crucial role in early disease detection and activity assessment. These markers possess high diagnostic sensitivity and specificity, ensuring an accurate and effective RA diagnosis.
Additionally, laboratory indicators such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) provide supplementary data for disease activity assessment.
Imaging techniques, particularly ultrasound and magnetic resonance imaging (MRI), serve as essential tools for early-stage detection, enabling prompt and effective treatment strategies.
For seronegative RA cases, additional immunological tests are necessary, encouraging further advancements in diagnostic methodologies. Integrating these diagnostic approaches enhances precision, improves treatment outcomes, and ultimately raises patient quality of life.

RECOMMENDATIONS

1. Broader Use of Immunological Markers:
To improve early RA detection and disease activity assessment, the application of RF and ACCP testing should be expanded.
These markers play a crucial role in accurate and efficient RA diagnosis.
2. Implementation of Advanced Imaging Techniques:
Ultrasound (US) and MRI should be widely utilized for early identification of joint damage.
These methods allow for detailed visualization of synovial inflammation, improving diagnostic accuracy.
3. Additional Testing for Seronegative RA Cases:
In cases where RF and ACCP results are negative, further immunological and biochemical tests should be conducted.

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4. Regular Monitoring of Acute-Phase Reactants:
Indicators such as ESR and CRP must be routinely assessed to evaluate disease activity and treatment effectiveness.
5. Early Diagnosis and Treatment Initiation:
Prompt detection and intervention help prevent disease progression and minimize joint destruction.
6. Personalized Treatment Strategies:
Treatment plans should be tailored based on each patient's clinical profile, ensuring optimal therapeutic outcomes.
By following these recommendations, the efficiency of RA diagnosis and treatment can be significantly enhanced, contributing to better patient management and improved quality of life.

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