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Review

Early Diagnosis of Multiple Sclerosis: The Role of Biomarkers - A Brief Review

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ABSTRACT

Multiple sclerosis (MS) is an inflammatory, demyelinating and progressive disease of the central nervous system that predominantly affects young adults and is the leading non-traumatic cause of neurological disability in this population. Robust evidence shows that therapeutic interventions initiated early reduce relapse rates, delay conversion to progressive forms and preserve cognitive function. However, traditional diagnostic criteria rely on clinical or radiological proof of dissemination in time and space of lesions, which can delay diagnosis by up to two years. Over the past two decades, fluid biomarkers such as neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP) and the chemokines CXCL13/CXCL10 have demonstrated high sensitivity for detecting axonal damage and subclinical inflammation. At the same time, advances in quantitative neuroimaging including myelin water fraction and diffusion tensor imaging have made it possible to identify microstructural changes that precede T2-hyperintense lesions. Genomic studies, in turn, have identified more than 200 susceptibility loci, enabling the calculation of polygenic risk scores. By integrating these biomolecular, imaging and genetic dimensions into machine-learning models, researchers achieve predictive accuracies above 85 % for conversion from clinically isolated syndrome to definite MS. Challenges such as inter-laboratory standardization, reference value definition and cost-effectiveness assessment remain, but multi-center initiatives are working to overcome them. In this context, integrated analysis of fluid, imaging and genetic biomarkers offers a multidimensional portrait of pathology even before symptom onset, allowing intervention while neural reserve is still preserved. Thus, the judicious adoption of these tools could redefine the MS management paradigm.

Keywords: Multiple sclerosis; Biomarkers; Neurofilament light chain; Advanced neuroimaging; Artificial intelligence

Introduction

Multiple sclerosis (MS) affects approximately 2.9 million people worldwide and is the leading non-traumatic cause of neurological disability in young adults[1]. It is characterized by chronic inflammation, multifocal demyelination and progressive axonal loss phenomena driven by a complex interplay of genetic predisposition, environmental factors and immune-regulatory failures[2]. The 2017 McDonald criteria made magnetic resonance imaging (MRI) central to diagnosis, but still depend on evidence of dissemination in time and space of lesions, a process that can take months[3]. Diagnostic delay deprives patients of disease-modifying therapies (DMTs) capable of reducing inflammatory activity and preserving neural reserve. Over the past two decades, translational research has focused on identifying biological markers that more sensitively and specifically reflect underlying pathological activity. Fluid biomarkers such as neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP) and CXCL13 correlate with inflammation and neuroaxonal damage[4]. Technological advances, notably ultra-sensitive platforms like the single molecule array (Simoa®), have enabled serum quantification of these markers in picograms per milliliter, reducing reliance on lumbar puncture[5]. Meanwhile, MRI has evolved from conventional T1/T2-weighted sequences to quantitative approaches capable of measuring myelin water fraction, magnetic susceptibility and microstructural integrity via diffusion tensor imaging[6]. Integrating these data into machine-learning algorithms enhances accuracy in predicting conversion from clinically isolated syndrome (CIS) to definite MS[7].

Furthermore, genome-wide association studies (GWAS) have identified over 200 MS-associated loci, of which HLA-DRB115:01 accounts for roughly 20 % of heritability[8]. Combining genetic risk scores with environmental exposures vitamin D deficiency, smoking and prior Epstein-Barr virus infection enables population stratification for surveillance and early intervention[9]. Adaptive immune responses in MS are orchestrated by Th1 and Th17 helper T cells that cross the blood–brain barrier, releasing pro-inflammatory cytokines and recruiting antibody-producing B cells, which differentiate into intrathecal plasma cells responsible for oligoclonal bands[10]. Myeloid-lineage cells-activated microglia and perivascular macrophages contribute to axonal injury through oxidative stress and protease release.

Another key pathophysiological vector is failure of endogenous remyelination. Although oligodendrocyte precursor cells are recruited, their differentiation is blocked by inhibitory signals in the inflammatory milieu. Biomarkers derived from this process such as myelin basic protein (MBP) degradation products and magnetic susceptibility patterns reflecting iron accumulation expand the diagnostic spectrum[11]. Clinically, MS's phenotypic heterogeneity as relapsing–remitting, primary progressive or secondary progressive reinforces the need for individualized predictive models. Multiparametric scores combining serum NfL levels, cortical lesion volume, functional connectivity metrics from resting-state fMRI and genetic variables have shown > 85 % accuracy in predicting five-year disability[7].

Objectives

To review contemporary advances in biomarkers applicable to the early diagnosis of MS, discuss their applications, limitations and prognostic impacts and propose perspectives for multiparametric integration aimed at clinical practice.

Materials and methods

A literature review was conducted using PubMed, SciELO, Google Scholar and ScienceDirect databases.

Discussion

The clinical utility of a biomarker depends on three fundamental premises: technical reproducibility, consistent temporal correlation with disease pathophysiology and tangible impact on decision-making. NfL meets these criteria: serum concentrations rise up to six months before significant clinical relapses and correlate linearly with T2 lesion volume, cortical atrophy indices and the Expanded Disability Status Scale (EDSS) score[5]. Multicenter trials report 84-92 % sensitivity for predicting CIS conversion when combined with MRI findings, with likelihood ratios > 10. While oligoclonal IgG bands in cerebrospinal fluid remain the gold standard for detecting intrathecal inflammation, their low specificity drives the search for complementary markers. For example, the free IgM anti-lipidoxine index associates with aggressive disease course and may guide early use of high-efficacy therapies[10]. Likewise, microRNA signatures regulating B and T cells demonstrate discriminative power between MS and other demyelinating disorders, though large-scale validation is pending.

Quantitative MRI adds substantial value to early diagnosis. Reduced magnetization transfer ratio and myelin water fraction appear in seemingly normal-appearing white matter, preceding classic hyperintense lesions[6]. Diffusion tensor imaging tractography reveals deep white matter tract compromise correlating with subclinical cognitive deficits. When fed into deep-learning algorithms, these imaging features reach an area under the curve (AUC) of 0.90 for three-year disability prediction. Genetic biomarkers stratify risk even before clinical manifestation. Polygenic scores combining variants in HLA-DRB1, IL2RA, CD58 and TYK2 achieve an AUC of 0.77 in European cohorts[8]. Their clinical utility is limited, however, by lack of specific preventive interventions and poor generalizability outside European populations.

Emerging digital biomarkers from wearables and smartphones subtle gait changes, typing speed and speech intonation precede clinical relapses and can be monitored remotely, offering a low-cost surveillance avenue[9]. Integrating these data into AI platforms creates real-time monitoring opportunities but requires telemedicine infrastructure and data-privacy safeguards.

Regarding economic viability, cost-utility analyses show that incorporating serum NfL into diagnostic algorithms can yield net savings by avoiding hospitalizations due to untreated relapses, particularly in regions with limited access to advanced MRI. Decision models using Brazilian public-health data indicate an incremental cost-effectiveness ratio below three times GDP per capita, meeting WHO thresholds. Patient acceptance is also critical: qualitative studies reveal a strong preference for minimally invasive blood tests over lumbar puncture, underscoring the relevance of serum biomarkers[4]. Digital education programs with intuitive mobile interfaces boost self-monitoring adherence and data retention. Yet global adoption hinges on clear regulations, ongoing professional training and adequate laboratory infrastructure variables still fragile in many settings[12-15].

Conclusion

Early diagnosis of MS has become feasible thanks to a constellation of biomarkers capturing distinct yet interrelated pathological events such as inflammation, demyelination and axonal loss. Among these, neurofilament light chain stands out as a robust indicator of imminent neuroaxonal damage, while quantitative MRI reveals microstructural changes invisible to conventional sequences. Integrating genetic risk scores and environmental variables into AI algorithms enables precise stratification, allowing personalized and timely interventions. At the population level, biomarkers facilitate shifting from a reactive to a preventive model, identifying susceptible individuals and enabling interventions before the first neurological symptom. Phase II trials investigating immunotherapy in asymptomatic high-risk carriers defined by elevated NfL and subclinical MRI lesions are already underway in Europe and may redefine ethical boundaries in treatment (Baror et al., 2019).

Organizationally, recent guidelines from the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) recommend annual serum NfL measurement as a monitoring standard, while the American Academy of Neurology emphasizes the need for further cost-effectiveness studies before routine adoption. In Brazil, the Brazilian Academy of Neurology has opened public consultation on incorporating NfL and quantitative MRI into the Unified Health System's mandatory procedures a move that could democratize access to cutting-edge technologies.

Multidisciplinary training is crucial: neurologists, radiologists, clinical biochemists and data scientists must collaborate to interpret complex results and translate them into personalized therapeutic decisions. Biomarker education programs offered by European universities could be adapted to the Latin American context, with modular content and e-learning support. Future perspectives include developing point-of-care tests delivering quantitative NfL and GFAP results in under 15 minutes in the clinic, enabling immediate treatment adjustments. Concurrent research in lipidomics and metabolomics points to sphingolipid signatures and kynurenine-pathway metabolites as potential progression markers, expanding the available panel (Petzold, 2021). In neuroimaging, emerging chemical-exchange saturation transfer MRI and multivoxel spectroscopy techniques promise unprecedented in vivo characterization of the inflammatory microenvironment.

Finally, AI ethics demand attention. Multimodal decision-support systems must be transparent, auditable and free of biases that could disadvantage underrepresented groups. Data governance and compliance with sensitive-information protection guidelines will be as important as algorithmic accuracy. The convergence of these factors outlines a future where MS diagnosis is early, precise, participatory and equitable across populations. In conclusion, rational and equitable incorporation of fluid, imaging and genetic biomarkers can transform the MS trajectory by anticipating initiation of disease-modifying therapies, personalizing approaches and improving patient quality of life. The success of this transition will depend on international collaboration, investment in translational research and commitment to social justice.

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