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Biomarkers in Progressive Multiple Sclerosis: An Updated Review

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ABSTRACT

Multiple sclerosis (MS) may begin with a relapsing-remitting course followed by insidious disability worsening independent of clinically apparent relapses. Sometimes the progression is subtle and cannot be detected with routine clinical and imaging assessments. In this review, we focus on emerging biomarkers that can be representatives of MS progression. Early detection of MS progression will result in choosing the appropriate treatments which would result in better long-term outcomes.

Keywords: Biomarker, CSF, MS, multiple sclerosis, progression, serum.

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I. Introduction

Multiple sclerosis (MS) as one of the immune-mediated CNS diseases is the leading cause of disability, especially among young adults [1]. MS is characterized by its divergence in symptoms, disease course, and outcomes. The characteristic is demyelination as well as axonal degeneration [2]. The common scenario is that MS starts with a relapsing-remitting course (RRMS) followed by disease worsening, labeled as secondary progressive MS (SMPS), which might be independent of clinically apparent relapses [3], [4]. Nonetheless, at some point, the differentiation between RRMS and SPMS is not straightforward. The classification is arbitrary, especially in the transition phase between RRMS and SPMS, where there might be overlaps. In many cases, relapses occur, but there are also signs of clinical progression which are usually viewed as prolonged relapses with inadequate response to steroid therapy. In later stages, progression may be the more prominent feature; however, relapses or MRI activity are still present [5]. In terms of Disability, even in RRMS, most of the increase in disability is not caused by relapses only, but by the underlying relapse-independent progression [6]. In other words, at some points during the disease course, the progression might develop too insidiously to be clinically or radiologically detected by the patient and/or the healthcare provider as some subtle disease worsening cannot be established by routine clinical and imaging criteria. Nonetheless, the identification of MS is critical in the sense that not only such conversion is correlated with disability progression, but also it affects the clinician's decision upon choosing the best available treatment. The latter is of great importance since the effectiveness of treatments for progressive MS might be different from those of relapsing-remitting ones, and available drugs are mainly approved only for certain types of MS courses [7]. Ongoing efforts have been done to identify the role of multiple Biomarkers in MS. In this review, we focus on emerging biomarkers that can be representatives of MS progression.

II. Methods

The search was conducted based on different databases including PubMed, EMBASE, CINAHL, and Cochrane Library. The search strategy consisted of medical subject heading (MeSH) terms including "Multiple Sclerosis," "MS," "biomarkers", "progress," "progression", "progressive" "marker," "indicator," and "novel biomarkers". To combine the terms in complete sentences, Boolean operators were applied. Editorials, Commentaries, dissertations, and abstracts without the full text were excluded. Papers published in English opted for evaluation, and only original research studies conducted on human subjects were selected. The title and abstract were evaluated for relevance, and finally, the relevant full-length papers were extracted and explored. Also, searches on the citations of the relevant articles were conducted. Studies lacking a definite clinical diagnosis of MS were excluded, as were. Following are the summaries of the reviewed biomarkers.

III. Biomarkers

A. Neurofilament Light Chain (NfL)

To date, neurofilament in CSF and blood as a biomarker is the most promising biomarker for its potential to show brain injury or neurodegeneration. NfL is part of the axonal cytoskeleton [3]. The correlation between NfL and disability progression has been studied so far. Some long-term follow up studies showed the progress of EDSS scores with higher mean baseline NfL levels independent of clinical or MRI signs of acute inflammatory disease activity [8]. In one study it was shown that the higher baseline level of Nfl was a predictor of converting to secondary progressive MS [8]. However, other studies have found no correlation with disease progression and no prognostic value for disability development or future disability progression in progressive MS [9]-[11]. Interestingly, in some studies, patients with higher levels of baseline NfL experienced greater reduction in brain volume. This suggestes that the baseline CSF NfL level predicts brain atrophy development [12], [13]. Also, it was shown that an increase in serum NfL of 10 ng/L was associated with an additional reduction in brain volume of 0.17% after two years [14]. On the other hand, in some studies NFL correlated with the clinical and/or radiological disease activity [15] and levels of the NFL were increased, peaking almost 10 times higher during acute relapses [16]. Nevertheless, in a study which monitored patients with MS, serum NfL (sNfL) indicated a gradually increased risk for future acute disease activity like relapse and lesion formation, along with chronic (disability worsening) disease activity [17]. Also, it was shown that an increase in serum NfL of 10 ng/L was associated with an additional reduction in brain volume of 0.17% after two years [14].

B. GFAP

Based on different studies, it can be alleged that GFAP is useful for diagnosis and monitoring the progression of MS. In a study which was performed on patients with RRMS, SPMS, and healthy controls for 8-10 years, it was shown that GFAP level was higher in patients with MS compared to the healthy subjects and that the GFAP level at the baseline was predictive of neurological disability and disease progression 8-10 years later (EDSS, $r = 0.45$, $p < 0.05$), yet not for EDSS increase between the examinations [10].

In line with this study, the highest levels of GFAP were detected through the secondary progressive course of MS with a strong significant correlation of disability progression ($p < 0.001$) [16]. Again, in another study, CSF level of GFAP was an independent prognostic marker for disability progression in patient with RRMS [18].

C. Chitinase 1-Like 1

Chitotriosidase (known as chitinase 1, CHIT1) is a marker of activated microglia [19], [20]. It has been postulated that CHIT1 level is associated with annualized relapse rate and the clinical and/or radiological disease activity of the entire disease course [15], [21]. Interestingly, it is suggested that the CSF CHI3L1/CHI3L2 ratio might distinguish PPMS from RRMS [22].

D. Chitinase 3-Like 1 (YKL-40)

Chitinase -3-Like protein-1 (CHI3L1) is a glycoside secreted by microglia, monocytes, and the activated astrocytes. Its presence in inflammatory lesions suggests that it might be a vital component of the astrocytic response to modulate CNS inflammation [23]. Chitinase -3-Like protein-1 (CHI3L1) has been considered a biomarker of both disease activity and disease progression. Higher levels of CSF CHI3L1 have been shown to be associated with disability progression [15], [24]. In this regard, the disability progression was shown in patients with either RRMS [23], PPMS [9], or SPMS [25]. In the latter study, it was shown that Chitinase -3-Like protein-1 (CHI3L1) can be a marker of active progressive MS in the sense that YKL-40 correlates with the number of T1 lesions. It is shown to be inversely correlated with the signal intensity of normal appearing white matter. This implies that the CSF level of YKL-40 in SPMS is suggesting the number of chronic active lesions which significantly attributes to the development of disability in SPMS patients. For this reason, authors suggested thatYKL-40 should be a good biomarker to monitor disease activity in SPMS [25]. However, in other studies, it was shown that CHI3L1 was significantly associated with relapse rates [21], and clinical and/or radiological disease activity [15]. Furthermore, in a study it was shown that compared to Nfl, CHI3L1 appears to be a better marker to differentiate Relapsing MS from Progressive MS [25].

E. Chitinase 3-Like 2 (CHI3L2)

There are debates regarding CHI3L2; There is evidence that indicates that CHI3L2 is either a biomarker of high disability progression [26], or it shows no predictive value in terms of MS progression [9]. Interestingly, patients with progressive MS had lower levels of CSF CHI3L2 compared to the RRMS patients in early stages of the disease. Consequently, the author suggested that the CSF CHI3L1/CHI3L2 ratio might differentiate PPMS from RRMS [22].

F. Chemokines

Chemokines are involved in the interactive process that includes inflammation, development, and cell migration during the immune surveillance. In the chronic inflammatory conditions, they also play a role in establishing the lymphoid tissue [27], [28]. They can regulate the accumulated and migration of monocytes/macrophages and lymphocytes to the damaged CNS districts and promote the differentiation, therefore maintaining the immune response process [29]. Chemokine receptors are named according to the chemokines group they bind [30]. Studies have showed that level of CXCL 8, CXCL 10, CCL18, CCL5 and sCD86 were higher in progressive MS compared to RRMS [31], [32]. Also, higher CCL 18 was found to be correlated significantly with brain atrophy. This may indicate that these chemokines are indicating the progression of MS [28]. In contrast, CXCL13 which is a B-cell chemokine, is increased in patients with active MS and correlates with the clinical and/or radiological disease activity [15], [32]. It has been highlighted that the levels of CNS C-C motif chemokine ligand 2 (CCL2), also known as monocyte chemoattractant protein-1, are diminished during the disease activities in MS [33]. This chemokine has a role in recruiting monocytes and macrophages to the CNS.

G. Tau

In a study, it was found that Tau protein decreases during the course of the disease from RRMS to SPMS and it also reflects the degree of brain atrophy [34]. However, in another study, authors did not find any significant difference between patients with SPMS and RRMS when authors evaluated Tau protein [35].

IV. Imaging Techniques

A. OCT

Many studies have suggested OCT as a useful tool for detecting progression in patients with MS but not in PPMS patients [36], compared with controls Lower ganglion cell-inner plexiform layer (GCIPL), peripapillary retinal nerve fiber layer (pRNFL), and total macular volume (TMV) was found in patients with SPMS compared to RRMS [37]-[43] and is a beneficial tool to monitor the disability progression [38]. This shows that Longitudinal assessment of retinal thinning could confirm those patients who converted to SPMS.

B. Slowly Expanding/Evolving Lesions (SLEs) as A Magnetic Resonance Imaging Marker

SELs are T1 hypointense lesions with increasing of MRI volume and suggest ongoing axonal injury. These indicateindicate chronic lesion activity made by smoldering inflammation as a pathological hallmark of progressive forms of MS. SELs are demyelinating plaques with ongoing destruction at the sides. It has been shown that the edges of these chronically active lesions have a rim of macrophages, activated microglia, and lymphocytes. Studies have suggested that SELs on MRI may denote chronically active MS lesions and may be a candidate biomarker for progression in MS [43]-[45].

V. Conclusions

With the search for biomarkers with more prognostic value in detecting MS progression, there have been exciting advances with different biomarkers. These biomarkers, in combination with clinical and MRI features, can help healthcare providers make better therapeutic decisions in cases of progression doubts. mind that there might be no clear cut answer to indicate whether each biomarker is showing relapse or progression. Serial and imaging assessments and clinical judgment should pair with the biomarker findings to draw a concise conclusion.

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Conflict of Interest

Dr. A. Z is on the advisory board of Alexion, Genentech-Roche, Novartis, Biogen, Genentech-Roche, Horizon Therapeutics, Sanofi-Genzyme, and has received speaking honoraria and travel grants from Alexion, Genentech-Roche, Novartis, Biogen, Genentech-Roche, Horizon Therapeutics, Sanofi-Genzyme, Bristol Myers Squibb, and has received the research grant from Alexion, NIH, PCORI, Genentech-Roche, Novartis.

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