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Review / Derleme

Prognostic-disability Biomarkers in Multiple Sclerosis: Review of the Literature from the Last Five Years

Multipl Skleroz Olgularında Prognoz-Özürlülük Biyoişaretçileri: Son Beş Yıla Ait Literatürün Gözden Geçirilmesi

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Abstract

With the advent of new agents in the treatment of multiple sclerosis, new treatment modalities have emerged (escalation-induction therapy) and the increased efficacy of the drugs has led to increased drug-related risks. The risk/benefit balance has become more carefully assessed. The increased need for reliable markers to predict prognosis-disability has also led to an increase in research conducted in this area. In this short review, studies published between 2012-2017, especially those related to prognosis and disability, were compiled.

Keywords: Multiple sclerosis, disability, prognosis, biomarker

Öz

Multipl skleroz hastalığı tedavisine yeni ajanların girmesi ile yeni tedavi modelleri oluşmuş (basamaklı tedavi-indüksiyon tedavisi) ve ilaçların artan etkinliği beraberinde ilaç ile ilişkili artan riskleri de taşımıştır. Risk/yarar dengesi daha dikkatle değerlendirilir hale gelmiştir. Prognozu-özürlülüğü tahmin ettiren güvenilir işaretçilere artan gereksinim ile bu alanda yapılan araştırmalar da artma göstermiştir. Bu kısa gözden geçirme çalışmasında 2012-2017 yılları arasında yapılmış yayınlarda özellikle prognoz ve özürlülük ile ilişkili olanlar derlenmiştir.

Anahtar Kelimeler: Multipl skleroz, özürlülük, prognoz, biyoişaretçi

Introduction

Neuroinflammation and neuroregeneration processes coexist in multiple sclerosis (MS). Although the clinical course differs in each patient, it is not known what the causative factor is in a favorable or unfavorable clinical course. Apart from clinical data, biochemical-serologic, radiologic, electrophysiologic studies and biomarker identification studies have been conducted in order to identify factors and markers related to clinical course. A biomarker is simply an indicator that can be objectively measured and evaluated in response to a normal biologic or pathologic process or response after a treatment. It can be used for diagnosis, staging, and as a prognostic indicator of the disease, predicting treatment response or follow-up of treatment (1). In this short review study, the aim was to compile biomarkers that reflect the progress and development of disability in MS that have been introduced in the past 5 years. The presence of biomarkers at the time of diagnosis will be of value in determining whether high-efficacy/high-risk treatment selection is required or whether monitoring at the time of treatment is effective/ineffective.

Which pathophysiologic processes are observed in MS and why do individual differences arise?

When the progression of MS is examined, it is observed, with the simplest approach, that there is a relapsing-remitting or progressive course. Tissue inflammation consisting predominantly of immune cells creates local areas of demyelination called plaques in brain regions in the course of the episodes, and a 'generalized inflammatory state,' which is a diffuse microglia activation in the entire brain, has been shown recently (2). Immune activation has its own cell destruction effect as well as causing disruption in the mitochondrial genetic structure, thus leading to a decrease in mitochondrial function and energy production (3). The trophic

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support cycle between neurons and glia is disturbed and the cell life cycle is diverted to apoptosis (4). Besides the reduction in energy production, the contribution of vascular deficiency was identified in recent years in the area of inflammation (5) and the excessive energy consumption of channel structures reorganized during the remyelination process lead to an energy bottleneck. Energy deficiency can lead to increased intracellular calcium accumulation and triggering of apoptotic processes, formation of toxic substances such as reactive oxygen products, and inadequate purification processes (6). Unlike the relapsing-remitting course, immune activation in the progressive course continues with microglia instead of T and B cells. After increased tissue damage, axonal degeneration becomes widespread with anterior-posterior extensions. Mechanisms that generate toxic responses are further activated by releasing iron accumulated in the tissue, the energy bottleneck increases, the regenerative ability decreases with advancing age, and consequently disability develops without episodes (7). Although disability appears to be a result of anatomic destruction and physiologic insufficiency in the neural structure in the relapsing-remitting course, anatomic destruction seems to be associated with physiologic destruction in the progressive course.

The neuroinflammation/neurodegeneration processes in MS pathophysiology could be summarized as follows;

1. Deformation or structural changes occur in normal tissue structure.

2. After the structural change, the energy demand increases and the inefficient-excessive energy consumption develops.

3. The processes developed for adaptation become maladaptive.

4. Cell death rate increases with insufficiency in the regeneration process or the amount of cell damage.

The presence of different prognosis-disability in patients with MS can be explained by the absence of therapeutic agents or differences in the efficacy of these agents, individual variability such as sex and age of onset, presence of toxic agents or other variables not yet defined along with this process.

What are the factors-biomarkers associated with disability?

Clinical, radiologic, and immunologic studies of the biomarkers will be grouped, but it should be remembered that these groups are intertwined (Tables 1, 2, 3). As negative factor and biomarker studies herald disability, they are more noticeable than positive factors and biomarker studies and their number is therefore greater (a summary of the studies is given in Table 4).

Table 1. Clinical prognosis-disability biomarkers

Clinical biomarkers	
Good	**Poor**
- Low relapse frequency in the first 5 years, complete remission, sensory relapses (7) - Female, younger age at onset, treatment (8) - Initiation of treatment within the first 3 years (12) - High baseline brain volume and treatment (19) - Age of onset under the age of 15 years, use of disease-modifying treatment, isolated supratentorial and isolated brain stem relapses (24) - Absence of relapses within the last 4 years (31)	- Male, African descent, non-recovery after the first relapse, two or more relapses during the first year, short interval between relapses, relapses with pyramidal and cerebellar dysfunction, no treatment prior to reaching EDSS 3 (16) - Older age at onset (19) - High baseline EDSS and EDSS increase (20) - Smoking (23) - Pyramidal, cerebellar, bowel/bladder involvement - Multifocal involvement, isolated spinal cord and isolated optic nerve involvement (24) - Presence of early cognitive impairment (28) - Age over 45 years and presence of high disease activity (32) - First-year EDSS and EDSS change (42)

EDSS: Expanded Disability Status Scale

Table 2. Radiologic prognosis-disability biomarkers

Radiologic biomarkers	
Good	**Poor**
- Higher observed brain volume than the expected brain volume (44) - Baseline volumes of thalamus, caudate and putamen (47)	- New or enlarging T2 lesions (37,42) - Lesion in the spinal cord (39,40) - Involvement of cerebellar gray matter (41) - Baseline T2 lesion number, T1 and T2 lesion volumes, corpus callosum, and thalamic fractions, corpus callosum volume change (42) - Whole brain and central atrophy (43) - Observed brain volume is lower than expected brain volume (44), increased brain volume loss rate (45) - Lower cortical NAA/Cr (46)

NAA/Cr: N-acetyl aspartate/creatine

Table 3. Immunologic prognosis-disability biomarkers

Immunologic biomarkers	
Good	**Poor**
- Presence of HLA-A2 (52) - Presence of *TYK2*, *RGS1 CLEC16A* gene locus (55) - High serum vitamin D level (60) - Absence of oligoclonal band (69)	- Presence of HLA-B7 and B4 (52) - Presence of HLA-DRB11 and HLA-DRB14 (53) - Presence of re12959006 variant in *MBP* gene (54) - Presence of BATF, CYP27BI, ILI2B, NFKB1, IL7, PLEK, EV15, TAGAP, nrs669607 gene locus (55) - High CSF-soluble CD27 level (56) - High CSF chitinase 3-like 1 level (57,58,59) - CSF neurofilament light-chain levels (57,64) - IL-33, IL-37, VEGFR2 levels (61) - Serum lactate, creatinine, purine-pyrimidine levels (62) - Low CSF β-amyloid levels (63) - CSF neurofilament heavy-chain levels (65) - Presence of IgG oligoclonal bands (68,69) - Presence of IgM oligoclonal bands (71) - Presence of neutralizing antibody (72)

HLA: Human leukocyte antigen, *MBP: Myelin basic protein*, CSF: Cerebrospinal fluid, IL: Interleukin, VEGFR2: Vascular endothelial growth factor receptor 2, Ig: Immunoglobulin

Table 4. Features and brief descriptions of the studies

Author-reference number	Year	Number of cases	Follow-up time	Objective/monitored parameters	Significant parameters/implications
Skoog et al. (8)	2012	307	15 years	Progression monitoring-relapse frequency, clinical, EDSS	Benign MS features; Low relapse frequency in the first 5 years, complete remission of the onset attack and dominating afferent symptoms.
Zivadinov et al. (9)	2016	6258	4 years-retrospective	Having EDSS values below 2 and 3 for 10-year disease duration 19.8% to 33.3% baseline benign MS.	Benign MS features; Baseline; female sex and younger age at onset. At the end of 4th year; disease-modifying treatment and longer disease duration.
Leray et al. (10)	2013	874	30 years	Having EDSS values below 2 and 3 for 10-year disease duration. 50% decline in benign MS cases every 10 years	Benign MS features; Female sex and presence of fully recovering attacks with low number of attacks at the 30th year.
Capra et al. (12)	2017	1324	30 years	Case rate with EDSS 6	Disease-modifying treatment affects disability development; the prevalence of EDSS 6 was significantly lower before 2000 (15-27%).
Kavaliunas et al. (13)	2017	639	8 years	The effect of time to initiate treatment at 1, 1-3 or 3 years on reaching EDSS 4 Disability Age	The initiation of treatment within 1 year has an impact on disability. In addition, development of early disability and late age at onset were independent variables.
Cree et al. (14)	2016	512	17 years	EDSS NEDA Progression to SPMS	Progression to SPMS rate is reduced with disease-modifying treatment. Treatment/natural course rates 36/11.3%.
Bsteh et al. (15)	2017	532	11 years	Age, sex, disability, MR, initial symptoms, OCD, treatment	Atypical/cortical symptoms as initial symptoms are not benign.

Table 4. Continued

Author-reference number	Year	Number of cases	Follow-up time	Objective/monitored parameters	Significant parameters/implications
Vasconselos et al. (16)	2016	303	10 years	Initial symptoms (mono-polysymptomatic) EDSS, age of onset, sex, race, number of relapses during the first year, interval between two relapses, recovery after the first relapse, treatment status prior to reaching EDSS 3	Risk factors for rapid progression; male sex, being of African descent, non-recovery after the first relapse, two or more relapses during the first year, a short interval between two relapses, initial polysymptomatic presentation of pyramidal and cerebellar dysfunction, no treatment prior to reaching EDSS 3.
Aurenção et al. (17)	2016		Systematic review; 14 articles	Comparison of black race and white race in terms of MS development and progression	Rarer, but faster development of disability in black race.
Tutuncu et al. (18)	2012	964	10 years	Sex, age at onset of MS and age of onset of progression, age of onset of progression, time to reach EDSS 6 from the onset of progression	Age was related to disability independently of previous disease activity or disease duration.
Guillemin et al. (19)	2017	3597		Reaching EDSS 4 and 6 Transition to SP	Age of onset after age 50 is a risk factor for disability increase.
Traboulsee et al. (20)	2016	382	8 years	Age, disease duration, baseline brain volume, EDSS score, T2 lesion burden, early increase in EDSS, receiving treatment	Good prognosis; higher baseline brain volume and receiving treatment. Poor prognosis; higher baseline and greater early increase in EDSS score.
Calabrese et al. (21)	2013	334	5 years	Age of onset, cortical lesion volume, and cerebellar cortical volume	Age of onset, cortical lesion volume, and cerebellar cortical volume identified 94% RRMS patients and 88% SPMS patients.
Scalfari et al. (22)	2014	806	28 years	Sex, age of onset, number of attacks in the first 2 years, number of symptoms and type	Risk factors for transition to SPMS; male sex, onset after the age of 30, and 3 or more relapses in the early period. Three or more relapses, and had cerebellar and brainstem symptoms during relapses were risk factors for reaching to EDSS 8.
Ramanujam et al. (23)	2015	728	3 years	Sex, age at onset of disease, smoking prior to diagnosis, current smoking	Current smoking accelerates the development of secondary progression.
Stewart et al. (24)	2017	19504	Patients with at least one year follow-up	Relationship between disability and frequency of relapses and relapse types	Relapses in pyramidal, cerebellar and bowel/bladder systems lead to higher EDSS increase compared with relapses with brainstem, visual, sensory, and cerebral involvement.
Iaffaldano et al. (25)	2017	602	10 years	Factors related to disability in pediatric CIS and MS cases; Sex, relapse frequency, relapse location, treatment use	The use of disease-modifying treatment was a factor that decreased the risk of disability development, while relapses with multifocal or isolated spinal cord or optic neuritis involvement had higher incidence of disability development compared with relapses with isolated supratentorial or brainstem syndrome.
Ruano et al. (26)	2017	1040	Cross-sectional-10 months	Cognitive impairment	There is a relationship between cognitive impairment and age, long duration of illness and high EDSS values. This relationship also occurs independently of disease subtypes and is higher in progressive cases.

Table 4. Continued

Author-reference number	Year	Number of cases	Follow-up time	Objective/monitored parameters	Significant parameters/implications
Johnen et al. (27)	2017	4460	Systematic review; 47 articles	Cognitive impairment	In SPMS cases, processing speed, verbal learning and verbal memory were worse than RRMS. RRMS patients had more deterioration in working memory, cognitive fluency and higher executive functions.
Pitteri et al. (28)	2017	78	8 years	The importance of the cognitive status at the onset of disease	Early cognitive impairment was predictive of conversion to definite MS, disability increase, transition to secondary progressive phase and cortical thinning.
Raffel et al. (30)	2017	161	7 years	The importance of first year MRI activity and relapses in prediction of long-term disability in patients under natalizumab treatment	Disability increase was predicted with Rio score for 1-2 years, but not for 3-7 years.
Matell et al. (31)	2015	1872	6 years	Change in natalizumab efficacy with age Duration of disease, EDSS, age, SMDT test result, CSF CXCL13 level, NfL	Discontinuation was higher in patients >50 years (18.7/7.7%), also deterioration in EDSS and SDMT were higher.
Bsteh et al. (32)	2017	221	4 years	Demographic and clinical data, MRI data	Absence of relapses; age >45 years at discontinuation, absence of relapses for ≥4 years and absence of contrast enhancing lesions Relapses; high EDSS score, over 45 years of age and long disease duration.
Kiylioglu et al. (33)	2015	67	Cross-sectional-2 years	The relationship between SEP + MEP scores obtained by ordinal scoring and EDSS	Ordinal SEP + MEP scores explained 58% of EDSS variability (r^2=0.584).
London et al. (34)	2017	108	15 years	The relationship between composite evoked potential score and EDSS score at 10th and 15th years	The change in multimodal evoked potential score predicts future disability score and is related to EDSS.
Schlaeger et al. (35)	2014	28	20 years	Estimation of disability rate after 20 years with MEP + VEP score in RRMS and SPMS cases	Evoked potential scores together with age and treatment status were able to predict 58% of EDSS variability at 20 years.
Martinez-Lapiscina et al. (36)	2016	879	5 years	Predicting the development of disability in MS cases following retinal nerve fiber layer	Thickness less than 87 µm-88 µm was has a risk of increased EDSS.
Río and Ruiz-Peña (37)	2016		Systematic review; 8 articles	New or enlarging T2-weighted lesions ≥1, new or enlarging T2-weighted lesions ≥2 and Rio score ≥2 Predicting EDSS increase between 2-5 years	Sensitivity values are good, but predictive values are not sufficient.
Hagström et al. (38)	2017	220	2 years	The relationship between EDSS, upper cervical spinal cord area, pyramidal and sensory function score, motor fatigue at baseline, 12th and 24th months in CIS and RRMS	Atrophy change rate was higher in the upper cervical cord area compared with white matter and gray matter, and this might have a potential value.
Brownlee et al. (39)	2015	131	5 years	The relationship between brain MRI lesion burden and brain atrophy, number of spinal cord lesions, upper cervical spinal cord cross-sectional area and EDSS	Baseline asymptomatic spinal cord lesion number, change in cord lesion number and change in upper cervical cord area were associated with EDSS.

Table 4. Continued

Author-reference number	Year	Number of cases	Follow-up time	Objective/monitored parameters	Significant parameters/implications
D'Amico et al. (40)	2016	239	7 years	The relationship between the presence of early spinal cord lesion in RRMS and disability	The presence of spinal cord lesion is a predictor of poor prognosis in patients with RRMS.
Damasceno et al. (41)	2014	72	Cross-sectional	Relationship between cerebellar gray matter involvement and clinical and cognitive impairment in MS cases	Cerebellar intracortical lesions predict EDSS - cerebellar - limb functions. Patients with high burden of intracortical lesions had worse SDMT scores and leukocortical lesions are associated with low PASAT score.
Uher et al. (42)	2017	177	12 years	Clinical and MRI parameters were used for prediction of worsening, T2 lesion number, T1 and T2 lesion volumes, corpus callosum, and thalamic fraction at baseline, EDSS and its change, corpus callosum volume change and number of new or enlarging T2 lesions at 1st year	A composite score generated from clinical and MRI parameters was shown that scores of ≥4 had greater specificity for predicting worsening compared with the individual predictors.
Popescu et al. (43)	2013	261	12 years	MRI imaging and disability status after 10 years	EDSS at 10 years was related to whole brain and central atrophy, and T2-weighted lesion volume change at 2 years.
Sormani et al. (44)	2017	2342	4 years	MRI-based brain volume measurements were used to calculate observed and expected normalized brain volume based on age, sex, T2-lesion volume, and baseline EDSS	There was a relationship between baseline brain volume and 2-4 year disability development.
Jeffery et al. (45)	2016	1272	4 years	The relationship between brain volume loss rate in the first 2 years and 2-4 year disability development	MS disease activity and severity and baseline brain volume, and brain volume loss rate in the first 2 years were related to 2-4 year disability development.
Sormani et al. (46)	2014	13500	Meta-analysis; 13 articles	Therapeutic effect of disease-modifying treatment on disability was examined	Brain atrophy and active MRI lesions affect 75% of these two factors in preventing EDSS increase.
Nourbakhsh et al. (47)	2016	40	30 months	The relationship between thalamus, caudate and putamen volumes, clinical EDSS, subsequent 25-ft walk test and MSFC	While atrophy in subcortical structures was observed as a continuous process, the baseline volumes of these structures predicted the 25-ft walk test and MSFC.
Wu et al. (49)	2014	6	7 years	Relation of NAA/Cr ratio to EDSS	Baseline cortical NAA/Cr and EDSS were negatively correlated and there was a significant difference between patients with EDSS ≥4 and others.
Giannetti et al. (50)	2014	19	Cross-sectional	Investigating T1 lesions by 11C-PK11195 PET (PK-PET) that shows microglial activity and its relationship with clinical status	T1 black holes were found to be not inactive, but surrounded by activated microglia and associated with disability.
Rocca et al. (51)	2015	111	Cross-sectional	Relationship between hippocampal-resting state functional connectivity and T2 lesion load, disease duration, disability and depression	Reduced hippocampal-resting state functional connectivity was found to be associated with higher T2 lesion volume, longer disease duration, and the severity of depression and disability.

Table 4. Continued

Author-reference number	Year	Number of cases	Follow-up time	Objective/monitored parameters	Significant parameters/implications
Lysandropoulos et al. (52)	2017	118	2 years	The relationship between HLA types and MS prognosis	HLA-A2 favor a better prognosis, HLA-B7 and B44 favor a poor prognosis, and HLA-DRB115, HLA-DQB16 and HLA-B8 alleles are inconclusive.
Romero-Pinel et al. (53)	2011	1468	Cross-sectional	Investigation of risk characteristics of HLA-DRB1 alleles in MS	HLA-DRB1*01 and DRB1*04 alleles were found to be associated with a worse prognosis.
Zhou et al. (54)	2017	127	5 years	Relation of *MBP* re12959006 variant to disability	rs12959006 was found to be associated with worse clinical outcomes.
Akkad et al. (55)	2014	141	Cross-sectional	Relationship between genetic loci, clinical status, upper cervical spinal cord parameters in MRI	The upper cervical spinal cord area was associated with disability, linear relationship between 9 loci (BATF, CYP27B1, IL12B, NFKB1, IL7, PLEK, EVI5, TAGAP, nrs669607), inverse relationship with 3 loci (*TYK2*, *RGS1*, *CLEC16A*).
van der Vuurst de Vries et al. (56)	2017	77	5 years	Relationship between CSF-soluble CD27 at the time of initial relapse and MS diagnosis and relapse rate	CSF-soluble CD27 predicted the conversion to MS in patients with CIS and was also associated with a high relapse rate.
Modvig et al. (57)	2015	86	14	MRI, CSF leukocyte, IgG index, OCB, CSF chitinase-3-like-1, osteopontin, NfL, *MBP*, CCL2, CXCL10, CXCL13 and MMP-9	Together with MRI parameters, chitinase 3-like 1 and age predicted conversion to MS. Chitinase-3-like-1 predicted cognitive impairment by PASAT test and NfL predicted disability by the MS severity scale and nine-hole-Peg-test.
Cantó et al. (58)	2015	813	5 years	The relationship between CSF chitinase-3-like-1 level and transition to MS and development of disability	CSF chitinase-3-like-1 is an independent risk factor for conversion to MS. High CSF chitinase-3-like-1 was also associated with early conversion to MS and early development of disability.
Martínez et al. (59)	2015	301	11 years	Predicting conversion to MS and disability increase in CIS and RRMS with CSF NfL, t-tau, p-tau, glial fibrillary acidic protein, S-100B, chitinase-3-like-1, monocyte chemoattractant protein, α-sAPP, β-sAPP, Aβ38, Aβ40 and Aβ42 levels	High NfL level was associated with CIS-MS conversion. High GFAP and chitinase-3-like-1 levels were associated with early EDSS 3 increase. Chitinase-3-like-1 was associated with early progression to EDSS 6.
Ascherio et al. (60)	2014	334	5 years	The relationship between disability and Vitamin D and MRI variables	Increment in average serum vitamin D levels within the first year predicted a lower relapse rate (57%), lower rate of new active lesions on MRI (57%), lower yearly increase in T2 lesion volume (25%), lower yearly loss in brain volume (41%) and less disability.
Kouchaki et al. (61)	2017	159	Cross-sectional	Relationship between serum IL-33, IL-37 and sVEGFR2 and EDSS	There was a relationship between serum IL-33, IL-37 and sVEGFR2 and EDSS severity.

Table 4. Continued

Author-reference number	Year	Number of cases	Follow-up time	Objective/monitored parameters	Significant parameters/implications
Lazzarino et al. (62)	2017	685	Cross-sectional	The relationship between serum energy metabolism biomarkers, serum lactate, creatinine, purines (hypoxanthine, xanthine, uric acid, inosine) and pyrimidines (uracil, beta-pseudouridine, uridine), and disability, disease course and MRI	Different scores were observed in RRMS and progressive MS cases and they were also related to EDSS and MRI parameters. There was a relationship between MRI and mitochondrial dysfunction findings.
Pietroboni et al. (63)	2017	93	3 years	Relationship between CSF amyloid beta and tau levels and MRI and disability	Lower CSF β-amyloid levels at baseline were a disability predictor at 3-year follow-up. CSF tau levels correlated with T2- and T1-lesion load on MRI.
Håkansson et al. (64)	2017	63	2 years	The relationship between clinical status and MRI and CSF CXCL1, CXCL8, CXCL10, CXCL13, CCL20, CCL22, NfL, NfH, GFAP, chitinase-3-like-1 MMP-9, osteopontin levels in RIS and RRMS cases	The CSF NfL values are not different from the controls in the NEDA group, but are different in the EDA group. NfL values predicted disease activity alone with 85% accuracy during 2 years of follow-up.
Petzold (65)	2015	51	15 years	Relationship between CSF NfH values and clinical EDSS	NfH values correlate with EDSS and reflect axonal degradation.
Petzold et al. (66)	2016	15	15 years	Relationship between CSF NfH values and MRI atrophy	High CSF NfH levels estimate the amount of brain and spinal cord atrophy on MRI.
Farina et al. (68)	2017	50	10 years	The relationship between cognitive, clinical status, MRI and CSF profiles CXCL13, CXCL12, CXCL10, *TNFSF13*, *TNFSF13B*, IL-6, IL-10, IFN-γ, TNF, MMP2, GM-CSF, osteopontin and sCD163 in OCB + and - cases	The occurrence of baseline OCB was associated with physical and cognitive impairment over a 10-year follow-up OCB + positivity were found associated with an increase in gray matter lesions, high NfH ratio, B lymphocyte activity, lymphoid neogenesis as well as proinflammatory activity.
Rojas et al. (69)	2012	196	13 years	The relationship between OCB and EDSS	OCB-patients had a better prognosis and milder EDSS values.
Ozakbas et al. (71)	2017	81	Cross-sectional	The relationship between MRI and EDSS, and IgG index, as well as, IgM index in RRMS and SPMS patients	IgM index values, unlike IgG index, were correlated with EDSS and MRI parameters, and were higher in SPMS cases.
Paolicelli et al. (72)	2013	567	5 years	Neutralizing antibody status and effects on disease course in patients using IFN-beta 1a/b therapy	Neutralizing antibody was observed in 14% with treatment. There was an increase in the relapse rate, decrease of the time to 1st relapse and a negative trend on the time to reach EDSS 4.

EDSS: Expanded Disability Status Scale, MS: Multiple sclerosis, NEDA: No evidence of disease activity, SPMS: Secondary progressive multiple sclerosis, MRI: Magnetic resonance imaging, OCB: Oligoclonal bands, CIS: Clinical isolated syndrome, RRMS: Relapsing-remitting multiple sclerosis, SDMT: Symbol digit modalities test, CSF: Cerebrospinal fluid, SEP: Somatosensory evoked potentials, VEP: Visual evoked potential, MSFC: Multiple sclerosis functional composition, NAA/Cr: N-acetyl aspartate/creatine, PET: Positron emission tomography, HLA: Human leukocyte antigen, *MBP: Myelin basic protein*, VEGFR2: Vascular endothelial growth factor receptor 2, IL: Interleukin, NfL: Neurofilament light-chain, NfH: Neurofilament heavy-chain, PASAT: Paced auditory serial addition test, GFAP: Glial fibrillary acidic protein, Ig: Immunoglobulin, IFN: Interferon, TNF: Tumor necrosis factor, GM-CSF: Granulocyte-macrophage colony-stimulating factor, NEDA: no evidence of disease activity.

Clinical Biomarkers

Disability does not develop in some clinical and radiologic MS cases and these phenomena are known as 'benign MS'. Although benign MS contains different definitions, it is commonly defined as "Expanded Disability Status Scale (EDSS) values being below 2 or 3 within 10-15 years". In a study that questioned the characteristics of patients with benign MS, 307 patients were followed prospectively for 15 years and it was seen that patients with benign MS included those with complete remission of the onset attack, low or moderate

initial relapse frequency, and dominating afferent symptoms (8). In another study, benign MS was defined as having EDSS values below 2 and 3 separately for 10-year disease duration and 19.8% to 33.3% among 6258 patients were characterized as having benign MS. Positive prognostic factors at baseline included female sex and younger age at onset, and disease-modifying treatment and longer disease duration were found to be positive predictors at the end of 4th year (9). In another study with long-term follow-up, the benign MS definitions of the previous study were used, female sex and the presence of fully recovering attacks with a low number of attacks indicated favorable outcome at the 20th and 30th years and 30th year, respectively. In this study, the number of cases in the 10th, 20th, and 30th year groups decreased by half every 10 years, and the benign characteristics of the patients disappeared (10). This result shows that patients with benign MS with better outcomes have a long-term risk of developing disability.

A meta-analysis of placebo-controlled, randomized trials of disease-modifying treatments in patients with relapsing MS has shown that disease-modifying treatment reduces the frequency and severity of relapses and slows down disability, independently of the route of administration and their classification as first or second-line therapies (11). It was questioned in a study whether there was any difference in clinical course and disability development before and after the disease-modifying treatment period. The time to reach an EDSS value of 6 during the period between 1980 and 2013 was examined with 5-year intervals, and it was shown that the course had changed after 2000 and the time to EDSS increase had extended. For example, the proportion of patients who reached EDSS 6 at the age of 50 years before 2000 was 27%, whereas it was significantly lower (15%) after 2000. Decreased age of diagnosis due to changing disease definitions, shortening of the delay period in taking the treatment, and the emergence of more effective treatments were emphasized among the reasons for this change, and treatment has been shown to postpone the increase in EDSS (12). The effect of time to initiate treatment on disability was questioned in relapsing MS and it was shown that the initiation of treatment before 3 years from MS onset had a significant decreasing effect on disability (13). The study was conducted with 639 patients for 8 years, and development of early disability and late age at onset were other prognostic factors. In another study in which 512 patients receiving disease-modifying treatment were followed for 17 years, both the duration of disability development and the time of secondary progression were found to be longer than those of natural history studies, which was attributed to the treatment affect (14). During the 17-year follow-up period, 36-50% of the cases were expected to have secondary progressive MS (SPMS), but only 11.3% had progressed to SPMS.

When the role of paroxysmal symptoms (lasting seconds to minutes and occurring many times a day) and unusual cortical findings (aphasia or epileptic seizures) as initial manifestations of MS was examined in a cohort of 512 patients with relapsing onset MS who were followed up for a mean period of 12 years, it was shown to be similar to classic symptoms and findings in terms of conversion rates to MS and causing disability, thus not being benign as it is supposed to be (15).

In a study investigating clinical prognostic factors affecting EDSS elevation, it was found that male sex, being of African descent, non-recovery after the first relapse, two or more relapses during the first year, a short interval between initial relapses, initial polysymptomatic presentation of pyramidal and cerebellar dysfunction and no treatment prior to reaching EDSS 3 were factors associated with EDSS increase (16). The incidence of MS is low among those with African ancestry, but the EDSS increase is early and the clinical course is worse (17).

The age of onset of illness is an important variable in disability worsening. When the relationship between MS disease type, patient age, and disability was examined, it was revealed that disability in progressive MS [SPMS, primary progressive MS (PPMS)] was related to age independently of previous disease activity or disease duration (18). The EDSS increase in patients with an onset age of 50 years or less was shorter than that in those aged less than 50 years, independent of disease course (19). In addition to the age variable, MS duration, baseline brain volume, EDSS score, and T2 disease burden were investigated in another study; higher baseline brain volume and receiving treatment predicted better long-term clinical outcomes, and higher baseline and greater early increase in EDSS score predicted worse outcomes (20). When the importance of the age of onset, cortical lesion volume, and cerebellar cortical volume variables in patients with relapsing-remitting MS (RRMS) were questioned at the time of entry into the study, the model correctly identified 94% of patients who maintained the relapsing-remitting course and 88% patients who became secondary progressive at the end of 5 years (21). The period of transition to a secondary progressive course was observed to be shortened in the presence of male sex, onset after the age of 30 years, and 3 or more relapses in the early period. It was observed that patients reaching EDSS 8 from onset of progression had 3 or more relapses, and had cerebellar and brainstem symptoms during relapses (22). The effect of smoking on the development of secondary progression was investigated with the age of onset of progression, and reaching SP disease was found to be at 48 years in patients who continued to smoke and 56 years of age in patients who quit smoking. Therefore, it was concluded that smoking worsens the course of the disease (23).

Relapse frequency is an indication of disease activity and also a risk factor for an increase in disability. It is one of the treatment targets. In addition to the frequency of relapses, the domain affected by the relapse is also important in the increase in disability. It has been shown that relapses in pyramidal, cerebellar, and bowel/bladder systems lead to higher EDSS increases compared with relapses with brainstem, visual, sensory, and cerebral involvement (24). In pediatric MS, the use of disease-modifying treatment and age of onset under the age of 15 years were factors that decreased the risk of EDSS increase, and relapses increased the risk. It has been reported that relapses with multifocal or isolated spinal cord or optic nerve involvement during follow-up had a higher incidence of EDSS-worsening compared with relapses with isolated supratentorial or brainstem syndrome (25).

Cognitive impairment is a condition observed during the course of MS. There is a relationship between age and cognitive impairment, as well as a relationship between long duration of illness and high EDSS values and cognitive impairment. This relationship also occurs independently of disease subtypes. Cognitive impairment was observed in 35% of patients with clinical isolated syndrome (CIS), 45% of patients with RRMS,

80% of patients with SPMS, and 91% of patients with PPMS (26). In a meta-analysis study, there were differences in the subfunctions of cognitive impairment observed in patients with RRMS and PPMS. In patients with SPMS, processing speed, and verbal learning and memory were shown to be worse than in those with RRMS. Patients with RRMS had more deterioration in working memory, cognitive fluency, and higher executive functions, and it was emphasized that both groups needed more specialized disease management (27).

When the importance of cognitive status at the onset of disease was investigated in a retrospective series of 78 patients for 8 years, early cognitive impairment was predictive of conversion to definite MS, disability increase, transition to the secondary progressive phase, and cortical thinning (28). Despite a decrease in the frequency of relapses, no difference in progression in the meta-analysis of patients with SPMS treated with interferon-beta (IFN-β) was interpreted as that the anti-inflammatory effect of IFN-β was unable to prevent MS progression (29). In a study with natalizumab, inflammatory activity was defined by the Rio score. According to the Rio score, ≤4 new T2 lesions on magnetic resonance imaging (MRI) was scored as 0 points, >4 new T2 lesions on MRI as 1 point, no relapses as 0 points, 1 relapse as 1 point, and ≥2 relapses as 2 points. This scoring was predictive of short-term (1-2 years) EDSS progression, but did not predict longer term (3-7 years) EDSS progression (30). In patients treated with natalizumab, those receiving treatment aged over 50 years were found to be less responsive to treatment patients aged under 50 years (31).

In patients with MS, disease-modifying treatment may be interrupted or discontinued. It can be discontinued due to compulsory reasons such as treatment adverse effects, pregnancy, as well as due to personal preferences such as planning to have a baby, or stable disease course. Patients who discontinued glatiramer acetate and IFN therapy due to similar reasons were retrospectively investigated, and age >45 years at discontinuation, absence of relapses for ≥4 years, and absence of contrast enhancing lesions were found to be independent predictors of absence of relapse after discontinuation. It has also been shown that demographic and clinical data can be predicted well without MRI data. The predictors of EDSS increase after discontinuation of therapy were high EDSS scores, age over 45 years, and long disease duration (32).

The relationship between somatosensory evoked potentials (SEP) and motor evoked potentials (MEP) scores, which are evoked potential examinations, and EDSS values was examined in a cross-sectional study, and found to be related (33). SEP and MEP scores explained 58% of EDSS variability. Consecutive studies have shown that the relationship between EDSS scores and evoked potentials persisted at ten years and up to 15 years after disease onset. This suggests that the EDSS increase may be predicted by the early stage increased evoked potential scores (34). MEP and visual evoked potential data together with age and treatment status were able to predict 58% of EDSS variability at 20 years (35). Neither baseline EDSS nor T2-lesion or gadolinium-enhancing lesion quantities improved the prediction of EDSS.

The relationship between retinal nerve fiber layer thickness measurement by optical coherence tomography and EDSS was evaluated in a 5-year retrospective study, and thickness less than or equal to 87 µm or less than or equal to 88 µm was shown to have a risk of increased EDSS in patients with all other disease variables under control (36).

Radiologic Biomarkers

In a review study examining the effectiveness of first-line treatment, it was investigated whether early-onset MRI parameters could predict clinical response and EDSS increase between 2-5. years. New or enlarging T2-weighted lesions ≥1, new or enlarging T2-weighted lesions ≥2, and Rio score ≥2 were used as criteria. As a result, it was observed that all criteria had a limited predictive value and that more sensitive measures of treatment failure at short term were needed (37).

Upper cervical cord area on MRI has been as reduced in CIS and RRMS, and negatively correlated with muscular weakness and fatigability. The atrophy change rate was higher in the upper cervical cord area compared with white matter and gray matter, and this might have potential value (38). It has been shown that spinal cord lesion number, change in cord lesion number in 5 years, and change in upper cervical cord area in patients with CIS with no spinal involvement were associated with EDSS, and that asymptomatic spinal cord lesions contribute to the development of disability over the first 5 years (39). Regarding the absence of lesions, the presence of at least 1 lesion in the spinal cord was predictive of reaching EDSS 4 (40).

Involvement of cerebellar gray matter is associated with disability scores, independent of cerebral gray matter involvement. Disability scores are EDSS, cerebellar functional system score, and arm and leg functions. In addition, patients with a high burden of cerebellar leukocortical lesions had lower paced auditory serial addition test (PASAT) scores, whereas patients with greater volumes of cerebellar intracortical lesions had worse symbol digit modalities test scores (41). In a study aimed at detecting variables for prediction of disability outcomes using clinical and MRI parameters, T2 lesion number, T1 and T2 lesion volumes, corpus callosum, and thalamic fraction were the best predictors at baseline, and EDSS and its change, corpus callosum volume change and number of new or enlarging T2 lesions at 12 months were the best predictors. Based on 12-year follow-up data, a composite score was generated from a subset of the best predictors and it was shown that scores of ≥4 had greater specificity for predicting worsening compared with the individual predictors (42).

In a retrospective study, the relationship between baseline and first 2-years MRI imaging and EDSS scoring after 10 years was investigated, and it was seen that EDSS at 10 years could be predicted by whole brain and central atrophy, and T2-weighted lesion volume change (43).

In another study, MRI-based brain volume measurements were used to calculate observed and expected normalized brain volume based on age, sex, T2-lesion volume, and baseline EDSS. Low, normal, and high values were calculated, and the difference between observed and expected values was found; there was a relationship between baseline brain volume and 2-4-years disability development (44). The brain volume loss rate in the first 2 years was similarly related to 2-4-years disability development (45). However, more time is needed for using in clinical practice, because brain volume measurements have not yet entered routine

practice and the method requires experience. When patients with RRMS in randomized controlled trials were examined by meta-analysis, it was found that the treatment effect on disability progression was independently correlated with brain atrophy and the presence of active MRI lesions (46).

In a group of 42 patients with MRI volume measurement and with a mean follow-up of 30 months, baseline thalamus, caudate, and putamen volumes predicted subsequent 25-ft walk test and MSFC, and as well as loss of volume in these structures (47). A broad review of MRI parameters has also been published recently (48).

Baseline cortical N-acetyl aspartate/creatine (NAA/Cr) and EDSS at month 24 and at the 7-year follow-up were correlated, whereas patients with EDSS ≥4 had a lower baseline cortical NAA/Cr (49).

In a study investigating black holes using 11C-PK11195 positron emission tomography, which shows microglial activity in progressive subjects, black holes were found not to be inactive, but surrounded by activated microglia and associated with disability (50).

Another method of study associated with MRI is to examine the default mode network with functional MRI. In one study, the network connections of the hippocampus region with other cortical-subcortical structures were questioned and reduced hippocampal-resting state functional connectivity was found to be associated with higher T2 lesion volume, longer disease duration, and the severity of depression and disability (51).

Immunologic Biomarkers

Human leukocyte antigen (HLA) is divided into major histocompatibility complex (MHC) class 1 (HLA A, B, C) and MHC class 2 (HLA-DR-DQ). In a study investigating the relationship between HLA genotype and MS prognosis, it was reported that HLA-A2 favored a better prognosis, HLA-B7 and B44 favored a poor prognosis, and HLA-DRB115, HLA-DQB16 and HLA-B8 alleles were inconclusive (52). In another study, HLA-DRB1*01 and DRB1*04 alleles were found to be associated with a worse prognosis when considering the time to reach an EDSS 6 (53). It was investigated whether variations in the myelin basic protein gene altered clinical course (conversion to MS and change in disability) in 127 persons who had had a first demyelinating event and followed up to the 5-years review, and rs12959006 was found to be associated with worse clinical outcomes. It was decisive for relapse and disability progression (54). In a study aimed at identifying loci bearing genetic risk associated with MS, there was a linear relationship between the upper cervical cord area, which is an MRI parameter, and 9 loci and an inverse relationship with 3 loci (55).

Conversion to MS in CIS can be interpreted as a poor prognostic criterion. Cerebrospinal fluid (CSF)-soluble CD27, a T cell activation marker, predicted the conversion to MS in patients with CIS and was also associated with a high relapse rate (56). In a study with a 14-year follow-up period, it was observed that, together with MRI parameters, chitinase-3-like-1 and age predicted conversion to MS. Chitinase-3-like-1 predicted long-term cognitive impairment 1 the PASAT test, and neurofilament light-chain (NfL) predicted long-term disability in the MS severity scale and nine-hole-Peg-test (57). In a study involving 813 patients with CIS, it was shown that CSF chitinase-3-like-1 was an independent risk factor for conversion to MS and reaching EDSS 3 (58). High CSF chitinase-3-like-1 was also associated with early conversion to MS and early development of disability. In a study involving patients with CIS and RRMS with a mean follow-up time of 11 years, glial fibrillary acidic protein and chitinase-3-like-1 were associated with conversion to MS and progression to EDSS 3, and chitinase-3-like-1 was associated with progression to EDSS 6 (59).

Vitamin D and MRI variables were examined during IFN treatment, and a 50 nmol/L (20 ng/mL) increment in average serum vitamin D levels within the first 12 months predicted a lower relapse rate (57%), lower rate of new active lesions on MRI (57%), lower yearly increase in T2 lesion volume (25%), lower yearly loss in brain volume (41%), and less disability (60).

In a cross-sectional study, there was a correlation between higher serum levels of interleukin (IL)-33, a member of the inflammatory IL family, IL-37, a member of the anti-inflammatory IL family, and a soluble form of vascular endothelial growth factor receptor 2 with disease severity according to EDSS (61). However, these parameters, which are high in other diseases with immunopathogenesis, are not specific for MS, thus drawing attention to the necessity of repeating the results and long-term follow-up. The relationship between serum energy metabolism biomarkers and disability, disease course, and MRI was examined, and serum lactate, creatinine, purines (hypoxanthine, xanthine, uric acid, inosine) and pyrimidines (uracil, beta-pseudouridine, uridine) were scored. Although there were different scores among patients with RRMS and progressive MS, there was a relationship with EDSS and MRI parameters (62).

CSF β-amyloid levels were reduced in patients compared with controls, lower CSF β-amyloid levels at baseline were a disability predictor at 3-year follow-up and CSF tau levels correlated with T2- and T1-lesion load on MRI (63). When CSF NfL at baseline in NEDA + (patients who showed no evidence of disease activity) and EDA + (patients who showed evidence of disease activity) patients with CIS and RRMS were compared with normal subjects, NEDA + patients were found to be similar to the normal group, and EDA + patients were different. NfL values predicted disease activity alone with 85% accuracy during 2 years of follow-up (64). CSF neurofilament heavy-chain (NfH) values were found to correlate with EDSS in a 17-year follow-up period, to reflect chronic axonal destruction (65), and also to estimate the amount of brain and spinal cord atrophy on MRI (66). Although it is stated that there is a relationship between CSF-serum values and that they can be used interchangeably, it should be remembered that NfH is not specific to MS (67). The occurrence of CSF oligoclonal bands (OCB) was found associated with an increase in gray matter lesions, high NfH ratio, and increased levels of pro-inflammatory mediators and several inflammatory mediators linked to B lymphocyte activity over a 10-year follow-up. It has also been shown that the occurrence of OCB was associated with physical and cognitive impairment (68), and that OCB- patients had a better prognosis and milder disability than OCB+ patients (69). However, the prognostic value of OCB remains unclear because some other studies have not shown a relationship (70). In a study investigating the value of the immunoglobulin (Ig) M index in patients with RRMS and SPMS, IgM index values, unlike

IgG index, were correlated with EDSS and MRI parameters, and were higher in patients with SPMS (71).

Neutralizing antibodies observed during biologic agent treatment can also be a countervailing factor in reducing treatment efficacy. Fourteen percent of patients had neutralizing antibody during IFN-β-1a/1b treatment; neutralizing antibodies lead to an increase of the relapse rate, decreased time to 1st relapse, and a negative trend in the time to reach the EDSS 4 milestone (72).

Conclusion

In addition to current treatments aimed at reducing the frequency and severity of relapses, as well as disability development, it is hoped that treatments providing regeneration and disability-free course will be added to clinical use. The most utopian point is preventive treatment, which can prevent disease formation before it starts. Until these goals are achieved, there is a need to recognize and use disease-related prognosis-disability biomarkers to demonstrate correct behavior at the right time.

In this study, the data obtained in the last 5 years were searched from the PubMed database using the keywords "multiple sclerosis", "disability", "prognosis OR prognostic" and "predictive OR prediction" and 1068 publications were found between 2012-2017. Of these, 295 were reached in full text and 33 different publications were also reviewed. Although the study reflects the recent data, it has limitations due to reasons such as the fact that data from previous years have been partially evaluated and only one database was scanned in the English language.

Ethics

Peer-review: Externally and internally peer-reviewed.

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