

Bölüm 24

MULTİPL SKLEROZ

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GİRİŞ

Multipl skleroz (MS) santral sinir sisteminin (SSS) en sık görülen kronik, inflamatuvar, demiyelinizan ve nörodejenaratif bir hastalıdır. Kompleks gen-çevre ilişkisinin neden olduğu heterojen ve multifaktoriyel immun aracılı mekanizmalar sonucu oluştuğu düşünülmektedir. Hastalığın kesin nedeni hala bilinmemektedir. MS'in patolojik özelliği beyin ve spinal kord beyaz ve gri cevherinde görülen demiyelizan lezyonların birikimidir. MS insidansı ve prevalansı gelişmiş ve gelişmekte olan ülkelerde giderek artmaktadır ve coğrafik bölgelere göre değişir. Genellikle genç erişkinleri (tipik olarak 20-40 yaşlar arasında) etkiler ve bu yaş grubunda en sık travmaya bağlı olmayan özüllülüğün nedenidir. Dünya çapında yaklaşık 2.5 milyon kişiyi etkiler ve sosyoekonomik yükü yüksektir. Buna bağlı erken tanı ve tedavisi önemlidir(1-6).

Epidemiyoloji

Prevalans ve insidans ülke ve coğrafik bölgelere göre çok değişir. Ekvatordan uzaklaştıkça insidans ve prevalans artar. Tropik bölgelerde nadirdir ve kuzey ve güney yarı kürede yükselen enlem ile birlikte (>40 derece) oranlar artar. MS prevalansı Avrupa, Kuzey Amerika, Kanada ve Avustralya'da yüksektir(7,8,9). Irklara göre farklılık gösterir. Avrupa kökenli irklarda daha sık, Asyalılar,

siyahlar, yerli Amerikalılar ve Maorilerde daha nadirdir(1). Ortalama prevalans tahminleri Asyada 100.000 kişide 2, Avrupada 1000 kişide 1 ve yüksek enlem bölgesinde bazı ülkelerde prevalans 400'de 1'dir(1,6). Dünya çapında ortalama tahmini insidansı 100.000 kişi-yılına başına 5.2 (0,5-20,6), prevalansı 112.0(her 100.000 kişi için 5.2-.235 aralığında) ve ortalama hastalık süresi 20.2(7.6-36.2 yıl) olarak saptanmıştır(7,8,9).

Kadın cinsiyet hakimiyeti vardır ve erkeklerden üç kat kadar fazladır. Bu oran hastalığın progresif başlangıçlı formunda daha düşüktür. Yükselen enlem ile K/E oranı artmaktadır. MS'de K/E oranı 1900 yıllarının başında eşit iken, giderek arttığı görülmektedir. Kadın hakimiyeti prevalansın artmasına bağlanabilir. Bununla birlikte, özellikle kadınları etkilen çevresel risk faktörlerinde(örn; meslek, artan sigara içme, obezite, doğum kontrolü ve doğum) artışın olası bir rolü olduğu ileri sürülmektedir(1,6,10). En en sık 20-40 yaşları arasında görülür ve insidans 30 yaşında, prevalans 50 yaşında pik yapar. %10 kadar hastada 18 yaşından önce başlar. Çocukluk çağında ve 60 yaş sonrasında gelişebilir Çocukluk ve ergenliğin, tetikleyici faktörlere karşı kritik bir duyarlılık dönemi olduğu düşünülmektedir. %50' den fazlasında ölüm nedeni hastalık semptomlarıdır. Ölüm nedeni olarak enfeksiyonlar ve özkıyımın önemli ölçüde artığı görülür. Tahmini yaşam süresi 7-14

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oidler ve BTA, kannaboidlerin kullanımları için güvenli kanıtlar yoktur(183,224). Bağırsak fonksiyon bozukluğu hastalarının %50'sinden fazlasında görülür. Kabızlık en sıktır, ancak sık çıkma, sızıntı ve inkontinans meydana gelebilir. Bağırsak semptomlarının tedavisi büyük ölçüde empiriktir. Cinsel işlev bozukluğu, hastalık sırasında MS'li hastaların% 90'ına kadarını etkiler. Erkekler öncelikle erektil disfonksiyon ve ejakülatör bozuklukları görülür. Kadınlarda en yaygın semptomlar anorgasmi ve azaltılmış libidodur. Hem erkeklerde hem de kadınlarda cinsel işlevi iyileştirmek için konservatif yöntemler önerilir(88,183,186).

Sonuç

MS halen etiyopatogenezi tam olarak bilinmeyen, özellikle gençleri etkileyen, özürüllüğe yol açan ve yaşam kalitesini önemli ölçüde etkileyen bir hastalıktır. Hastalık süreci süreklilik gösterir ve dinamiktir. Bu yüzden hastalığın erken tanısı, erken tedavisi ve yakından izlenmesi önemlidir.

KAYNAKLAR

- Filippi M, Bar-Or A, Piehl F, et al. Multiple Sclerosis. *Nat Rev Dis Primers*. 2018;8;4(1):43. doi: 10.1038/s41572-018-0041-4.
- Dobson R, Giovannoni G. Multiple Sclerosis-a review. *Eur J Neurol*. 2019 ;26(1):27-40. doi: 10.1111/ene.13819.
- Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. *N Engl J Med*. 2018;11;378(2) :169-180. doi: 10.1056/NEJMra1401483.
- Lassmann H. Pathogenic Mechanisms Associated With Different Clinical Courses of Multiple Sclerosis. *Front Immunol*. 2019;10;9:3116. doi:10.3389/fimmu.2018.03116.
- Ömerhoca S, Yazici Akkaş S, Kale İcen N. Multiple Sclerosis: Diagnosis and Differential Diagnosis. *Noro Psikiyatr Ars*. 2018;55(1);1-9.doi: 10.29399/npa.23418.
- Hunter SF, Overview and Diagnosis of Multiple Sclerosis. *Am J Manag Care*. 2016; 22: 141-150
- Eskandarieha S, Heydarpoura P, Minagarc A, et al. Multiple Sclerosis Epidemiology in East Asia, South East Asia and South Asia: A Systematic Review. *Neuroepidemiology* 2016; 46:209–221 doi:10.1159/000444019.
- Bowne P, Chandraratna D, Angood C, et al: Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. *Neurology* 2014;83:1022–1024.
- Evans C, Beland SG, Kulaga S, et al: Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. *Neuroepidemiology* 2013;40:195–210.
- Cotsapas C, Mitrovic M. Genome-wide association studies of multiple sclerosis. *Clinical& Translational Immunology*. 2018;7:e1018.doi:10.1002/cti2.1018
- Scalfari A, Knappertz V, Cutter G, et al. Mortality in patients with multiple sclerosis. *Neurology*. 2013;9;81(2):184-192. doi:10.1212/WNL.0b013e31829a33 88.
- Kingwell E, van der Kop M, Zhao Y, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. *J. Neurol. Neurosurg. Psychiatry* .2011; 83, 61–66 (2012). doi: 10.1136/jnnp-2011-300616.
- Lunde HMB, Assmus J, Myhr K.M, et al. Survival and cause of death in multiplesclerosis: a 60-year longitudinal population study. *J. Neurol. Neurosurg. Psychiatry*. 2017;88,621–625. doi: 10.1136/jnnp-2016-315238.
- Harirchian MH, Fatehi F, Sarraf, P, et al. Worldwide prevalence of familial multiple sclerosis: a systematic review and meta- analysis. *Mult. Scler. Relat. Disord*. 2017;20, 4347. doi:10.1016/j.msard.2017.12.015.
- Compston, A. & Coles, A. Multiple sclerosis. *Lancet* 2002;359(9313) 1221–1231 (2002) .doi:10.1016/S0140-6736(02)08220-X
- Baecher-Allan C, Kaskow BJ, Weiner HL. Multiple Sclerosis: Mechanisms and Immuno therapy. *Neuron*.2018;21;97(4):742-768.doi:10.1016/j.neuron.2018.01.021.
- Baranzini SE, Oksenberg JR. The genetics of multiple sclerosis: from 0 to 200 in 50 years. *Trends.Genet*.2017;33(12),960–970.doi:10.1016/j.tig.2017.09.00
- Lazibat I, Rubinić-Majdak M, Županić S, Multiple Sclerosis: New Aspects of Immuno pathogenesis. *Acta Clin Croat*. 2018;57(2):352-361. doi:10.20471/acc.2018.57.02.17.
- Hedström AK, Sundqvist E, Bäärnhielm M, et al. Smoking and two human leukocyte antigen genes interact to increase the risk for multiple sclerosis. *Brain*. 2011;134 (3):653-64.doi:10.1093/brain/awq37 1.8.
- Sundqvist E, Sundström P, Lindén M, et al. Epstein-Barr virus and multiple sclerosis: interaction with HLA. *Genes Immun*. 2012;13,14–20. doi:10.1038 /gene. 2011.42.
- Nardin C, Latache C, Soudant M, et al. Generational changes in multiple sclerosis phenotype in North African immigrants in France: A population-based observational study. *PLoSOne*.2018;13(3):e019415.doi:10.1371/journal.pone.0194115.
- Pierrot-Deseilligny, Souberbielle J-C. Is hypovitaminosis D one of the environmental risk factors for multiple sclerosis? *Brain* 2010; 133; 1869-1888. doi: 10.1093/brain/awq147.
- Balbuena LD, Middleton RM, Tuite-Dalton, K et al. Sunshine, Sea, and Season of Birth:MS Incidence in Wales. *PLoS One*. 2016;16;11(5): e01 55181. doi:10.1371/journal.pone.0155181.
- Orton S-M, Wald L, Confavreux C, et al. Association of UV radiation with multiple sclerosis prevalence and sex ratio in France. *Neurology*. 2011;1; 76(5): 425–431. doi: 10.1212 /WNL.0b013e31820a0a9f.
- Tarlinton R, Khaibullin T, Granatov E, et al. The Interaction between Viral and Environmental Risk Factors in the Pathogenesis of Multiple Sclerosis. *Int J Mol Sci*. 2019; 14;20(2). pii: E303. doi: 10.3390/ijms20020303.
- Dobson R, Giovannoni G, Ramagopalan S. The month of birth effect in multiple sclerosis: Systematic review, me-

- ta-analysis and effect of latitude. *J. Neurol. Neurosurg. Psychiatry* 2013;84;427-432. doi:10.1136/jnnp-2012-303934.
27. Willer CJ, Dyment DA, Sadovnick AD, et al. Timing of birth and risk of multiple sclerosis: Population based study. *BMJ* 2005;330;120. doi:https/ 10.1136/bmj.38301.686030.63.
 28. Torkildsen OI, Grytten N, Aarseth J, et al. Month of birth as a risk factor for multiple sclerosis: an update. *Acta Neurol Scand Suppl.* 2012;(195):58-62. doi: 10.1111/ane.12040.
 29. McKay KA, Kwan V, Duggan T, et al. Risk Factors Associated with the Onset of Relapsing-Remitting and Primary Progressive Multiple Sclerosis: A Systematic Review. *Biomed Res Int.* 2015;2015:817238. doi:10.1155/2015/817238.
 30. Bartosik-Psujek H, Psujek M. Vitamin D as an immune modulator in multiple sclerosis. *NeurolNeurochirPol.* 2019;53(2):113-122. doi:10.5603/PJNNS.a2019.0015.
 31. RuniaTF, Hop WCJ, de Rijke YB, et al. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. *Neurology* 2012;79:261-6. doi: 10.1212/WNL.0b013e31825fdec7.
 32. Mowry EM, Krupp LB, Milazzo M, et al. Vitamin D status is associated with relapse rate in pediatric-onset multiple sclerosis. *Ann Neurol* 2010; 67:618-624. doi: 10.1002/ana.21972.
 33. Sistani SS, Moghtaderi A, Dashipoor AR, et al. Seasonal variations of 25-OH vitamin D serum levels in Multiple Sclerosis patients with relapse using MRI. *Eur J Transl Myol.* 2019 2;29(3):8361.
 34. Simpson S, Blizzard L, Otahal P, et al. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. *J Neurol Neurosurg Psychiatry* 2011;82:1132-41.
 35. Wawrzyniak S, Emilia Mikołajewska E, Kuczko-Piekarska E, Association of vitamin D status and clinical and radiological outcomes in a treated MS population in Poland. *Brain Behav.*2017;7(2):e00609. doi:10.1002/brb3.609.
 36. Fitzgerald KC1, Munger KL, Köchert K, Arnason BG, et al. Association of Vitamin D Levels With Multiple Sclerosis Activity and Progression in Patients Receiving Interferon Beta-1b. *JAMA Neurol.*2015;72(12):1458-65. doi:10.1001/jamaneurol.2015.274
 37. Martinelli V, Dalla Costa G, Colombo B, et al. Vitamin D levels and risk of multiple sclerosis in patients with clinically isolated syndromes. *Mult Scler.* 2014;20:147-55. doi: 10.1177/1352458513494959.
 38. Muris AH1, Rolf L2, Broen K3, et al. A low vitamin D status at diagnosis is associated with an early conversion to secondary progressive multiple sclerosis. *J Steroid Biochem Mol Biol.* 2016 Nov;164:254-257. doi: 10.1016/j.jsbmb.2015.11.009.
 39. Ascherio A, Munger KL, White R, Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA Neurol.* 2014;71(3):306-14. doi:10.1001/jama-neurol.2013.5993.
 40. Rhead B, Bäärnhielm M, Gianfrancesco M, et al. Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk. *Neurol Genet.* 2016;13;2(5):e97. doi: 10.1212/NXG.0000000000000097.
 41. Agnello L, Scazzone C, Lo Sasso B, et al. CYP27A1, CYP24A1, and RXR-α Polymorphisms, Vitamin D, and Multiple Sclerosis: a Pilot Study. *J Mol Neurosci.* 2018; 66(1):77-84. doi:10.1007/s12031-018-1152-9.
 42. Karaky M, Alcina A, Fedetz M, et al. The multiple sclerosis-associated regulatory variant rs10877013 affects expression of CYP27B1 and VDR under inflammatory or vitamin D stimuli. *Mult Scler.* 2016;22(8):999-1006. doi: 10.1177/1352458515610208.
 43. Munger KL, Levin LI, Hollis BW, ET AL. Serum 25-Hydroxyvitamin D Levels and Risk of Multiple Sclerosis. *JAMA.* 2006;296(23):2832-2838. doi: 10.1001/jama.296.23.2832.
 44. Pender MP, Burrows SR, Epstein-Barr virus and multiple sclerosis: potential opportunities for immunotherapy. *Clin Transl Immunology.* 2014 Oct 31;3(10):e27. doi: 10.1038/cti.2014.25.
 45. Michel L. Environmental factors in the development of multiple sclerosis. *Rev Neurol(Paris).*2018;174(6):372-377. doi:10.1016/j.neurol.2018.03.010.
 46. Levin LI, Munger KL, O'Reilly EJ, et al. Primary infection with the Epstein-Barr virus and risk of multiple sclerosis. *Ann Neurol.* 2010 Jun;67(6):824-30. doi:10.1002/ana.21978.
 47. Burnard S1, Lechner-Scott J2, Scott RJ3. EBV and MS: Major cause, minor contribution or red-herring? *Mult Scler Relat Disord.* 2017 ;16:24-30. doi:10.1016/j.msard.2017.06.002.
 48. Huitema MJD, Guerrero-García JJ, Carrera-Quintanar L, et al. Multiple Sclerosis and Obesity: Possible Roles of Adipokines. *Mediators Inflamm.*2016;4036232. doi:10.1155/2016/4036232.
 49. Schenk GJ2. Insights into the Mechanisms That May Clarify Obesity as a Risk Factor for Multiple Sclerosis. *Curr Neurol Neurosci Rep.* 2018;10;8(4):18. doi:10.1007/s11910-018-0827-5.
 50. Nourbakhsh B, Mowry EM. Multiple Sclerosis Risk Factors and Pathogenesis. *Continuum(-Minneapolis).*2019;25(3):596-610. doi:10.1212/CON.0000000000000725
 51. Wang Z, Xie J, Wu C, Correlation Between Smoking and Passive Smoking with Multiple Sclerosis and the Underlying Molecular Mechanisms. *Med Sci Monit.* 2019;31;25:893-902. doi:10.12659/MSM.912863.
 52. Alfredsson L, Olsson T. Lifestyle and Environmental Factors in Multiple Sclerosis. *Cold Spring Harb Perspect Med.* 2019 Apr 1;9(4). pii:a028944. doi: 10.1101/cshperspect.a028944.
 53. Farez MF, Fiol MP, Gaitán MI, et al. Sodium intake is associated with increased disease activity in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2015 Jan;86(1):26-31. doi: 10.1136/jnnp-2014-307928.
 54. Bhise V, Dhib-Jalbut S. Further understanding of the immunopathology of multiple sclerosis: impact on future treatments. *Expert Rev Clin Immunol.* 2016 Oct;12(10):1069-89. doi:10.1080/1744666X.2016.1191351.
 55. Yadav SK, Mindur JE, Ito K, Advances in the immunopathogenesis of multiple sclerosis. *CurrO-*

- pinNeurol.2015Jun;28(3):206-19.doi:10.1097/WCO.0000000000000205.
56. Zéphir H. Progress in understanding the pathophysiology of multiple sclerosis. *Rev Neurol (Paris)*. 2018 Jun;174(6):358-363. doi:10.1016/j.neurol.2018.03.006
 57. Hartung HP, Aktas O, Menge T, et al. *Handbook of Clinical Neurology, Vol. 122 (3rd series) Multiple Sclerosis and Related Disorders*. D.S. Goodin, Editor© 2014 Elsevier B.V.
 58. Pröbstel AK, Hauser SL. Multiple Sclerosis: B cells Take Center Stage. *J Neuro ophthalmol*. 2018 June;38(2):251-258. doi:10.1097/WNO.0000000000000642.
 59. Häusser-Kinzel S, Martin Weber MS. The Role of B Cells and Antibodies in Multiple Sclerosis, Neuromyelitis Optica, and Related Disorders. *Front Immunol*. 2019;10,201. doi: 10.3389/fimmu.2019.00201.
 60. Ortiz GG, Pacheco-Moisés FP, Macías-Islas MÁ, et al. Role of the blood-brain barrier in multiple sclerosis. *Arch Med Res*. 2014;45(8):687-97. doi:10.1016/j.arcmed.2014.11.013.
 61. Yadav SK, Mindur JE, Ito K, et al. Advances in the immunopathogenesis of multiple sclerosis. *Curr Opin Neurol*. 2015 Jun;28(3):206-19. doi:10.1097/WCO.0000000000000205.
 62. Lassmann H. Multiple Sclerosis Pathology. January 2018 Cold Spring Harbor Perspectives in Medicine 8(3):a028936 doi:10.1101/cshperspect.a028936.
 63. Correale J, Marrodan M, Ysraelit MC. Mechanisms of Neurodegeneration and Axonal Dysfunction in Progressive Multiple Sclerosis. *Biomedicines*. 2019 Feb 20;7(1). pii: E14. doi: 10.3390/biomedicines7010014.
 64. Ohno N, Ikenaka K. Axonal and neuronal degeneration in myelin diseases *Neurosci Res*. 2019;139:48-57. doi:10.1016/j.neures.2018.08.013.
 65. Faissner S, Plemel JR, Gold R, et al. Progressive multiple sclerosis: from patho physiology to therapeutic strategies. *Nat Rev Drug Discov*. 2019 Dec;18(12):905-922. doi:10.1038/s41573-019-0035-2.
 66. Ontaneda D, Thompson AJ, Fox RJ, et al. Progressive multiple sclerosis: prospects for disease therapy, repair, and restoration of function. *Lancet*. 2017;1;389(10076):1357-1366. doi:10.1016/S0140-6736(16)31320-4.
 67. Howell OW, Reeves CA, Nicholas R, et al. Meningeal inflammation is widespread and linked to cortical pathology in multiple sclerosis. *Brain*. 2011;134(9):2755-71. doi: 10.1093/brain/awr182.
 68. Matthews PM. Chronic inflammation in multiple sclerosis - seeing what was always there. *Nat Rev Neurol*. 2019 Oct;15(10):582-593. doi: 10.1038/s41582-019-0240-y.
 69. Bo L, Vedeler CA, Nyland HI. Subpial demyelination in the cerebral cortex of multiple sclerosis patients. *J Neuropathol Exp Neurol*. 2003;62(7):723-32. doi: 10.1093/jnen/62.7.723.
 70. Howell OW, Reeves CA, Nicholas R, et al. Meningeal inflammation is wide spread and linked to cortical pathology in multiple sclerosis. *Brain*. 2011;134(9):2755-71. doi:10.1093/brain/awr182.
 71. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. *Brain* 2009; 132(5): 1175-1189. doi:10.1093/brain/awp07.
 72. Dekker I, Wattjes MP. Brain and Spinal Cord MR Imaging Features in Multiple Sclerosis and Variants. *Neuroimaging Clin N Am* 2017; 27(2), 205-227. doi:10.1016/j.nic.2016.12.002.
 73. Rosenthal JF, Hoffman BM, Tyor WR. CNS inflammatory demyelinating disorders: MS, NMOSD and MOG antibody associated disease. *J Investig Med*. 2019 Oct 3. pii: jim-2019-001126. doi:10.1136/jim-2019-001126.
 74. Kale N. Optic neuritis as an early sign of multiple sclerosis. *Eye Brain*. 2016 Oct 26;8:195-202. doi:10.2147/EB.S54131.
 75. Abel A, Mc Clelland C, Lee MS. Critical review: Typical and atypical optic neuritis. *Surv Ophthalmol*. 2019;64(6):770-779. doi:10.1016/j.survophthal.2019.06.001.
 76. Sand IK. Classification, diagnosis, and differential diagnosis of multiple sclerosis. *Curr Opin Neurol* 2015;28:193-205. doi:10.1097/WCO.0000000000000206
 77. Nerrant E, Tilikete C. Ocular Motor Manifestations of Multiple Sclerosis. *J Neuro ophthalmol*. 2017;37(3):332-340. doi:10.1097/WNO.0000000000000507.
 78. Triplett JD, Buzzard KA, Lubomski M, et al. Immune-mediated conditions affecting the brain, eye and ear (BEE syndromes). *J Neurol Neurosurg Psychiatry* 2019;0:1-13. doi:10.1136/jnnp-2018-319002.
 79. Di Stadio A, Dipietro L, Ralli M, et al. Sudden hearing loss as an early detector of multiple sclerosis: a systematic review. *Eur Rev Med Pharmacol Sci*. 2018 ;22(14):4611-4624. doi:10.26355/eurrev-201807-15520.
 80. Teoli D, Rocha Cabrero F, Ghassemzadeh S. Lhermitte Sign. *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2019-.2019 Jul 31.
 81. Filingeri D, Chaseling G, Hoang P, et al. Afferent thermosensory function in relapsing-remitting multiple sclerosis following exercise-induced increases in body temperature. *Exp Physiol* 102.8(2017)pp887-893. doi:10.1113/EP086320.
 82. Davis SL, Jay O, Wilson TE. Thermoregulatory dysfunction in multiple sclerosis. *Handb Clin Neurol*. 2018;157:701-714. doi: 10.1016/B978-0-444-64074-1.00042-2.
 83. Jain A, Rosso M, Santoro JD. Wilhelm Uhthoff and Uhthoff's phenomenon. *Mult Scler*. 2019;17:1352458519881950. doi:10.1177/1352458519881950.
 84. Boonstra FMC, Noffs G, Perera T, et al. Functional neuroplasticity in response to cerebello-thalamic injury underpins the clinical presentation of tremor in Multiple Sclerosis. *Mult Scler*, 1352458519837706 2019 Mar 25 [Online ahead of print]. doi:10.1177/1352458519837706
 85. Mehanna R, Jankovic J. Movement disorders in multiple sclerosis and other demyelinating diseases. *J Neurol Sci*. 2013;15;328(1-2):1-8. doi:10.1016/j.jns.2013.02.007.
 86. Abboud H, Yu XX, Knusel K, et al. Movement disorders in early MS and related diseases: A prospective observational study. *Neurol Clin Pract*. 2019;9(1):24-31. doi: 10.1212/CPJ.0000000000000560.
 87. Candeias da Silva C, Bichuetti DB1, Azevedo Silva SMC, et al. Movement disorders in multiple sclerosis and neuromyelitis optica: A clinical marker of neurological disability. *Parkinsonism Relat Disord*. 2018;51:73-78.

- doi:10.1016/j.parkreldis.2018.03.001.
88. Shah P. Symptomatic management in multiple sclerosis. *Ann Indian Acad Neurol.* 2015 Sep; 18(1 1): 35–42. doi: 10.4103/0972-2327.164827 .
 89. Lublin F. New multiple sclerosis phenotypic classification. *Eur Neurol.* 2014; 72(1:1-5). doi: 10.1159/000367614.
 90. Oh J, Vidal-Jordana A, Montalban X. Multiple sclerosis: clinical aspects. *Curr Opin Neurol.*2018;31(6):752-759. doi: 10.1097/WCO.0000000000000622.
 91. Okuda DT, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. *Neurology* 2009;72(9): 800–5. doi: 10.1212/01.wnl.0000335764.14513.1
 92. Lebrun C, Kantarci OH, Siva A, et al; RISConsortium. Anomalies Characteristic of Central Nervous System Demyelination: Radiologically Isolated Syndrome. *Neurol Clin.* 2018 Feb;36(1):59-68. doi:10.1016/j.ncl.2017.08.004.
 93. Forslin Y, Granberg T, Antwan Jumah A, et al. Incidence of Radiologically Isolated Syndrome: A Population-Based Study. *AJNR*2016;37(6)1017-1022; doi:10.3174/ajnr.A4660.
 94. Yamout B, Khawajah MA. Radiologically isolated syndrome and multiple sclerosis. *Mult Scler Relat Disord.* 2017;17:234-237. doi:10.1016/j.msard.2017.08.016.
 95. Tornatore C, Phillips JT, Khan O, et al. Practice patterns of US neurologists in patients with CIS, RRMS, or RIS: a consensus study. *Neurol Clin Pract* 2014;2:48–57. doi:10.1212/CPJ.0b013e31824cb09b.
 96. Thouvenot É. Update on clinically isolated syndrome. *Presse Med.* 2015;44(4 Pt 2):e121-36.doi:10.1016/j.lpm.2015.03.002.
 97. Miller DH1, Weinshenker BG, Filippi M, Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Mult Scler.* 2008;14(9):1157-74. doi:10.1177/1352458508096878.
 98. Klineova S, Lublin FD. Clinical Course of Multiple Sclerosis. *Cold Spring Harb Perspect Med.* 2018;4:8(9). pii: a028928. doi:10.1101/cshperspect.a028928.
 99. Beck RW1, Trobe JD, Moke PS, High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. *Arch Ophthalmol.* 2003;121(7):944-9.
 100. Ramsaransing GS, De Keyser J. Predictive value of clinical characteristics for ‘benign’ multiple sclerosis. *Eur J Neurol.* 2007;14(8):885-9. doi:10.1111/j.1468-1331.2007.01810.x.
 101. Sartori A, Abdoli M, Freedman MS, Can we predict benign multiple sclerosis? Results of a 20-year long-term follow-up study. *J Neurol.* 2017;264(6): 1068-1075. doi:10.1007/s00415-017-8487-y.
 102. Pittock S, Mayr W, McClelland R, et al. Change in MS-related disability in a population-based cohort: a 10-year follow-up study. *Neurology* 2004;62:51–9. doi: 10.1212/01.wnl.0000101724.93433.00.
 103. Reynders T, D’haeseleer M, De Keyser J, Definition, prevalence and predictive factors of benign multiple sclerosis. *eNeurologicalSci.* 2017 May 13;7:37-43. doi:10.1016/j.ensci.2017.05.002.
 104. Sayao AL, Devonshire V, Tremlett H. Longitudinal follow-up of “benign” multiple sclerosis at 20 years. *Neurology.* 2007;13;68(7):496-500. doi:10.1212/01.wnl.0000253185.03943.66.
 105. Kalincik T. Multiple Sclerosis Relapses: Epidemiology, Outcomes and Management. A Systematic Review. *Neuroepidemiology.* 2015;44(4):199-214. doi:10.1159/000382
 106. Repovic P. Management of Multiple Sclerosis Relapses. *Continuum (Minneapolis Minn).* 2019 Jun;25(3):655-669. doi: 10.1212/CON.0000000000000739.
 - 107; Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of Multiple Sclerosis: 2017 Revisions of the McDonald Criteria. *Lancet Neurol.* 2018.17(2).162-173. doi:10.1016/S1474-4422(17)30470-2.
 108. Galea I, Ward-Abel N, Heesen C. Relapse in multiple sclerosis. *BMJ.* 2015;14;350: h1765. doi: 10.1136/bmj.h1765.
 109. Kamel FO. Factors Involved in Relapse of Multiple Sclerosis. *J Microsc Ultrastuct.* 2019;7(3):103-108. doi: 10.4103/JMAU.JMAU-59-18.
 110. D’Hooghe MB, Nagels G, Bissay V, et al. Modifiable factors influencing relapses and disability in multiple sclerosis. *Mult Scler* 2010;16:773-785. doi: 10.1177/1352458510367721.
 111. Inojosa H, Proschmann U, Akgün K, et al. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. *J Neurol.* 2019 Jul 30. doi: 10.1007/s00415-019-09489-5.
 112. Cree BAC, Hollenbach JA, Bove R, University of California, San Francisco MS-EPIC Team, et al. Silent progression in disease activity-free relapsing multiple sclerosis. *Ann Neurol.* 2019;85(5):653-666. doi:10.1002/ana.25463.
 113. Lorscheider J, Buzzard K2, Jokubaitis V1, et al. Defining secondary progressive multiple sclerosis. *Brain.* 2016;139(9):2395-405. doi:10.1093/brain/aww173.
 114. Nandoskar A, Raffel J, Scalfari AS, et al. Pharmacological Approaches to the Management of Secondary Progressive Multiple Sclerosis. *Drugs.* 2017;77(8): 885-910. doi:10.1007/s40265-017-0726-0.
 115. Kantarci OH. Phases and Phenotypes of Multiple Sclerosis. *Continuum (Minneapolis Minn).* 2019;25(3):636-654. doi:10.1212/CON.0000000000000737.
 116. Rovaris M, Confavreux C, Furlan R, et al. Secondary progressive multiple sclerosis: current knowledge and future challenges. *Lancet Neurol.* 2006;5(4):343-54. doi: 10.1016/S1474-4422(06)70410-0.
 117. Fambiatos A, Jokubaitis V, Horakova D, Risk of secondary progressive multiple sclerosis: A longitudinal study. *Mult Scler.* 2019 Aug 9:1352458519868990. doi:10.1177/1352458519868990.
 118. Plantone D, De Angelis F, Doshi A, et al. Secondary Progressive Multiple Sclerosis: Definition and Measurement. *CNS Drugs.* 2016;30(6):517-26. doi:10.1007/s40263-016-0340-9.
 119. Ontaneda D. Progressive Multiple Sclerosis. *Continuum (Minneapolis Minn).* 2019 ;25(3): 736-752. doi: 10.1212/CON.0000000000000727.
 120. Scalfari A, Neuhaus A, Daumer M, et al. Onset of secondary progressive phase and long-term evolution of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2014;85:67–75. doi:10.1136/jnnp-2012-304333.

121. Gajofatto A, Calabrese M, Benedetti MD, et al. Clinical, MRI, and CSF markers of disability progression in multiple sclerosis. *Dis Markers*. 2013;35(6):687-99. doi:10.1155/2013/484959.
122. Zeydan B, Kantarci OH. Progressive Forms of Multiple Sclerosis: Distinct Entity or Age-Dependent Phenomena. *Neurol Clin*. 2018;36(1):163-171. doi:10.1016/j.ncl.2017.08.006.
123. Lycke J, Zetterberg. The role of blood and CSF biomarkers in the evaluation of new treatments against multiple sclerosis. *Expert Rev Immunol*. 2017; 13(12): 1143-1153. doi: 10.1080/1744666X.2017.1400380.
124. Barro C, Leocani L, Leppert D, Fluid biomarker and electrophysiological outcome measures for progressive MS trials. *Mult Scler*. 2017;23(12):1600-1613. doi:10.1177/1352458517732844.
125. Katz Sand I, Krieger S, Farrell C, et al. Diagnostic uncertainty during the transition to secondary progressive multiple sclerosis. *Mult Scler*. 2014;20(12):1654-7. doi:10.1177/1352458514521517.
126. Sastre-Garriga J, Pareto D, Rovira À. Brain Atrophy in Multiple Sclerosis: Clinical Relevance and Technical Aspects. *Neuroimaging Clin N Am*. 2017;27(2):289-300. doi: 10.1016/j.nic.2017.01.002.
127. Britze J, Frederiksen JL. Optical coherence tomography in multiple sclerosis. *Eye (Lond)* 2018;32(5):884-888. doi:10.1038/s41433-017-0010-2.
128. Brown JW, Coles A, Horakova D, et al. Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis. *JAMA*. 2019; 15;321(2):175-187. doi:10.1001/jama.2018.20588.
129. Willis MA, Fox RJ. Progressive Multiple Sclerosis. *Continuum (Minneapolis)*. 2016; 22(3):785-98. doi: 10.1212/CON.0000000000000323.
130. Antel JI, Antel S, Caramanos Z, Arnold DL, Kuhlmann T. Primary progressive multiple sclerosis: part of the MS disease spectrum or separate disease entity? *Acta Neuropathol*. 2012; 123(5):627-38. doi:10.1007/s00401-012-0953-0.
131. Vural A, Derle E, Sayat-Gürel G. Predictors of progression in primary progressive multiple sclerosis in a large Turkish cohort. *Mult Scler Relat Disord*. 2019;12;38:101520. doi: 10.1016/j.msard.2019.101520.
134. Siva A. Common Clinical and Imaging Conditions Misdiagnosed as Multiple Sclerosis: A Current Approach to the Differential Diagnosis of Multiple Sclerosis. *Neur Clin*. 2018;36 (1);69-121. doi: 10.1016/j.ncl.2017.08.014
135. Freedman MS, Thompson EJ, Deisenhammer F, et al. Recommended Standard of Cerebrospinal Fluid Analysis in the Diagnosis of Multiple Sclerosis: A Consensus Statement. *Arch Neurol* 2005; 62 (6), 865-70. doi: 10.1001/archneur.62.6.865.
136. Regeniter A, Kuhle J, Mehling M, et al. A Modern Approach to CSF Analysis: Pathophysiology, Clinical Application, Proof of Concept and Laboratory Reporting. *Clin Neurol Neurosurg*. 2009; 111 (4), 313-8. doi: 10.1016/j.clineuro.2008.12.004.
137. Yamasaki R, Kira Y. Multiple Sclerosis Myelin, 2019; 1990; 217-247. doi:10.1007/978-981-32-9636-7-14
138. Matute-Blanch C, Montalban X, Comabella M Multiple Sclerosis, and Other Demyelinating and Autoimmune Inflammatory Diseases of the Central Nervous System. *Hand.Clin. Neurol*.2017;146, 67-84. 10.1016/B978-0-12-804279-3.00005-8
149. Luque FA, Jaffe SL. Cerebrospinal Fluid Analysis in Multiple Sclerosis *Int Rev Neurobiol* 2007;79:341-56. doi: 10.1016/S0074-7742(07)79015-3.
140. Sasso BL, Agnello L, Giulia Bivona G, et al. Cerebrospinal Fluid Analysis in Multiple Sclerosis Diagnosis: An Update. *Medicina(Kaunas)*. 2019;55(6). doi:10.3390/medicina55060245.
141. Inglesea M, Petracca M, MRI in multiple sclerosis: clinical and research update. *Curr Opin Neurol*, 2018; 31(3), 249-255. doi: 10.1097/WCO.0000000000000559.
142. Chen JJ, F Carletti F, V Young V, et al. MRI Differential Diagnosis of Suspected Multiple Sclerosis. *Clin Radiol*.2016;71(9):815-27. doi: 10.1016/j.crad.2016.05.010.
143. Cahalane AM, Kearney H, Purcell YM. MRI and multiple sclerosis--the evolving role of MRI in the diagnosis and management of MS: the radiologist's perspective. *Ir J of Med Sci*. 2018, 187(3). 781-787. doi:10.1007/s11845-017-1714-9.
144. Rovira A, Auger C, Alonso J. Magnetic resonance monitoring of lesion evolution in multiple sclerosis. *Ther Adv Neurol Disord*. 2013; 6(5) 298-310. doi:10.1177/1756285613484079.
145. Rovira A, Auger C. Spinal Cord in Multiple Sclerosis: Magnetic Resonance Imaging Features and Differential Diagnosis. *Semin Ultrasound CT*. 2016;37(5), 396-410 doi:10.1053/j.sult.2016.05.005.
146. Muccilli A, Seyman E, Oh J. Spinal Cord MRI in Multiple Sclerosis. *Neurol Clin*. 2018; 36 (1), 35-57. doi: 10.1016/j.ncl.2017.08.009.
148. Wattjes MP, Rovira A, Miller D, Evidence-based Guidelines: MAGNIMS Consensus Guidelines on the Use of MRI in Multiple Sclerosis-Establishing Disease Prognosis and Monitoring Patients. *Nat. Rev. Neurol*. 2015;11(10):597-606 doi:10.1038/nrneurol.2015.157.
149. Splendiani A, Perri M, Marsecano C, et al. Effects of Serial Macrocyclic-Based Contrast Materials Gadoterate Meglumine and Gadobutrol Administrations on Gadolinium-Related Dentate Nuclei Signal Increases in Unenhanced T1-weighted Brain: A Retrospective Study in 158 Multiple Sclerosis (MS) Patients. *Radiol Med*. 2018;123(2):125-134. doi: 10.1007/s11.
150. Suh CH, Kim SJ, Jung CS, et al. The "Central Vein Sign" on T2*-weighted Images as a Diagnostic Tool in Multiple Sclerosis: A Systematic Review and Meta-analysis using Individual Patient Data. *Sci Rep*. 2019; 9(1): 18188. doi: 10.1038/s41598-019-54583-3.
151. Josefine Britze J, Pihl-Jensen G, Frederiksen JL Retinal ganglion cell analysis in multiple sclerosis and optic neuritis: a systematic review and meta-analysis. *J Neurol*. 2017; 264(9): 1837-1853. doi:10.1007/s00415-017-8531-y
152. Oreja-Guevara C, Ayuso Blanco T, Brieva Ruiz L, et al. Cognitive Dysfunctions and Assessments in Multiple Sclerosis. *Front Neurol*. 2019(4);10:581.. doi:10.3389/fneur.2019.00581.
153. Berkovich R. Treatment of acute relapses in multiple sclerosis. *Neurotherapeutics*. 2013 ;10(1):97-105. doi: 10.1007/s13311-012-0160-7.

154. Smets I, Van Deun L, Bohyn C. et al; Belgian Study Group for Multiple Sclerosis. Corticosteroids in the management of acute multiple sclerosis exacerbations. *Acta Neurol Belg.* 2017;117(3):623-633. doi:10.1007/s 13760-017-0772-0.
155. Krieger S, Sorrells SF, Nickerson M. et al. Mechanistic insights into corticosteroids in multiple sclerosis: war horse or chameleon? *Clin Neurol Neurosurg.* 2014;119:6-16. doi: 10.1016/j.clineuro.2013.12.021.
156. Dobson R, Dassan P, Roberts M. UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines. *Pract Neurol.* 2019 Apr;19(2):106-114. doi: 10.1136/practneurol-2018-002060.
157. Tintore M, Vidal-Jordana A, Sastre-Garriga J. Treatment of multiple sclerosis- success from bench to bedside. *Nat Rev Neurol.* 2019;15(1):53-58. doi: 10.1038/s 41582-018-0082-z.
158. Freedman MS, Selchen D, Prat A. et al. Managing Multiple Sclerosis: Treatment Initiation, Modification, and Sequencing. *Can J Neurol Sci.* 2018 Sep;45(5):489-503. doi:10.1017/cjn.2018.17.
159. Dendrou CA, Fugger L. Immunomodulation in multiple sclerosis: promises and pit falls. *Curr Opin Immunol.* 2017 Dec;49:37-43. doi: 10.1016/j.coi.2017.08.013.
160. Corboy JR, Weinschenker BG, Wingerchuk DM. Comment on 2018 American Academy of Neurology guidelines on disease-modifying therapies in MS. *Neurology.* 2018 12;90(24): 1106-1112. doi: 10.1212/WNL.0000000000005574.
161. Maarouf A, Boutière C, Rico A. How much progress has there been in the second-line treatment of multiple sclerosis: A 2017 update. *Rev Neurol (Paris).* 2018 Jun;174(6): 429-440. doi: 10.1016/j.neurol.2018.01.369
162. Díaz C, Zarco LA, Rivera DM. Highly active multiple sclerosis: An update. *Mult Scler Relat Disord.* 2019 May;30:215-224. doi: 10.1016/j.msard.2019.01.039.
163. Sormani MP, Rio J, Tintore M, et al. Scoring treatment response in patients with relapsing multiple sclerosis. *Mult Scler* 2013;19:605-12. doi: 10.1177/1352458512460605.
164. Freedman MS, Selchen D, Arnold DL, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. *Can J Neurol Sci* 2013;40:307-23. doi: 10.1017/s0317167100014244.
165. Sormani MP, Gasperini C, Romeo M, Rio J, Calabrese M, Cocco E, et al. Assessing response to interferon- β in a multicenter dataset of patients with MS. *Neurology* 2016;87(2): 134-40. doi.org/10.1212/ WNL.0000000000002830
166. Le Page E, Edan G. Induction or escalation therapy for patients with multiple sclerosis? *Rev Neurol.* 2018;174(6):449-457. doi:10.1016/j.neurol.2018.04.004.
167. Rafiee Zadeh A, Askari M, Azadani NN, et al. Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part I. *Int J Physiol Pathophysiol Pharmacol.* 2019 15;11(4):95-104.
168. Biotti D, Ciron J. First-line therapy in relapsing remitting multiple sclerosis. *Rev Neurol (Paris).* 2018; 174(6): 419-428. doi: 10.1016/j.neurol.2018.03.012.
169. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. *Clin Med (Lond).* 2017 Dec;17(6):530-536. doi: 10.7861/clinmedicine.17-6-530.
170. Rafiee Zadeh A, Ghadimi K, Ataei A, et al. Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 2. *Int J Physiol Pathophysiol Pharmacol.* 2019;15;11(4): 105-114.
171. Pardo G, Jones DE. The sequence of disease-modifying therapies in relapsing multiple sclerosis: safety and immunologic considerations. *J Neurol.* 2017 Dec;264(12): 2351-2374. doi: 10.1007/s00415-017-8594-9.
172. Taşkapılıoğlu Ö. Recent Advances in the Treatment for Multiple Sclerosis; Current New Drugs Specific for Multiple Sclerosis. *Arch Neuropsychiatry* 2018 ;55: (Supp 1): S15-S20. doi:10.29399/npa.23402.
173. Buc M. New biological agents in the treatment of multiple sclerosis. *Bratisl Lek Listy.* 2018;119(4):191-197. doi:10.4149/BLL-2018-035.
174. Rommer PS, Milo R, Han MH. et al. Immunological Aspects of Approved MS. *Therapeutics.Front Immunol.* 2019;11;10:1564. doi:10.3389/fimmu.2019.01564.
175. Gholamzad M, Ebtekar M, Ardestani MS. et al. A comprehensive review on the treatment approaches of multiple sclerosis: currently and in the future. *Inflamm Res.* 2019 J;68(1):25-38. doi: 10.1007/s00011-018-1185-0.
177. Vidal-Jordana A. New Advances in Disease-Modifying Therapies for Relapsing and Progressive Forms of Multiple Sclerosis. *Neurol Clin.* 2018;36(1):173-183. doi:10.1016/j.ncl.2017.08.011.
178. Gavriilaki M, Sakellari I, Gavriilaki E. et al. Autologous Hematopoietic Cell Transplantation in Multiple Sclerosis: Changing Paradigms in the Era of Novel Agents. *Stem Cells Int.* 2019 Jun 24;2019:5840286. doi:10.1155/2019/5840286.
179. Das J, Sharrack B, Snowden JA. Autologous Haematopoietic Stem Cell Transplantation in Multiple Sclerosis: a Review of Current Literature and Future Directions for Transplant Haematologists and Oncologists. *Curr Hematol Malig Rep.* 2019;14(2):127-135. doi: 10.1007/s11899-019-00505-z.
180. Scolding NJ, Pasquini M, Reingold SC. et al. Cell-based therapeutic strategies for multiple sclerosis. *Brain.* 2017;140(11):2776-2796. doi: 10.1093/brain/awx 154.
181. Tornic J, Panicker JN. The Management of Lower Urinary Tract Dysfunction in Multiple Sclerosis. *Neurol Neurosci Rep.* 2018; 18(8): 54. doi: 10.1007/s11910-018-0857-z
182. Aharony SM, Lam O, Corcos J, et al. Evaluation of lower urinary tract symptoms in multiple sclerosis patients: Review of the literature and current guidelines. *Can Urol Assoc J* 2017;11(1-2):61-4. doi:10.5489/cuaj.4058.
183. Crabtree-Hartman E. Advanced Symptom Management in Multiple Sclerosis. *Neurol Clin.* 2018;36(1):197-218. doi: 10.1016/j.ncl.2017.08.015.
184. Tudor KI, Sakakibara R, Panicker JN. Neurogenic lower urinary tract dysfunction: evaluation and management. *J Neurol.* 2016;263(12):2555-2564.
185. Sakakibara R. Neurogenic lower urinary tract dysfunction in multiple sclerosis, neuromyelitis optica, and related disorders. *Clin Auton Res.* 2019;29(3):313-320. doi:10.1007/s10286-018-0551-x.
186. Tobin WO. Management of Multiple Sclerosis Symptoms and Comorbidities. *Continuum (Min Minn).* 2019;25(3):753-772. doi:10.1212/CON.0000000000000000

- 732.
187. Aharony SM, Lam O, Corcos J. Treatment of lower urinary tract symptoms in multiple sclerosis patients: Review of the literature and current guidelines. *Can Urol Assoc J.* 2017 Mar-Apr;11(3-4):E110-E115. doi: 10.5489/ cuaj.4059.
 188. de Se'ze M, Ruffion A, Denys P. The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. *Mult Scler.* 2007;13: 915-928. doi:10.1177/1352458506075651
 189. Samar S Ayache SS, Chalah MA. Fatigue in Multiple Sclerosis-Insights Into Evaluation and Management. *Neurophysiol.* 2017;47(2), 139-171.doi;10.1016/j.neucli.2017.02.004
 190. Rottoli M, Gioia SL, Frigeni B, Pathophysiology, assessment and management of multiple sclerosis fatigue: an update. *Expert Rev Neurother.* 2017;17(4). 372-379. doi:10.1080/14737175.2017.1247695
 191. Gümüř H. Fatigue Can Be Objectively Measured in Multiple Sclerosis Multipl Sklerozda Yorgunluk Objektif Olarak Ölçülebilir. *Noro Psikiyatrs Ars.* 2018; 55(1): 76-79. doi:10.29399/npa.23396.
 192. Braley TJ; Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. *SLEEP* 2010;33(8):1061-1067. doi: 10.1093/sleep/33.8.1061.
 193. Murphy R, O'Donoghue S, Counihan T et al. Neuropsychiatric syndromes of multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2017;88(8):697-708. doi: 10.1136/jnnp-2016-315367.
 194. Chalah MA, Ayache SS. Psychiatric event in multiple sclerosis: could it be the tip of the iceberg? *Braz J Psychiatry.* 2017;39(4):365-368. doi:10.1590/1516-4446-2016-2105.
 195. Paparrigopoulos T, Ferentinos P, Kouzoupis A, et al. The neuropsychiatry of multiple sclerosis: focus on disorders of mood, affect and behaviour. *Int Rev Psychiatry.* 2010; 22(1):14-21. doi: 10.3109/09540261003589323.
 196. Sparaco M, Lavorgna L, Bonavita S. Psychiatric disorders in multiple sclerosis. *J Neurol.* 2019 Jun 13. doi:10.1007/s00415-019-09426-6.
 197. Silveira C, Guedes R, Maia D, et al. Neuropsychiatric Symptoms of Multiple Sclerosis: State of the Art. *Psychiatry Investig.* 2019 Dec 9. doi: 10.30773/pi.2019.0106.
 198. Turner AP, Alschuler KN. Anxiety is more important than depression in MS - No. *Mult Scler.* 2018 Apr;24(4):442-444. doi: 10.1177/1352458517748477.
 199. Patten SB, Marrie RA, Carta MG. Depression in multiple sclerosis. *Int Rev Psychiatry.* 2017;29(5):463-472. doi: 10.1080/09540261.2017.1322555.
 200. Solaro C, Gamberini G, Masuccio FG. Depression in Multiple Sclerosis: Epidemiology, Aetiology, Diagnosis and Treatment. *CNS Drugs.* 2018 Feb;32(2):117-133. doi:10.1007/s40263-018-0489-5.
 201. Sokolov AA, Grivaz P, Bove R. Cognitive Deficits in Multiple Sclerosis: Recent Advances in Treatment and Neurorehabilitation. *Curr Treat Options Neurol.* 2018;22(12): 53. doi: 10.1007/s11940-018-0538-x.
 202. Miller E1, Morel A, Redlicka J, et al. Pharmacological and Non-pharmacological Therapies of Cognitive Impairment in Multiple Sclerosis. *Curr Neuropharmacol.* 2018; 16(4):475-483. doi:10.2174/1570159X15666171109132650.
 203. Bakirtzis C, Ioannidis P, Messinis L, et al. The Rationale for Monitoring Cognitive Function in Multiple Sclerosis: Practical Issues for Clinicians. *Open Neurol J.* 2018 May 31;12:31-40. doi: 10.2174/1874205X01812010031.
 204. Pflugshaupt T1, Geisseler O2, Nyffeler T,et al. Cognitive Impairment in Multiple Sclerosis: Clinical Manifestation, Neuroimaging Correlates, and Treatment. *Semin Neurol.* 2016 Apr;36(2):203-11. doi:10.1055/s-0036-1579696.
 205. Penner IK. Cognition in multiple sclerosis. *Neurodegener Dis.Manag.*2017; 7(6s),19-21. 10.2217/nmt-2017-0036.
 206. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Mult Scler.* 2012 Jun;18(6):891-8. doi: 10.1177/1352458511431076.
 207. Hugos CL, Cameron MH. Assessment and Measurement of Spasticity in MS: State of the Evidence. *Curr Neurol Neurosci Rep.* 2019; 30;19(10):79. doi:10.1007/s11910-019-0991-2.
 208. Patejdl R, Zettl UK. Spasticity in multiple sclerosis: Contribution of inflammation, autoimmune mediated neuronal damage and therapeutic interventions. *Autoimmun Rev.* 2017 Sep;16(9):925-936. doi:10.1016/j.autrev.2017.07.004.
 209. Hughes C, Howard IM. Spasticity management in multiple sclerosis. *Phys Med Rehabil Clin N Am.* 2013 Nov;24(4):593-604. doi: 10.1016/j.pmr.2013.07.003.
 210. Gold R, Oreja-Guevara C. Advances in the management of multiple sclerosis spasticity: multiple sclerosis spasticity guidelines. *Expert Rev Neurother.* 2013;13(12 Suppl):55-9. doi: 10.1586/14737175.2013.865880.
 211. Vermersch P. Advances in the management of MS symptoms: recently proposed clinical management algorithms. *Neurodegener Dis Manag.* 2015;5(6):23-6. doi:10.2171/nmt.15.57.
 212. Maitin IB, Cruz E. Special Considerations and Assessment in Patients with Multiple Sclerosis. *Phys Med Rehabil Clin N Am.* 2018;29(3):473-481. doi:10.1016/j.pmr.2018.03.003.
 213. Otero-Romero S, Sastre-Garriga J, Comi G et al. Pharmacological management of spasticity in multiple sclerosis: Systematic review and consensus paper. *Mult Scler.* 2016 Oct;22(11):1386-1396.
 214. Gillian M. Keating GM. Delta-9-Tetrahydrocannabinol/Cannabidiol Oromucosal Spray (Sativex®): A Review in Multiple Sclerosis-Related Spasticity. *Drugs.* 2017; 77(5): 563-574. 10.1007/s40265-017-0720-6.
 215. Iorio R, Capone F2, Plantone D. et al. Paroxysmal ataxia and dysarthria in multiple sclerosis. *J Clin Neurosci.* 2014 Jan;21(1):174-5. doi:10.1016/j.jocn.2013.01.031.
 216. Ehling R, Bsteh G, Di Pauli F. Rethinking the importance of paroxysmal and unusual symptoms as first clinical manifestation of multiple sclerosis: They do matter. *Mult Scler Relat Disord.* 2016 Sep;9:150-4. doi: 10.1016/j.msard.2016.07.014.
 217. Rossi S, Studer V, Motta C. et al. Paroxysmal dysarthria-ataxia syndrome resolving after fingolimod treatment. *J Neurol Sci.* 2015 Mar 15;350(1-2):101-2. doi:10.1016/j.jns.2015.01.023.
 218. Di Stefano G, Maarbjerg S, Truini A. Trigeminal neu-

- ralgia secondary to multiple sclerosis: from the clinical picture to the treatment options. *J Headache Pain*. 2019 Feb 19;20(1):20. doi: 10.1186/s10194-019-0969-0.
219. Gasparini, S., Ferlazzo, E., Ascoli, M. et al. Risk factors for unprovoked epileptic seizures in multiple sclerosis: a systematic review and meta-analysis. *Neurol Sci* 38, 399–406 (2017) doi:10.1007/s10072-016-2803-7.
220. Bustuchina Vlaicu M. Epilepsy in multiple sclerosis as a network disease. *Mult Scler Relat Disord*. 2019 Nov;36:101390. doi: 10.1016/j.msard.2019.101390.
221. Dagiasi I, Vall V, Kumlien E. et al. Treatment of epilepsy in multiple sclerosis. *Seizure*. 2018 May;58:47-51. doi:10.1016/j.seizure.2018.04.001.
222. Mahamud Z, Burman J, Zelano J. Prognostic impact of epilepsy in multiple sclerosis. *Mult Scler Relat Disord*. 2019 Nov 5;38:101497. doi:10.1016/j.msard.2019.101497.
223. Aboud T, Schuster NM. Pain Management in Multiple Sclerosis: a Review of Available Treatment Options. *Curr Treat Options Neurol*. 2019 Nov 27;21(12):62. doi: 10.1007/s11940-019-0601-2.
224. Ceruti S. What role does multiple sclerosis play in the development of untreatable painful conditions? *Pain Manag*. 2018 Jan;8(1):37-44. doi: 10.2217/pmt-2017-0038.