



BÖLÜM 8

MİYELİN OLİGODENDROSİT GLİKOPROTEİN ANTİKOR İLİŞKİLİ HASTALIK (MOG-AD)

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GİRİŞ

Miyelin oligodendrosit glikoprotein (MOG) memelilerin santral sinir sisteminde (SSS) oligodendrosit üzerindeki miyelin yüzeyinde eksprese edilen 218 amino asitten oluşan bir glikoproteindir. Yalnızca memeli SSS'sinde ve insanlarda HLA lokusunun 6p21.3 - 6p22 telomer bölgesinde haritalandırılmıştır. Tek bir hücre dışı IgV benzeri alandan, bir transmembran domainden ve kısa bir sitoplazmik bölgeden oluşan tip 1 membran proteini olan MOG, ilk olarak 40 yıl önce cavia porcellus cinsi kemirgenlerde demiyelinizan antikorların hedefi olarak test edilmiştir (1). İnsanlarda ise neonatal dönemde corpus callosumda saptanan MOG proteininin üretimi ve seviyesi 2 yaşına kadar artmaktadır. MOG ekspreşyonu, diğer miyelin proteinlerinden sonra başlar ve bu da MOG'un oligodendrosit maturasyonunun bir belirteci olabileceği düşündürür (2,3).

MOG proteininin ve izoformlarının biyolojik rolleri net değildir. Yapılan çalışmalar MOG'un hücrenin bir reseptörü, bir adhezyon molekülü ya da mikrotübü stabilizasyonunu sağlayan düzenleyici olabileceğini göstermektedir (4,5). Bir reseptör olarak MOG, kompleman sisteminin klasik yoldan aktivasyonunu sağlayan C1q protein kompleksini ve sinir büyümeye faktörünü (NGF) bağlar (5,6). MOG proteininin biyolojik rolleri hakkında bilgilerimiz kısıtlı olmakla beraber MOG'un hücre dışı IgV benzeri domaini, antikorlar tarafından erişilebilir bir bölgededir. Bu özelliği ile MOG proteinini, santral sinir sisteminin erişilemeyen miyelin basic protein (MBP) ve proteolipid protein (PLP) gibi diğer ana yapısal bileşenlerinden ayırlır. İnflamatuar demiyelinizan hastalıkların deneysel model-

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SONUÇ

MOG-AD; NMO ve MS'ten farklı bir klinik fenotiptir ve farklı ele alınması gereklidir. Tanı konması tedavi ve takip açısından önemlidir. MOG-AD nükslerinde engellilik riski bulunmaktadır, immünsüpresyon tedavi başlangıcı ve süresine karar vermek önemlidir. MOG-AD'a özgü tanı kriterleri ve belirteçlerin tanımlanmasına ihtiyaç vardır.

KAYNAKLAR

1. Lebar R, Baudrimont M, Vincent C. Chronic experimental autoimmune encephalomyelitis in the guinea pig. Presence of anti-M2 antibodies in central nervous system tissue and the possible role of M2 autoantigen in the induction of the disease. *J Autoimmun.* 1989 Apr;2(2):115-32.
2. Pham-Dinh D, Mattei MG, Nussbaum JL, Roussel G, Pontarotti P, Roeckel N, Mather IH, Artzt K, Lindahl KF, Dautigny A. Myelin/oligodendrocyte glycoprotein is a member of a subset of the immunoglobulin superfamily encoded within the major histocompatibility complex. *Proc Natl Acad Sci U S A.* 1993 Sep 1;90(17):7990-4.
3. Delarasse C, Della Gaspera B, Lu CW, Lachapelle F, Gelot A, Rodriguez D, Dautigny A, Genain C, Pham-Dinh D. Complex alternative splicing of the myelin oligodendrocyte glycoprotein gene is unique to human and non-human primates. *J Neurochem.* 2006 Sep;98(6):1707-17.
4. Marta CB, Montano MB, Taylor CM, Taylor AL, Bansal R, Pfeiffer SE. Signaling cascades activated upon antibody cross-linking of myelin oligodendrocyte glycoprotein: potential implications for multiple sclerosis. *J Biol Chem.* 2005 Mar 11;280(10):8985-93.
5. Johns TG, Bernard CC. The structure and function of myelin oligodendrocyte glycoprotein. *J Neurochem.* 1999 Jan;72(1):1-9.
6. von Büdingen HC, Mei F, Greenfield A, Jahn S, Shen YA, Reid HH, McKemy DD, Chan JR. The myelin oligodendrocyte glycoprotein directly binds nerve growth factor to modulate central axon circuitry. *J Cell Biol.* 2015 Sep 14;210(6):891-8.
7. Iglesias A, Bauer J, Litzenburger T, Schubart A, Linington C T- and B-cell responses to myelin oligodendrocyte glycoprotein in experimental autoimmune encephalomyelitis and multiple sclerosis. *Glia* (2001) 36:220–234.
8. Peschl P, Bradl M, Höftberger R, et al. Myelin Oligodendrocyte Glycoprotein: Deciphering a Target in Inflammatory Demyelinating Diseases. *Front. Immunol.* 2017; 8:529.
9. Peschl P, Schanda K, Zeka B et al. Human antibodies against the myelin oligodendrocyte glycoprotein can cause complement-dependent demyelination. *J Neuroinflammation* 2017; 14:208.

10. Thomas Berger, Paul Rubner, Franz Schautzer,et al Antimyelin Antibodies as a Predictor of Clinically Definite Multiple Sclerosis after a First Demyelinating Event. *N Engl J Med* 2003; 349:139-145.
11. Tanaka M, Tanaka K. Anti-MOG antibodies in adult patients with demyelinating disorders of the central nervous system. *J Neuroimmunol* 2014; 270(1-2):98-99.
12. Thompson A, Banwell B L, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17(2):162-173.
13. Reindl M., Di Pauli F, Rostásy K. et al. The spectrum of MOG autoantibody-associated demyelinating diseases. *Nat Rev Neurol* 2013; 9:455-461.
14. Ramanathan S, Mohammad SS, Brilot F, Dale RC. Autoimmune encephalitis: recent updates and emerging challenges. *J Clin Neurosci*. 2014 May;21(5):722-30.
15. Ramanathan S, Reddel SW, Henderson A, Parratt JD, Barnett M, Gatt PN, Merheb V, Kumaran RY, Pathmanandavel K, Sinmaz N, Ghadiri M, Yiannikas C, Vucic S, Stewart G, Bleasel AF, Booth D, Fung VS, Dale RC, Brilot F. Antibodies to myelin oligodendrocyte glycoprotein in bilateral and recurrent optic neuritis. *Neurol Neuroimmunol Neuroinflamm*. 2014 Oct 29;1(4):e40.
16. Lassmann H, Brunner C, Bradl M, Linington C. Experimental allergic encephalomyelitis: the balance between encephalitogenic T lymphocytes and demyelinating antibodies determines size and structure of demyelinated lesions. *Acta Neuropathol*. 1988;75(6):566-76.
17. Kinzel S, Lehmann-Horn K, Torke S, Häusler D, Winkler A, Stadelmann C, Payne N, Feldmann L, Saiz A, Reindl M, Lalive PH, Bernard CC, Brück W, Weber MS. Myelin-reactive antibodies initiate T cell-mediated CNS autoimmune disease by opsonization of endogenous antigen. *Acta Neuropathol*. 2016 Jul;132(1):43-58.
18. Brilot F, Dale RC, Selter RC, Grummel V, Kalluri SR, Aslam M, Busch V, Zhou D, Cepek S, Hemmer B. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. *Ann Neurol*. 2009 Dec;66(6):833-42.
19. Kerlero de Rosbo N, Honegger P, Lassmann H, Matthieu JM. Demyelination induced in aggregating brain cell cultures by a monoclonal antibody against myelin/oligodendrocyte glycoprotein. *J Neurochem*. 1990 Aug;55(2):583-7.
20. Piddlesden SJ, Lassmann H, Zimprich F, Morgan BP, Linington C. The demyelinating potential of antibodies to myelin oligodendrocyte glycoprotein is related to their ability to fix complement. *Am J Pathol*. 1993 Aug;143(2):555-64.
21. Dale RC, Tantsis EM, Merheb V. et al. Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton. *Neurol Neuroimmunol Neuroinflamm* Jun 2014; 1:(1)e12.
22. Spadaro M, Gerdés LA, Mayer MC, Ertl-Wagner B, Laurent S, Krumbholz M, Breithaupt C, Högen T, Straube A, Giese A, Hohlfeld R, Lassmann H, Meinl E, Kümpfel T. Histopathology and clinical course of MOG-antibody-associated encephalomyelitis. *Ann Clin Transl Neurol*. 2015 Mar;2(3):295-301.

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23. Reindl M, Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. *Nat Rev Neurol* 2019;15:89–102.
24. Linington C, Morgan BP, Scolding NJ, et al. The role of complement in the pathogenesis of experimental allergic encephalomyelitis. *Brain* 1989;112:895–911.
25. Cobo-Calvo A, Ruiz A, Maillart E et al. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: the MOGADOR study. *Neurology* 2018; 90:e1858–69.
26. Hyun, J.W., Woodhall, M.R., Kim, S.H., Jeong, I.H., Kong, B., Kim, G., Kim, Y., Park, M.S., Irani, S.R., Waters, P., Kim, H.J., 2017. Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases. *J. Neurol. Neurosurg. Psychiatry* 88 (10), 811–817.
27. Schlueter H, Sobel RA, Linington C, et al. A monoclonal antibody against a myelin oligodendrocyte glycoprotein induces relapses and demyelination in central nervous system autoimmune disease. *J Immunol* 1987; 139(12):4016–4021.
28. Baumann M, Sahin K, Lechner C, et al. Clinical and neuroradiological differences of pediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. *J Neurol Neurosurg Psychiatry* 2015;86:265–72.
29. Baumann M, Hennes EM, Schanda K, et al. Children with multiphasic disseminated encephalomyelitis and antibodies to the myelin oligodendrocyte glycoprotein (MOG): extending the spectrum of MOG antibody positive diseases. *Mult Scler* 2016;22:1821–9.
30. Ramanathan S, Prelog K, Barnes E H, et al. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. *Mult Scler J* 2015; 22(4):470–482.
31. Biotti D, Bonneville D, Tournaire E et al. Optic neuritis in patients with anti-MOG antibodies spectrum disorder: MRI and clinical features from a large multicentric cohort in France. *J Neurol* 2017; 264(10):2173–2175.
32. Stiebel-Kalish H, Lotan I, Brody J et al. Retinal nerve fiber layer may be better preserved in MOG-IgG versus AQP4-IgG optic neuritis: a cohort study. *PLoS One* 2017; 12(1):e0170847.
33. Kitley J, Waters P, Woodhall M, et al. Neuromyelitis optica spectrum disorders with aquaporin-4 and myelinoligodendrocyte glycoprotein antibodies: a comparative study. *JAMA Neurol* 2014;71:276–8.
34. Sato DK, Callegaro D, Lana-Peixoto MA, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. *Neurology* 2014; 82:474–81.
35. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. *J Neuroinflammation* 2016; 13:280.

36. Hennes EM, Baumann M, Schanda K, et al. Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. *Neurology* 2017; 89:900–8.
37. Hacohen Y, Rossor T, Mankad K, et al. ‘Leukodystrophylike’ phenotype in children with myelin oligodendrocyte glycoprotein antibody-associated disease. *Dev Med Child Neurol* 2018;60:417–23.
38. Jurynczyk M, Geraldes R, Probert F, et al. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. *Brain* 2017;140:617–27.
39. Mariotto S, Ferrari S, Monaco S, et al. Clinical spectrum and IgG subclass analysis of anti-myelin oligodendrocyte glycoprotein antibody-associated syndromes: a multi-center study. *J Neurol* 2017; 264(12):2420–2430.
40. Chang VTW, Chang H-M. Review: recent advances in the understanding of the pathophysiology of neuromyelitis optica spectrum disorder. *Neuropathol Appl Neurobiol* 2020; 46:199–218.
41. Haider L, Zrzavy T, Hametner S, et al. The topography of demyelination and neurodegeneration in the multiple sclerosis brain. *Brain* 2016; 139:807–15.
42. Cobo-Calvo Á, Ruiz A, D’Indy H, et al. MOG antibody-related disorders: common features and uncommon presentations. *J Neurol* 2017; 264(9):1945–1955.
43. Waters P, Woodhall M, O’Connor KC, et al. MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. *Neurol Neuroimmunol Neuroinflamm* 2015; 2(3):e89.
44. Banwell BL. Pediatric multiple sclerosis. *Curr Neurol Neurosci Rep* 2004; 4:245–52.
45. Hacohen Y, Absoud M, Deiva K, et al. Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. *Neurol Neuroimmunol Neuroinflamm* 2015; 2:e81.
46. Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Mult Scler* 2008; 14:1157–74.
47. Juryńczyk M, Tackley G, Kong Y, et al. Brain lesion distribution criteria distinguish MS from AQP4-antibody NMOSD and MOG-antibody disease. *J Neurol Neurosurg Psychiatry* 2017; 88:132–6.
48. Ramanathan S, Mohammad S, Tantsis E, et al. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. *Journal of Neurology, Neurosurgery & Psychiatry* 2018; 89:127–137.
49. Jarius, S., Ruprecht, K., Kleiter, I. et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. *J Neuroinflammation* 2016; 13: 280
50. Alvaro Cobo-Calvo, Anne Ruiz, Elisabeth Maillart et al. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults The MOGADOR study. *Neurology* May 2018, 90 e1858-e1869.
51. Song H, Zhou H, Yang M, et al. Different characteristics of aquaporin-4 and myelin oligodendrocyte glycoprotein antibody-seropositive male optic neuritis in China. *J Ophthalmol* 2019; Article 4015075

▲ Demyelinizan Hastalıklar

52. Weinshenker, B.G., O'Brien, P.C., Pettersson, T.M., et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol.*, 1999; 46: 878-886
53. A.L. Bruijstens, E.-M. Wendel, C. Lechner et al. E.U. paediatric MOG consortium consensus: Part 5 e Treatment of paediatric myelin oligodendrocyte glycoprotein antibody-associated disorders. *European Journal of Paediatric Neurology* 2020;29: 41e53.
54. Juryńczyk M, Jacob A, Fujihara K, et al. Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease: practical considerations. *Pract Neurol* 2019; 19:187–195.
55. Hacohen Y, Wong YY, Lechner C, et al. Disease Course and Treatment Responses in Children With Relapsing Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. *JAMA Neurol.* 2018 Apr 1;75(4):478-487.
56. Chen JJ, Flanagan EP, Bhatti MT, et al. Steroid-sparing maintenance immunotherapy for MOG-IgG associated disorder. *Neurology*. 2020 Jul 14;95(2):e111-e120.
57. Cobo-Calvo A, Sepúlveda M, Rollot F, et al. Marignier R. Evaluation of treatment response in adults with relapsing MOG-Ab-associated disease. *J Neuroinflammation*. 2019 Jul 2;16(1):134.
58. Armangue T, Olivé-Cirera G, Martínez-Hernandez E, et al; Spanish Pediatric anti-MOG Study Group. Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: a multicentre observational study. *Lancet Neurol.* 2020 Mar;19(3):234-246.
59. Durozard P, Rico A, Boutiere C, et al. Comparison of the Response to Rituximab between Myelin Oligodendrocyte Glycoprotein and Aquaporin-4 Antibody Diseases. *Ann Neurol.* 2020 Feb;87(2):256-266.
60. Bai P, Zhang M, Yuan J, Zhu R, Li N. A comparison of the effects of rituximab versus other immunotherapies for MOG-IgG-associated central nervous system demyelination: A meta-analysis. *Mult Scler Relat Disord.* 2021 Aug;53:103044.