

Bölüm 12

NÖROMUSKÜLER KAVŞAK FİZYOLOJİSİ VE NÖROMUSKÜLER KAVŞAK HASTALIKLARINDA İMМUNOPATOGENEZ

Fatma Gülhan ŞAHBAZ¹

GİRİŞ

Çizgili kas plazma membranı ile motor nöron akson terminali arasındaki aksiyon potansiyelinin yani sinir iletiminin aktarımını sağlayan bağlantı yapısına nöromusküler kavşak (NMK) adı verilmektedir. Bu kavşaktaki gerçekleşen elektriksel uyarı iletimi sayesinde çizgili kasın kontraksiyonu sağlanır. NMK ilişkili patolojilerde kaslarda güçsüzlük, solunum zorluğu gibi ciddi nörolojik tablolar ortaya çıkmaktadır. Anestezide kullanılan birçok ilaç grubu da NMK üzerinden sinir iletimi engelleyerek etkisini göstermektedir. Birçok nörolojik hastalık temelinde bu yapıdaki bozukluklar suçlanmakta olduğundan NMK fizyolojisini iyi anlayabilmek büyük önem arz etmektedir. (1,2,3) NMK hastalıkları arasında Miyastenia Gravis (MG), konjenital miyastenik sendromlar, Lambert Eaton Sendrom (LEMS), edinsel botulizm ve periferik sinir hiperreksitabilite sendromları sayılmaktadır. Bu hastalıkların çoğunun immunopatogenezinde otoimmunité sorumlu tutulmaktadır ve spesifik otoantikorlar tanımlanmıştır. Nikotinik asetilkolin reseptör antikoru, voltaj kapılı kalsiyum ve potasyum kanallarına karşı gelişen antikorlar gibi birçok antikor saptanmış olan NMK hastalıklarının tedavilerinde, patogeneze yönelik immunoterapi yöntemleri kullanılmaktadır. (4,5)

Nöromusküler Kavşak Fizyolojisi

Medulla spinalis ön boynuz motor nöronlarından miyelinli sinir lifleri çıkar ve bunlar çizgili kası uyarır. Sinir terminali kas lifiyle NMK adı verilen sinaps yapar. Sinir lifi tarafından ulaştırılan aksiyon potansiyeli NMK aracılığıyla kasa

¹ Uzm. Dr., Afyonkarahisar Devlet Hastanesi, Nöroloji Kliniği, gul_shbz@hotmail.com

KAYNAKLAR

1. Slater CR. The Structure of Human Neuromuscular Junctions: Some Unanswered Molecular Questions. *Int J Mol Sci.* 2017 Oct 19;18(10):2183. doi: 10.3390/ijms18102183.
2. Slater CR. The functional organization of motor nerve terminals. *Prog Neurobiol.* 2015 Nov;134:55-103. doi: 10.1016/j.pneurobio.2015.09.004. Epub 2015 Oct 9.
3. Jones RA, Harrison C, Eaton SL, Llavero Hurtado M, Graham LC, Alkhammash L, Oladiran OA, Gale A, Lamont DJ, Simpson H, Simmen MW, Soeller C, Wishart TM, Gillingwater TH. Cellular and Molecular Anatomy of the Human Neuromuscular Junction. *Cell Rep.* 2017 Nov 28;21(9):2348-2356. doi: 10.1016/j.celrep.2017.11.008.
4. Jimsheleishvili S, Marwaha K, Sherman AL. Physiology, Neuromuscular Transmission. 2022 Mar 9. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.
5. Ratliff WA, Saykally JN, Kane MJ, Citron BA. Neuromuscular Junction Morphology and Gene Dysregulation in the Wobbler Model of Spinal Neurodegeneration. *J Mol Neurosci.* 2018 Sep;66(1):114-120. doi: 10.1007/s12031-018-1153-8. Epub 2018 Aug 13.
6. Martyn JA, Fagerlund MJ, Eriksson LI. Basic principles of neuromuscular transmission. *Anaesthesia.* 2009 Mar;64 Suppl 1:1-9. doi: 10.1111/j.1365-2044.2008.05865.x.
7. Patton BL. Basal lamina and the organization of neuromuscular synapses. *J Neurocytol.* 2003 Jun-Sep;32(5-8):883-903. doi: 10.1023/B:NEUR.0000020630.74955.19.
8. Hirsch NP. Neuromuscular junction in health and disease. *Br J Anaesth.* 2007 Jul;99(1):132-8. doi: 10.1093/bja/aem144.
9. Querol L, Illa I. Myasthenia gravis and the neuromuscular junction. *Curr Opin Neurol.* 2013 Oct;26(5):459-65. doi: 10.1097/WCO.0b013e328364c079.
10. Roux B. Ion channels and ion selectivity. *Essays Biochem.* 2017 May 9;61(2):201-209. doi: 10.1042/EBC20160074.
11. Sudhof TC. The presynaptic active zone. *Neuron.* 2012;75(1):11-25.
12. Guyton and Hall Textbook of Medical Physiology. 13th ed. p.75-95.
13. Liang CL, Han S. Neuromuscular junction disorders. *PM R.* 2013;5(5):81-8.
14. Hall ZW, Sanes JR. Synaptic structure and development: the neuromuscular junction. *Cell.* 1993;72 Suppl:99-121.
15. Sanes JR, Apel ED, Burgess RW, Emerson RB, Feng G, Gautam M, et al. Development of the neuromuscular junction: genetic analysis in mice. *J Physiol Paris.* 1998;92(3-4):167-72.
16. Wang H, Yu M, Tracey KJ, et al. Nicotinic acetylcholine receptor $\alpha 7$ subunit is an essential regulator of inflammation. *Nature.* 2003;421:384-8.
17. Romano SJ, Pugh PC, McIntosh JM, Berg DK. Neuronal type acetylcholine receptors and regulation of alpha 7 gene expression in vertebrate skeletal muscle. *J Neurobiol.* 1997;32:69-80.
18. Yu FH, Catterall WA. Overview of the voltage gated sodium channel family. *Genome Biol.* 2003;4:207.
19. titula T, Jahn R. Core proteins of the secretory machinery. *Send to Handb Exp Pharmacol.* 2008;(184):107.

20. Fraterman S, Khurana TS, Rubinstein NA. Identification of acetylcoline receptor subunits differentially expressed in singly and multiply innervated fibers of extraocular muscles. *Invest Ophthalmol Vis Sci.* 2006;47:3828.
21. Song Y, Panzer JA, Balice-Gordon RJ, et al. Formation and plasticity of neuromuscular synaptic connections. *Int Anesthesiol Clin.* 2006;44:145-78.
22. Sanes JR, Lichtman JW. Development of the vertebrate neuromuscular junction. *Annu Rev Neurosci.* 1999;22:389-442.
23. Lacomis D, Puwanant A. What is in the Neuromuscular Junction Literature? *J Clin Neuromuscul Dis.* 2018 Dec;20(2):76-84. doi: 10.1097/CND.0000000000000218.
24. Omar A, Marwaha K, Bollu PC. Physiology, Neuromuscular Junction. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK470413/>
25. Kusner LL, Losen M, Vincent A, et al. Guidelines for pre-clinical assessment of the acetylcholine receptor--specific passive transfer myasthenia gravis model-Recommendations for methods and experimental designs. *Exp Neurol.* 2015;270:3-10. doi:10.1016/j.expneurol.2015.02.025
26. Lee JY, Stathopoulos P, Gupta S, Bannock JM, Barohn RJ, Cotzomi E, Dimachkie MM, Jacobson L, Lee CS, Morbach H, Querol L, Shan JL, Vander Heiden JA, Waters P, Vincent A, Nowak RJ, O'Connor KC. Compromised fidelity of B-cell tolerance checkpoints in AChR and MuSK myasthenia gravis. *Ann Clin Transl Neurol.* 2016 Apr 27;3(6):443-54. doi: 10.1002/acn3.311.
27. Vander Heiden JA, Stathopoulos P, Zhou JQ, Chen L, Gilbert TJ, Bolen CR, Barohn RJ, Dimachkie MM, Ciafaloni E, Broering TJ, Vigneault F, Nowak RJ, Kleinstein SH, O'Connor KC. Dysregulation of B Cell Repertoire Formation in Myasthenia Gravis Patients Revealed through Deep Sequencing. *J Immunol.* 2017 Feb 15;198(4):1460-1473. doi: 10.4049/jimmunol.1601415. Epub 2017 Jan 13.
28. Romi F, Hong Y, Gilhus NE. Pathophysiology and immunological profile of myasthenia gravis and its subgroups. *Curr Opin Immunol.* 2017;49:9-13.
29. Plomp JJ, Morsch M, Phillips WD, Verschuuren JJ. Electrophysiological analysis of neuromuscular synaptic function in myasthenia gravis patients and animal models. *Exp Neurol.* 2015; 270: 41-54.
30. Huijbers MG, Marx A, Plomp JJ, Le Panse R, Phillips WD. Advances in the understanding of disease mechanisms of autoimmune neuromuscular junction disorders. *Lancet Neurol.* 2022 Feb;21(2):163-175. doi: 10.1016/S1474-4422(21)00357-4.
31. Poëa-Guyon S, Christadoss P, Le Panse R, Guyon T, De Baets M, Wakkach A, Bidault J, Tzartos S, Berrih-Aknin S. Effects of cytokines on acetylcholine receptor expression: implications for myasthenia gravis. *J Immunol.* 2005 May 15;174(10):5941-9. doi: 10.4049/jimmunol.174.10.5941
32. Dragin N, Bismuth J, Cizeron-Clairac G, Biferi MG, Berthault C, Serraf A, Nottin R, Klatzmann D, Cumano A, Barkats M, Le Panse R, Berrih-Aknin S. Estrogen-mediated downregulation of AIRE influences sexual dimorphism in autoimmune diseases. *J Clin Invest.* 2016 Apr 1;126(4):1525-37. doi: 10.1172/JCI81894. Epub 2016 Mar 21
33. Cavalcante P, Barzago C, Mantegazza R, et al. Toll-like receptors 7 and 9 in myasthenia

- gravis thymus: amplifiers of autoimmunity? *Ann N Y Acad Sci.* 2018;1413(1):11-24.
34. Cufi P, Dragin N, Ruhimann N, Weiss JM, Fadel E, Serraf A, et al. Central role of interferon-beta in thymic events leading to myasthenia gravis. *J Autoimmun.* 2014;52:44-52.
35. Shiono H, Wong YL, Matthews I, Liu JL, Zhang W, Sims G, et al. Spontaneous production of anti-IFN-alpha and anti-IL2 autoantibodies by thymoma cells from myasthenia gravis patients suggest autoimmunization in the tumor. *Int Immunol.* 2003;15(8):903-13.
36. Vrolix, K.; Fraussen, J.; Losen, M.; Stevens, J.; Lazaridis, K.; Molenaar, P.C.; Somers, V.; Bracho, M.A.; Le Panse, R.; Stinissen, P.; et al. Clonal Heterogeneity of Thymic B Cells from Early-Onset Myasthenia Gravis Patients with Antibodies against the Acetylcholine Receptor. *J. Autoimmun.* 2014, 52, 101–112.
37. Vinuesa, C.G.; Linterman, M.A.; Yu, D.; MacLennan, I.C.M. Follicular Helper T Cells. *Annu. Rev. Immunol.* 2016, 34, 335–368.
38. Gradolatto, A.; Nazzal, D.; Truffault, F.; Bismuth, J.; Fadel, E.; Foti, M.; Berrih-Aknin, S. Both Treg Cells and Tconv Cells Are Defective in the Myasthenia Gravis Thymus: Roles of IL-17 and TNF- α . *J. Autoimmun.* 2014, 52, 53–63.
39. Ashida, S.; Ochi, H.; Hamatani, M.; Fujii, C.; Kimura, K.; Okada, Y.; Hashi, Y.; Kawamura, K.; Ueno, H.; Takahashi, R.; et al. Immune Skew of Circulating Follicular Helper T Cells Associates With Myasthenia Gravis Severity. *Neurol. Neuroimmunol. Neuroinflamm.* 2021, 8.
40. Hohlfeld R, Wekerle H. The role of the thymus in myasthenia gravis. *Adv Neuroimmunol.* 1994;4(4):373-86.
41. Cataneo AJM, Felisberto G Jr, Cataneo DC. Thymectomy in nonthymomatous myasthenia gravis- systematic review and metaanalysis. *Orphanet J Rare Dis.* 2018;13(1):99.
42. Cao M, Koneczny I, Vincent A. Myasthenia gravis with antibodies against muscle specific kinase: an update on clinical features, pathophysiology and treatment. *Front Mol Neurosci* 2020; 13: 159.
43. Clifford KM, Hobson-Webb LD, Benatar M, et al. Thymectomy may not be associated with clinical improvement in MuSK myasthenia gravis. *Muscle Nerve* 2019; 59: 404–10
44. Zisimopoulou P, Evangelakou P, Tzartos J, et al. A comprehensive analysis of the epidemiology and clinical characteristics of anti-LRP4 in myasthenia gravis. *J Autoimmun* 2014; 52: 139–45.
45. Koneczny I, Rennspieß D, Marcuse F, et al. Characterization of the thymus in Lrp4 myasthenia gravis: four cases. *Autoimmun Rev* 2019; 18: 50–55.
46. Christadoss P, Poussin M, Deng C. Animal models of myasthenia gravis. *Clin Immunol.* 2000;94(2):75-87
47. Ulusoy C, Çavuş F, Yılmaz V, Tüzün E. Immunization with recombinantly expressed LRP4 induces experimental autoimmune myasthenia gravis in C57BL/6 mice. *Immunol Invest.* 2017;46(5):490-9.
48. Compston DA, Vincent A, Newsom-Davis J, Batchelor JR. Clinical, pathological, HLA antigen and immunological evidence for disease heterogeneity in myasthenia gravis. *Brain.* 1980;103(3):579-601
49. Alahgholi-Hajibehzad M, Yilmaz v, Gulsen-Parman Y, Aysal F, Oflazer P, Deymeer F, et al. Association of HLA-DRB1*14, DRB1*16 and DQB1*05 with MuSK*myasthenia gravis in patients from Turkey. *Hum Immunol.* 2013;74(12):1633-5

50. Çebi, M.; Durmus, H.; Aysal, F.; Özkan, B.; Gül, G.E.; Çakar, A.; Hocaoglu, M.; Mercan, M.; Yentür, S.P.; Tütüncü, M.; et al. CD4+ T Cells of Myasthenia Gravis Patients Are Characterized by Increased IL-21, IL-4, and IL-17A Productions and Higher Presence of PD-1 and ICOS. *Front. Immunol.* 2020, 11, 809.
51. Uzawa, A.; Kuwabara, S.; Suzuki, S.; Imai, T.; Murai, H.; Ozawa, Y.; Yasuda, M.; Nagane, Y.; Utsugisawa, K. Roles of cytokines and T cells in the pathogenesis of myasthenia gravis. *Clin. Exp. Immunol.* 2021, 203, 366–374.
52. Huan, X.; Luo, S.; Zhong, H.; Zheng, X.; Song, J.; Zhou, L.; Lu, J.; Wang, Y.; Xu, Y.; Xi, J.; et al. In-depth peripheral CD4 + T profile correlates with myasthenic crisis. *Ann. Clin. Transl. Neurol.* 2021, 8, 749–762
53. Yi, J.; Guidon, A.; Sparks, S.; Osborne, R.; Juel, V.; Massey, J.; Sanders, D.; Weinhold, K.; Guptill, J. Characterization of CD4 and CD8 T cell responses in MuSK myasthenia gravis. *J. Autoimmun.* 2014, 52, 130–138.
54. Morgan, B.P.; Chamberlain-Banoub, J.; Neal, J.W.; Song, W.; Mizuno, M.; Harris, C.L. The membrane attack pathway of complement drives pathology in passively induced experimental autoimmune myasthenia gravis in mice. *Clin. Exp. Immunol.* 2006, 146, 294–302
55. Vincent A, Palace J, Hilton-Jones D.Myasthenia gravis.*Lancet* 2001;357(9274):2122-8.
56. Ruff, R.L.; Lisak, R.P. Nature and Action of Antibodies in Myasthenia Gravis. *Neurol. Clin.* 2018, 36, 275–291.
57. Ruff, R.L.; Lennon, V.A. How Myasthenia Gravis Alters the Safety Factor for Neuromuscular Transmission. *J. Neuroimmunol.* 2008, 201–202, 13–20.
58. Laura D, Richard W, Kourosh R, Betty S. Myasthenia Gravis: Epidemiology, Pathophysiology and Clinical Manifestations *J Clin Med.* 2021 May 21;10(11):2235. DOI: 10.3390/jcm10112235
59. Wu X, Tuzun E, Saini SS, Wang J, Li J. Aguilera-subunit immunization in HLA DR3 transgenic mice.*Immunol Lett.* 2015;168(2):306-12
60. Polizzi A, Huson SM, Vincent A.Teratogen update: maternal myasthenia gravis as a cause of congenital arthrogryposis. *Teratology.*2000;62(5):332-41.
61. Al-Haidar M, Benatar M, Kaminski HJ.Ocular Myasthenia.*Neurol clin.*2018;36(2):241-251.
62. Wong SH, Huda S, Vincent A, Plant GT.Ocular myasthenia gravis:controversies and updates.*Curr Neurol Neurosci Rep.*2014;14(1):421.
63. Yan M, Xing GL, Xiong WC, Mei L.Agrin and LRP4 antibodies as new biomarkers of myasthenia gravis.*Ann N Y Acad Sci.*2018;1413(1):126-35.
64. IIIa I, Cortes-Vicente E, Martinez MA, Gallardo E.Diagnostic utility of contactin antibodies in myasthenia gravis.*Ann N Y Acad Sci.*2018;1412(1):90-4
65. Cordts I, Bodart N, Hartmann K, Karagiorgou K, Tzartos JS, Mei L, et al.Screening for lipoprotein receptor-related protein4-, agrin- and titin-antibodies and exploring the autoimmune spectrum in myasthenia gravis.*J Neurol.*2017;264(6):1193-203.
66. Ha JC, Richman DP.Myasthenia gravis and related disorders:Pathology and molecular pathogenesis.*Biochim Biophys Acta.*2015; 1852(4);651-7.
67. Guptill, J.T.;Sanders, D.B.;Evoli, A.Anti-MuSK antibody myasthenia gravis:Clinical findings and response to treatment in two large cohorts.*Muscle Nerve* 2011,44,36–40.

68. Huijbers MG, Querol LA, Niks EH, Plomp JJ, van der Maarel SM, Graus F, et al. The expanding field of IgG4-mediated neurological autoimmune disorders. Eur J Neurol. 2015;22(8):1151-61.
69. Titulaer MJ, Wirtz PW, Kuks JB, Schelhaas HJ, van der Kooi AJ, Faber CG, van der Pol WL, de Visser M, Sillevits Smitt PA, Verschuuren JJ. The Lambert-Eaton myasthenic syndrome 1988-2008: a clinical picture in 97 patients. J Neuroimmunol 2008; 201-202:153-158
70. Vincent, A. Antibodies And Receptors: From Neuromuscular Junction To Central Nervous System. *Neuroscience* 2020 , 439 , 48-61.
71. Tarr TB, Wipf P, Meriney SD. Synaptic Pathophysiology and Treatment of Lambert-Eaton Myasthenic Syndrome. *Mol Neurobiol*. 2015;52(1):456-63.
72. Waterman SA, Lang B, Newsom-Davis J. Effect of Lambert-Eaton myasthenic syndrome antibodies on autonomic neurons in the Mouse. *Ann Neurol*. 1997;42(2):147-56.
73. Bekircan-Kurt CE, Çiftçi ED, Kurne AT, Anlar B. Voltage gated calcium channel antibody-related neurological diseases. *World J Clin Cases* 2015; 3(3): 293-300 [PMID: 25789302 DOI: 10.12998/wjcc.v3.i3.293]
74. Titulaer MJ, Lang B, Verschuuren JJ. Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. *Lancet Neurol*. 2011;10:1098-1107.
75. Fukuda M, Moreira JE, Liu V, Sugimori M, Mikoshiba K, Llinás RR. Role of the conserved WHXL motif in the C terminus of synaptotagmin in synaptic vesicle docking. *Proc Natl Acad Sci USA*. 2000;97:14715-14719.
76. Tani T, Tanaka K, Idezuka J, Nishizawa M. Regulatory T cells in paraneoplastic neurological syndromes. *J Neuroimmunol*. 2008;196:166-169.
77. Lang B, Newsom-Davis J, Wray D, Vincent A, Murray N. Autoimmune etiology for myasthenic (eaton-lambert) syndrome. *Lancet*. 1981;2(8240):224-6.
78. Pinto A, Gillard S, Moss F, Whyte K, Brust P, Williams M, et al. Human autoantibodies specific for the alpha1A calcium channel subunit reduce both P-type and Q-type calcium currents in cerebellar neurons. *Proc Natl Acad Sci U S A*. 1998;95(14):8328-33.
79. Newsom-Davis J, Buckley C, Clover L, Hart I, Maddison P, Tuzun E, Vincent A. Autoimmune disorders of neuronal potassium channels. *ann N Y Acad Sci*. 2003;998:202-10.
80. Irani SR, Vincent A. Voltage-gated potassium channel-complex autoimmunity and associated clinical syndromes. *Handb Clin Neurol*. 2016;133:185-97.
81. Poyraz M, Matur Z, Aysal F, Tüzün E, Hanoğlu L, Öğre AE. Clinical Electrophysiological and serological Evaluation of Patients with Cramp-Fasciculation syndrome. *Nöro Psikiyat Arş*. 2017;54(2):183-6.
82. Sanders DB. Advancing research in autoimmune neuromuscular disorders. *Lancet Neurol*. 2022 Feb;21(2):108-110. doi: 10.1016/S1474-4422(21)00469-5. PMID: 35065029.