

## OTİZM ve MİKRORNA

Hilal AKKÖPRÜ<sup>1</sup>

### GİRİŞ

OTİZM Spektrum Bozukluğu (OSB) iletişim ve sosyal etkileşimdeki bozulma ile kısıtlı ve tekrarlayıcı ve davranış kalıplarını içeren bir grup heterojen nörogeleşimsel bozukluk olarak tanımlanmaktadır (1). Bu bozukluğun şiddeti bireyden bireye hafiften ağıra doğru değişmekte ve etkilenen bireylerin yaklaşık %40' ında bilişsel defisit bulunmaktadır (2). OSB semptomları ilk olarak erken çocukluk döneminde fark edilir ve tanı yaş ortalaması genelde 4 yaş civarındadır (3). Erkeklerde OSB insidansının kadınlara göre daha yüksek olduğu bildirilmiştir (4). Ayrıca OSB' ye dikkat eksikliği hiperaktivite bozukluğu, karşıt olma karşıt gelme bozukluğu, anksiyete ve duygudurum bozukluğu, obsesif kompulsif bozukluk gibi diğer birçok psikiyatrik tanı da eşlik etmektedir (5). OSB'nin prevalansında yıllar içinde dikkate değer bir artış gözlenmiştir; Hastalık Kontrol ve Önleme Merkezi dünya çapındaki prevalansın 2004'te 1/166, 2018'de ise bunun 1/59 olduğunu açıklamıştır (6). Bu büyük orandaki artışla ilgili henüz ortak bir fikir birliği olmamasına rağmen; bazıları bunu bozukluğun farkındalığındaki bir artışa ve daha iyi tanı kriterlerine bağlarken, diğerleri bunun yaygınlığındaki gerçek bir artıştan veya tüm bu faktörlerin bir kombinasyonundan kaynaklandığını öne sürmektedir (6).

<sup>1</sup> Uzm. Dr., Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Bölümü, Bingöl Kadın Doğum ve Çocuk Hastalıkları Hastanesi, hilalakkopru@hotmail.com

## KAYNAKÇA

1. Psychiatry APAJAJo. Diagnostic and statistical man. 2000;167:312-20.
2. Bauman MLJN. Medical comorbidities in autism: challenges to diagnosis and treatment. 2010;7(3):320-7.
3. Baio J. Prevalence of autism spectrum disorder among children aged 8 years-autism and developmental disabilities monitoring network, 11 sites, United States, 2010. 2014.
4. Fombonne EJRDiar, MF Casanova, ed. The epidemiology of pervasive developmental disorders. 2005:1-25.
5. Rosen TE, Mazefsky CA, Vasa RA, Lerner MDJIROP. Co-occurring psychiatric conditions in autism spectrum disorder. 2018;30(1):40-61.
6. Salloum-Asfar S, J Sathesh N, Abdulla SJFimn. Circulating miRNAs, small but promising biomarkers for Autism Spectrum Disorder. 2019;12:253.
7. Vaishnavi V, Manikandan M, Tiwary BK, Munirajan AKJPO. Insights on the functional impact of microRNAs present in autism-associated copy number variants. 2013;8(2):e56781.
8. Wu YE, Parikshak NN, Belgard TG, Geschwind DHJNn. Genome-wide, integrative analysis implicates microRNA dysregulation in autism spectrum disorder. 2016;19(11):1463-76.
9. Bourgeron TJNRN. From the genetic architecture to synaptic plasticity in autism spectrum disorder. 2015;16(9):551-63.
10. Geschwind DH, State MWJTLN. Gene hunting in autism spectrum disorder: on the path to precision medicine. 2015;14(11):1109-20.
11. Trzybulska D, Vergadi E, Tsatsanis CJE. miRNA and other non-coding RNAs as promising diagnostic markers. 2018;29(3):221.
12. Fiddes IT, Lodewijk GA, Mooring M, Bosworth CM, Ewing AD, Mantalas GL, et al. Human-specific NOTCH2NL genes affect Notch signaling and cortical neurogenesis. 2018;173(6):1356-69. e22.
13. Mazzio EA, Soliman KFJE. Basic concepts of epigenetics: impact of environmental signals on gene expression. 2012;7(2):119-30.
14. van Rooij E, Kauppinen S. Development of microRNA therapeutics is coming of age. EMBO Mol Med 6: 851–864. 2014.
15. O'Brien J, Hayder H, Zayed Y. Overview of microRNA biogenesis, mechanisms of actions, and circulation, Front. Endocrinol., 2018, vol. 9, no. 402. 2018.
16. Pillai RSJR. MicroRNA function: multiple mechanisms for a tiny RNA? 2005;11(12):1753-61.
17. Fregeac J, Colleaux L, Nguyen LSJN, Reviews B. The emerging roles of MicroRNAs in autism spectrum disorders. 2016;71:729-38.
18. Wang W, Kwon EJ, Tsai L-HJL, Memory. MicroRNAs in learning, memory, and neurological diseases. 2012;19(9):359-68.
19. Mellios N, Sur MJFip. The emerging role of microRNAs in schizophrenia and autism spectrum disorders. 2012;3:39.
20. Tonacci A, Bagnato G, Pandolfo G, Billeci L, Sansone F, Conte R, et al. MicroRNA cross-involvement in Autism Spectrum Disorders and Atopic Dermatitis: a literature review. 2019;8(1):88.

21. Hammond SMJAddr. An overview of microRNAs. 2015;87:3-14.
22. Bail S, Swerdel M, Liu H, Jiao X, Goff LA, Hart RP, et al. Differential regulation of microRNA stability. 2010;16(5):1032-9.
23. Penzes P, Cahill ME, Jones KA, VanLeeuwen J-E, Woolfrey KMJNn. Dendritic spine pathology in neuropsychiatric disorders. 2011;14(3):285-93.
24. Schrott GM, Tuebing F, Nigh EA, Kane CG, Sabatini ME, Kiebler M, et al. A brain-specific microRNA regulates dendritic spine development. 2006;439(7074):283-9.
25. Edbauer D, Neilson JR, Foster KA, Wang C-F, Seeburg DP, Battersby MN, et al. Regulation of synaptic structure and function by FMRP-associated microRNAs miR-125b and miR-132. 2010;65(3):373-84.
26. Siegel G, Obernosterer G, Fiore R, Oehmen M, Bicker S, Christensen M, et al. A functional screen implicates microRNA-138-dependent regulation of the depalmitoylation enzyme APT1 in dendritic spine morphogenesis. 2009;11(6):705-16.
27. Hollander JA, Im H-I, Amelio AL, Kocerha J, Bali P, Lu Q, et al. Striatal microRNA controls cocaine intake through CREB signalling. 2010;466(7303):197-202.
28. Im H-I, Hollander JA, Bali P, Kenny PJJNn. MeCP2 controls BDNF expression and cocaine intake through homeostatic interactions with microRNA-212. 2010;13(9):1120.
29. Mellios N, Sugihara H, Castro J, Banerjee A, Le C, Kumar A, et al. miR-132, an experience-dependent microRNA, is essential for visual cortex plasticity. 2011;14(10):1240-2.
30. Tognini P, Putignano E, Coatti A, Pizzorusso TJNn. Experience-dependent expression of miR-132 regulates ocular dominance plasticity. 2011;14(10):1237-9.
31. Gao J, Wang W-Y, Mao Y-W, Gräff J, Guan J-S, Pan L, et al. A novel pathway regulates memory and plasticity via SIRT1 and miR-134. 2010;466(7310):1105-9.
32. Basu SN, Kollu R, Banerjee-Basu SJNar. AutDB: a gene reference resource for autism research. 2009;37(suppl\_1):D832-D6.
33. Marralle M, Albanese NN, Cali F, Romano VJPO. Assessing the impact of copy number variants on miRNA genes in autism by Monte Carlo simulation. 2014;9(3):e90947.
34. Iwai N, Naraba HJB, communications br. Polymorphisms in human pre-miRNAs. 2005;331(4):1439-44.
35. Saunders MA, Liang H, Li W-HJPotNAoS. Human polymorphism at microRNAs and microRNA target sites. 2007;104(9):3300-5.
36. Li L, Meng T, Jia Z, Zhu G, Shi BJAJoMGPA. Single nucleotide polymorphism associated with nonsyndromic cleft palate influences the processing of miR-140. 2010;152(4):856-62.
37. Duan R, Pak C, Jin PJHmg. Single nucleotide polymorphism associated with mature miR-125a alters the processing of pri-miRNA. 2007;16(9):1124-31.
38. Kunej T, Skok DJ, Horvat S, Dovc P, Jiang ZJJobs. The glypican 3-hosted murine mir717 gene: sequence conservation, seed region polymorphisms and putative targets. 2010;6(7):769.
39. Lewis MA, Quint E, Glazier AM, Fuchs H, De Angelis MH, Langford C, et al. An ENU-induced mutation of miR-96 associated with progressive hearing loss in mice. 2009;41(5):614-8.

40. Toma C, Torrico B, Hervás A, Salgado M, Rueda I, Valdés-Mas R, et al. Common and rare variants of microRNA genes in autism spectrum disorders. 2015;16(6):376-86.
41. Amaral DG, Schumann CM, Nordahl CWJTin. Neuroanatomy of autism. 2008;31(3):137-45.
42. Stamova B, Ander BP, Barger N, Sharp FR, Schumann CMJJocn. Specific regional and age-related small noncoding RNA expression patterns within superior temporal gyrus of typical human brains are less distinct in autism brains. 2015;30(14):1930-46.
43. Ziats MN, Rennert OMJMp. Identification of differentially expressed microRNAs across the developing human brain. 2014;19(7):848-52.
44. Voineagu I, Eapen VJFihn. Converging pathways in autism spectrum disorders: interplay between synaptic dysfunction and immune responses. 2013;7:738.
45. Nguyen LS, Lepleux M, Makhlof M, Martin C, Fregeac J, Siquier-Pernet K, et al. Profiling olfactory stem cells from living patients identifies miRNAs relevant for autism pathophysiology. 2016;7(1):1-13.
46. Molofsky AV, Krenick R, Ullian E, Tsai H-h, Deneen B, Richardson WD, et al. Astrocytes and disease: a neurodevelopmental perspective. 2012;26(9):891-907.
47. Aronica E, Fluiter K, Iyer A, Zurolo E, Vreijling J, Van Vliet E, et al. Expression pattern of miR-146a, an inflammation-associated microRNA, in experimental and human temporal lobe epilepsy. 2010;31(6):1100-7.
48. Iyer A, Zurolo E, Prabowo A, Fluiter K, Spliet WG, van Rijen PC, et al. MicroRNA-146a: a key regulator of astrocyte-mediated inflammatory response. 2012;7(9):e44789.
49. Taganov KD, Boldin MP, Chang K-J, Baltimore DJPotNAoS. NF- $\kappa$ B-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. 2006;103(33):12481-6.
50. Lukiw WJ, Zhao Y, Cui JGJJJoBC. An NF- $\kappa$ B-sensitive micro RNA-146a-mediated inflammatory circuit in Alzheimer disease and in stressed human brain cells. 2008;283(46):31315-22.
51. Li YY, Cui JG, Dua P, Pogue AI, Bhattacharjee S, Lukiw WJJNI. Differential expression of miRNA-146a-regulated inflammatory genes in human primary neural, astroglial and microglial cells. 2011;499(2):109-13.
52. Boldin MP, Taganov KD, Rao DS, Yang L, Zhao JL, Kalwani M, et al. miR-146a is a significant brake on autoimmunity, myeloproliferation, and cancer in mice. 2011;208(6):1189-201.
53. Guo Q, Zhang J, Li J, Zou L, Zhang J, Xie Z, et al. Forced miR-146a expression causes autoimmune lymphoproliferative syndrome in mice via downregulation of Fas in germinal center B cells. 2013;121(24):4875-83.
54. Jin P, Alish RS, Warren STJNcb. RNA and microRNAs in fragile X mental retardation. 2004;6(11):1048-53.
55. Caudy AA, Myers M, Hannon GJ, Hammond SMJG, development. Fragile X-related protein and VIG associate with the RNA interference machinery. 2002;16(19):2491-6.
56. Ishizuka A, Siomi MC, Siomi HJG, development. A Drosophila fragile X protein interacts with components of RNAi and ribosomal proteins. 2002;16(19):2497-508.

57. Jin P, Zarnescu DC, Ceman S, Nakamoto M, Mowrey J, Jongens TA, et al. Biochemical and genetic interaction between the fragile X mental retardation protein and the microRNA pathway. 2004;7(2):113-7.
58. Lu R, Wang H, Liang Z, Ku L, O'Donnell WT, Li W, et al. The fragile X protein controls microtubule-associated protein 1B translation and microtubule stability in brain neuron development. 2004;101(42):15201-6.
59. Stefani G, Fraser CE, Darnell JC, Darnell RBJJoN. Fragile X mental retardation protein is associated with translating polyribosomes in neuronal cells. 2004;24(33):7272-6.
60. Bird AJBST. The methyl-CpG-binding protein MeCP2 and neurological disease. 2008;36(4):575-83.
61. Szulwach KE, Li X, Smrt RD, Li Y, Luo Y, Lin L, et al. Cross talk between microRNA and epigenetic regulation in adult neurogenesis. 2010;189(1):127-41.
62. Urdinguio RG, Fernandez AF, Lopez-Nieva P, Rossi S, Huertas D, Kulis M, et al. Disrupted microRNA expression caused by Mecp2 loss in a mouse model of Rett syndrome. 2010;5(7):656-63.
63. Cheng T-L, Wang Z, Liao Q, Zhu Y, Zhou W-H, Xu W, et al. MeCP2 suppresses nuclear microRNA processing and dendritic growth by regulating the DGCR8/Drosha complex. 2014;28(5):547-60.
64. Goldani AA, Downs SR, Widjaja F, Lawton B, Hendren RLJFip. Biomarkers in autism. 2014;5:100.
65. Van Rooij E, Kauppinen SJEmm. Development of micro RNA therapeutics is coming of age. 2014;6(7):851-64.
66. Montgomery RL, Yu G, Latimer PA, Stack C, Robinson K, Dalby CM, et al. Micro RNA mimicry blocks pulmonary fibrosis. 2014;6(10):1347-56.
67. Kolata G, Narayan A, Harrell E, Naldini L, Anonymous, Stern V, et al. Therapeutic Silencing of MicroRNA-122 in Primates with Chronic Hepatitis C Virus Infection. 2010;21(1):5-7.
68. Janssen HL, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, et al. Treatment of HCV infection by targeting microRNA. 2013;368(18):1685-94.
69. Halle B, Marcusson EG, Aaberg-Jessen C, Jensen SS, Meyer M, Schulz MK, et al. Convection-enhanced delivery of an anti-miR is well-tolerated, preserves anti-miR stability and causes efficient target de-repression: a proof of concept. 2016;126(1):47-55.