BÖLÜM 36

NÖROLOJİK HASTALIKLARDA VİTAMİN VE ESER ELEMENTLERİN ETKİSİ

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GİRİŞ

Organizmada sinir sistemi ile ilgili hastalıklar nörolojik hastalıklar olarak tanımlanır. Nörolojik hastalıklar vücuttaki diğer sistemleri de etkileyerek fonksiyon bozukluklarına neden olabilir. Demans, alzheimer, epilepsi, multiple skleroz, parkinson hastalığı, baş ağrısı bozuklukları, nöro-enfeksiyonlar, malnutrisyonla ilgili nörolojik bozukluklar, inme, travmatik beyin yaralanmaları nörolojik hastalıklar olarak sınıflandırılır (1–3). Demans bilinçte bozulma olmaksızın, bilişsel fonksiyonların deliryum dışında bir nedenle süregelen, ilerleyici ve genellikle geri dönüşümsüz bozulması olarak tanımlanır. Demans hastalarında hafıza, yargılama, hesaplama, planlama ve organize davranışlar gibi yürütücü işlevlerde bozulma, duygu kontrolü ve çevreye olan ilginin azalması gibi klinik tablolar görülmektedir. Demans hastalarının yaklaşık %50-70'ini oluşturan alzheimer bellek kaybı, konuşma, karar verme işlevlerinde, dikkat, oryantasyon ve kişilik bozukluklarının ortaya çıktığı, ilerleyici ve ölümcül bir hastalık olarak tanımlanır (2, 4). Yaş, kadın cinsiyet ve aile öyküsü gibi faktörler alzheimer risk faktörleri arasında belirtilmesine rağmen; hipertansiyon, diyabet gibi kronik hastalıklar, düşük eğitim ve sosyoekonomik seviye, metal toksisitesine maruz kalma, inflamasyon, oksidatif stres, beslenme yetersizliği, homosistein seviyesinin artması ve B12 vitamini eksikliğinin de alzheimer gelişiminde ve ilerlemesinde etkisi olabileceği rapor edilmiştir (1, 5, 6).

Organizmada çeşitli vitaminlerin eksikliği ya da birikiminde sinir sistemi fonksiyonunun etkilendiği ve bu durumun alzheimer ve parkinson başta olmak üzere nörolojik hastalıklar ile ilişkili olduğu rapor edilmektedir. Yapılan pek çok çalışmada beslenme ve antioksidan bakımından zengin diyetin demans, alzheimer, parkinson, travmatik beyin hasarı, epilepsi, multipl skleroz gibi nörodejeneratif hastalıklarda koruyucu etkisi olduğu bildirilmiştir (7, 8). Diyet ile alınan besin öğeleri arasında protein, yağ ve karbonhidratlar makrobesin; vitamin, elektrolit ve eser elementler mikrobesin olarak nitelendirilmektedir. Mikrobesinler arasında yer alan vitamin ve eser element metabolizmasındaki bozukluklar sonucu nörodejeneratif hastalıkların gelişiminin arttığı, bu

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nin nörolojik hastalıkların gelişimi ile ilişkilendirildiği bildirilmiştir (14, 36, 70).

Mikrobesin seviyesi ve nörolojik hastalıklar yakından ilişkili olduğu için bu mikrobesinlerin homeostazındaki değişikliklerin takip edilmesi hastalıkta erken tanıyı sağlamak ve hastalığın seyrinin takibi açısından faydalı olabilecektir.

KAYNAKLAR

1. Morley JE, Farr SA, Nguyen AD. Alzheimer Disease. *Clin Geriatr Med.* 2018;34(4):591-601. doi: 10.1016/j.cger.2018.06.006.
2. Bendlin BB, Carlsson CM, Gleason CE, et al. Midlife predictors of Alzheimer's disease. *Maturitas.* 2010;65(2):131-137. doi: 10.1016/j.maturitas.2009.12.014
3. Reynolds EH, Bottiglieri T, Laundy M, et al. Vitamin B12 metabolism in multiple sclerosis. *Arch Neurol.* 1992;49(6)649-652. doi:10.1001/archneur.1992.00530300089014.
4. Daviglus ML, Plassman BL, Pirzada A, et al. Risk factors and preventive interventions for alzheimer disease: State of the science. *Arch Neurol.* 2011;68(9):1185-1190. doi: 10.1001/archneurol.2011.100.
5. Ulep MG, Saraon SK, McLea S. Alzheimer Disease. *J Nurse Pract.* 2018;14:129-135. doi: 10.1016/j.nurpra.2017.10.014.
6. Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. *Nat Med.* 2004;10:10-18. doi: 10.1038/nm1066.
7. Refsum H, Smith AD. Low vitamin B-12 status in confirmed Alzheimer's disease as revealed by serum holotranscobalamin. *J Neurol Neurosurg Psychiatry.* 2003;74(7):959-961. doi: 10.1136/jnnp.74.7.959.
8. Miller A, Korem M, Almog R, et al. Vitamin B12, demyelination, remyelination and repair in multiple sclerosis. *J Neurol Sci.* 2005;233(1-2):93-97. doi: 10.1016/j.jns.2005.03.009.
9. Aliev G, Ashraf GM, Kaminsky YG SI, et al. Implication of the nutritional and non-nutritional factors in the context of preservation of cognitive performance in patients with dementia/depression and alzheimer diseas. *Am J Alzheimers Dis Other Demen.* 2013;28(7):660–70.
10. Gu Y, Luchsinger JA, Stern Y, et al. Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. *J Alzheimer's Dis.* 2010;22(2):483-92. doi: 10.3233/JAD-2010-100897.
11. Stafstrom CE, Rho JM. The ketogenic diet as a treatment paradigm for diverse neurological disorders. *Front Pharmacol.* 2012;3:59. doi: 10.3389/fphar.2012.00059
12. Baylink D, Stauffer M, Wergedal J, et al. Formation, mineralization, and resorption of bone in vitamin D-deficient rats. *J Clin Invest.* 1970;49(6):1122-1134. doi: 10.1172/JCI106328
13. Holick MF. The vitamin D epidemic and its health consequences. *J Nutr.* 2005;135(11):2739-2748. doi: 10.1093/jn/135.11.2739s.
14. Nawaz A, Khattak NN, Khan MS, et al. Deficiency of vitamin B12 and its relation with neurological disorders: a critical review. *J Basic Appl Zool.* 2020;81(10):1-9. doi: 10.1186/s41936-020-00148-0.
15. Kumar SS, Chouhan RS, Thakur MS. Trends in analysis of vitamin B12. *Anal Biochem.* 2010;398(2):139-149. doi: 10.1016/j.ab.2009.06.041
16. Herrmann W, Obeid R. Causes and early diagnosis of vitamin b12 deficiency. *Dtsch Arztebl Int.* 2008;105(40):680–685.doi: 10.3238/arztebl.2008.0680.
17. Gröber U, Kisters K, Schmidt J. Neuroenhancement with Vitamin B12-underestimated neurological significance. *Nutrients.* 2013;5(12):5031-5045. doi: 10.3390/nu5125031
18. Obeid R, Fedosov SN, Nexo E. Cobalamin coenzyme forms are not likely to be superior to cyano- and hydroxyl-cobalamin in prevention or treatment of cobalamin deficiency. *Mol Nutr Food Res.* 2015;59(7):1364-1372. doi: 10.1002/mnfr.201500019.
19. Oh RC, Brown DL. Vitamin B12 deficiency. *Am Fam Physician.* 2003;67(5):979-986. doi: 10.29309/tpmj/2018.25.05.321.
20. Calderón-Ospina CA, Nava-Mesa MO. B Vitamins in the nervous system: Current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. *CNS Neurosci Ther.* 2020;26(1):5-13. doi: 10.1111/cns.13207.
21. Adamo AM. Nutritional factors and aging in demyelinating diseases. *Genes Nutr.* 2014;9(1):360-369. doi: 10.1007/s12263-013-0360-8.
22. Kumar N. Neurologic aspects of cobalamin (B12) deficiency. *Handb Clin Neurol.* 2014;120:915-926. doi: 10.1016/B978-0-7020-4087-0.00060-7.
23. Briani C, Torre CD, Citton V, et al. Cobalamin deficiency: Clinical picture and radiological findings. *Nutrients.* 2013;5(11):4521-4539.doi: 10.3390/nu5114521.
24. Lauer AA, Grimm HS, Apel B, et al. Mechanistic Link between Vitamin B12 and Alzheimer's Disease. *Biomolecules.* 2022;14;12(1):129. doi: 10.3390/biom12010129.
25. Mattila P, Valaja J, Rossow L, et al. Effect of vitamin D2- and D3-enriched diets on egg vitamin D content, production, and bird condition during an entire production period. *Poult Sci.* 2004;83(3):433-440. doi: 10.1093/ps/83.3.433.
26. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. *Chem Biol.* 2014;21(3):319-329. doi: 10.1016/j.chembiol.2013.12.016.
27. Armas LAG, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab.* 2004;89(11):5387-5391. doi: 10.1210/jc.2004-0360.
28. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. *Am J Physiol Ren Physiol.* 2005;289(1):8-28. doi: 10.1152/ajprenal.00336.2004.
29. Hoenderop JGJ, Chon H, Gkika D, et al. Regulation of gene expression by dietary Ca^{2+} in kidneys of 25-hydroxyvitamin D3-1α-hydroxylase knockout mice. *Kidney Int.* 2004;65(2):531-539. doi: 10.1111/j.1523-1755.2004.00402.x.

30. Wilkinson RJ, Llewelyn M, Toossi Z, et al. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: A case-control study. *Lancet*. 2000; 19;355(9204):618-621. doi: 10.1016/S0140-6736(99)02301-6.
31. Tsiaras WG, Weinstock MA. Factors influencing vitamin d status. *Acta Derm Venereol*. 2011;91(2):115-124. doi: 10.2340/00015555-0980.
32. McGrath J. Does 'imprinting' with low prenatal vitamin D contribute to the risk of various adult disorders? *Med Hypotheses*. 2001;56(3):367-371.doi: 10.1054/mehy.2000.1226
33. Kjærgaard M, Waterloo K, Wang CEA, et al. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: Nested case-control study and randomised clinical trial. *Br J Psychiatry*. 2012;201(5):360-368. doi: 10.1192/bjp.bp.111.104349.
34. Yavuz D, Mete T, Yavuz R, Altunoğlu A. D Vitamini, kalsiyum & mineral metabolizması, d vitaminin iskelet dışı etkileri ve kronik böbrek yetmezliğinde nütrisyonel d vitamini kullanımı. *Ankara Med J*. 2014;14(4): 162-171. doi: 10.17098/amj.19812.
35. Annweiler C. Vitamin D-mentia: Is vitamin d optional or essential for preventing late-life cognitive decline? *J Am Geriatr Soc*. 2017;65(10):2155-2157. doi: 10.1111/jgs.15056.
36. Annweiler C, Schott AM, Berrut G, et al. Vitamin D and ageing: Neurological issues. *Neuropsychobiology*. 2010;62(3):139-150. doi: 10.1159/000318570.
37. Deibel MA, Ehmann WD, Markesbery WR. Copper, iron, and zinc imbalances in severely degenerated brain regions in Alzheimer's disease: Possible relation to oxidative stress. *J Neurol Sci*. 1996;143(1-2):137-142. doi: 10.1016/S0022-510X(96)00203-1.
38. Maret W, Sandstead HH. Zinc requirements and the risks and benefits of zinc supplementation. *J Trace Elem Med Biol*. 2006;20(1):3-18. doi: 10.1016/j.jtemb.2006.01.006.
39. Dobrowolska J, Dehnhardt M, Matusch A, et al. Quantitative imaging of zinc, copper and lead in three distinct regions of the human brain by laser ablation inductively coupled plasma mass spectrometry. *Talanta*. 2008;15;74(4):717-723. doi: 10.1016/j.talanta.2007.06.051.
40. Huang X, Moir RD, Tanzi RE, et al. Redox-active metals, oxidative stress, and Alzheimer's disease pathology. *Ann N Y Acad Sci*. 2004;1012:153-163. doi: 10.1196/annals.1306.012.
41. Perry G, Cash AD, Srinivas R, et al. Metals and oxidative homeostasis in Alzheimer's disease. *Drug Dev Res*. 2013;62(5):540-555. doi: 10.1002/ddr.10099.
42. Núñez MT, Urrutia P, Mena N, et al. Iron toxicity in neurodegeneration. *BioMetals*. 2012;25(4):761-776. doi: 10.1007/s10534-012-9523-0.
43. Zecca L, Youdim MBH, Riederer P, et al. Iron, brain ageing and neurodegenerative disorders. *Nat Rev Neurosci*. 2004;5(11):863-873. doi: 10.1038/nrn1537.
44. Kruer MC, Boddaert N, Schneider A, et al. Neuroimaging features of neurodegeneration with brain iron accumulation. *Am J Neuroradiol*. 2012;33(3):407-414. oi: 10.3174/ajnr.A2677.
45. Andrews NC. Iron homeostasis: Insights from genetics and animal models. *Nat Rev Genet*. 2000;1(3):208-217. doi: 10.1038/35042073.
46. Meng X, Zhang X, Liu M, et al. Fenton reaction-based nanomedicine in cancer chemodynamic and synergistic therapy. *Appl Mater Today*. 2020;100864:1-21. doi: 10.1016/j.apmt.2020.100864.
47. Muñoz M, García-Erce JA, Remacha ÁF. Disorders of iron metabolism. Part II: Iron deficiency and iron overload. *J Clin Pathol*. 2011;64(4):287-296. doi: 10.1136/jcp.2010.086991.
48. Berg D, Youdim MBH. Role of iron in neurodegenerative disorders. T*op Magn Reson Imaging*. 2006;17(1):5-17. doi: 10.1097/01.rmr.0000245461.90406.ad.
49. Marchan R, Cadenas C, Bolt HM. Zinc as a multipurpose trace element. *Arch Toxicol*. 2006;80(1):1-9. doi: 10.1007/s00204-012-0843-1.
50. Chasapis CT, Spiliopoulou CA, Loutsidou AC, et al. Zinc and human health: An update. *Arch Toxicol*. 2012;86(4):521-534. doi: 10.1007/s00204-011-0775-1.
51. Jarosz M, Olbert M, Wyszogrodzka G, et al. Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-κB signaling. *Inflammopharmacology*. 2017;25(1):11-24. doi: 10.1007/s10787-017-0309-4.
52. Guler I, Himmetoglu O, Turp A, et al. Zinc and homocysteine levels in polycystic ovarian syndrome patients with insulin resistance. *Biol Trace Elem Res*. 2014;158(3):297-304. doi: 10.1007/s12011-014-9941-7.
53. Prasad DKV, Shaheen U, Satyanarayana U, et al. Association of serum trace elements and minerals with genetic generalized epilepsy and idiopathic ıntractable epilepsy. *Neurochem Res*. 2014;39(12):2370-2376. doi: 10.1007/s11064-014-1439-3.
54. Donma MM, Donma O. Çocuklarda ve genç erişkinlerde görülen depresyonda eser elementler ve fiziksel aktivite. *Turkish J Med Sci*. 2010;14(40):101-110. doi: 10.3906/sag-0811-33
55. Tapiero H, Townsend DM, Tew KD. Trace elements in human physiology and pathology. Copper. *Biomed Pharmacother*. 2003;57(9):386-398. doi: 10.1016/S0753-3322(03)00012-X
56. Manto M. Abnormal copper homeostasis: Mechanisms and roles in neurodegeneration. *Toxics*. 2014;2:327-345. doi: 10.3390/toxics2020327.
57. Ala A. Wilson's disease. *Medicine*. 2015;43:661-663.doi:10.1016/j.mpmed.2019.09.001.
58. Linder MC, Hazegh-Azam M. Copper biochemistry and molecular biology. *Am. J. Clin. Nutr*. 1996;63(5):797-811. doi: 10.1093/ajcn/63.5.797.
59. Freedman JH, Ciriolo MR, Peisach J. The role of glutathione in copper metabolism and toxicity. *J Biol Chem*. 1989;264(10):5598-5605. doi: 10.1016/s0021-9258(18)83589-x
60. Steinebach OM, Wolterbeek HT. Role of cytosolic copper, metallothionein and glutathione in copper toxicity in rat hepatoma tissue culture cells. *Toxicology*. 1994;92(1-3):75-90. doi: 10.1016/0300-483X(94)90168-6.

61. Rosencrantz R, Schilsky M. Wilson disease: Pathogenesis and clinical considerations in diagnosis and treatment. *Semin Liver Dis.* 2011;31(3):245-259 doi: 10.1055/s-0031-1286056.
62. Larin D, Mekios C, Das K, et al. Characterization of the interaction between the Wilson and Menkes disease proteins and the cytoplasmic copper chaperone, HAH1p. *J Biol Chem.* 1999;274(40):28497-28504 doi: 10.1074/jbc.274.40.28497
63. Horn Campbell C, Brown R, Linder MC. Circulating ceruloplasmin is an important source of copper for normal and malignant animal cells. *BBA-Gen Subj.* 1981;678(1):27-38. doi: 10.1016/0304-4165(81)90044-1
64. Lee J, Prohaska JR, Thiele DJ. Essential role for mammalian copper transporter Ctr1 in copper homeostasis and embryonic development. *Proc Natl Acad Sci USA.* 2001;98(12):6842-6847. doi: 10.1073/pnas.111058698
65. Kuo YM, Zhou B, Cosco D, et al. The copper transporter CTR1 provides an essential function in mammalian embryonic development. *Proc Natl Acad Sci USA.* 2001;98(12):6836-6841. doi: 10.1073/pnas.111057298
66. Linder MC, Wooten L, Cerveza P, et al. Copper transport. *Am J Clin Nutr.* 1998;67(5):965-971. doi: 10.1093/ajcn/67.5.965S.
67. Amaravadi R, Glerum DM, Tzagoloff A. Isolation of a cDNA encoding the human homolog of COX17, a yeast gene essential for mitochondrial copper recruitment. *Hum Genet.* 1997;99(3):329-333. doi: 10.1007/s004390050367
68. Moira Glerum D, Shtanko A, Tzagoloff A. Characterization of COX17, a yeast gene involved in copper metabolism and assembly of cytochrome oxidase. *J Biol Chem.* 1996;14;271(24):14504-14509. doi: 10.1074/jbc.271.24.14504
69. Forget P, Echeverria G, Giglioli S, et al. Biomarkers in immunonutrition programme, is there still a need for new ones? A brief review. *Ecancermedicalscience.* 2015;9:546. doi: 10.3332/ecancer.2015.546.
70. Pfeiffer RF. Wilson's disease. *Continuum (Minneap Minn).* 2016;22(4 Movement Disorders):1246-1261. doi: 10.1055/s-2007-971173.