

# BÖLÜM 8

## NÖROLOJİ VE COVID-19

Türkan ACAR<sup>1</sup>

### GİRİŞ

Aralık 2019'dan beri yeni tip koronavirüsün neden olduğu ve “yenikorona virüs hastalığı (COVID-19)” olarak adlandırılan hastalık ilk Çin'de başlayıp tüm dünyaya hızla yayılmıştır [1]. Salgın ile birlikte tüm dünyada yaşamın akışı, yaşam tarzı, alışkanlıklar, eğitim, siyaset ve ekonomide sarsıcı değişiklikler meydana gelmiştir [2].

Hızla gelişen COVID-19 salgını, şiddetli akut solunum sendromu koronavirüs 2'den (SARS-CoV-2) kaynaklanmaktadır. COVID-19 hastalarının, daha şiddetli COVID-19 seyri gösterenlerde yüksek sıklıkta bilinc bozukluğu, inme ve nöbet gibi nörolojik belirtiler bildirilmiştir. Ancak bu belirtiler periferik sinir sistemi (PSS) veya santral sinir sisteminin (SSS) doğrudan enfeksiyonunu gerektirmez, sinir sistemi dışındaki bir viral enfeksiyona yanıt olarak şiddetli bir sistemik reaksiyona ikincil olarak da ortaya çıkabilir [3-4].

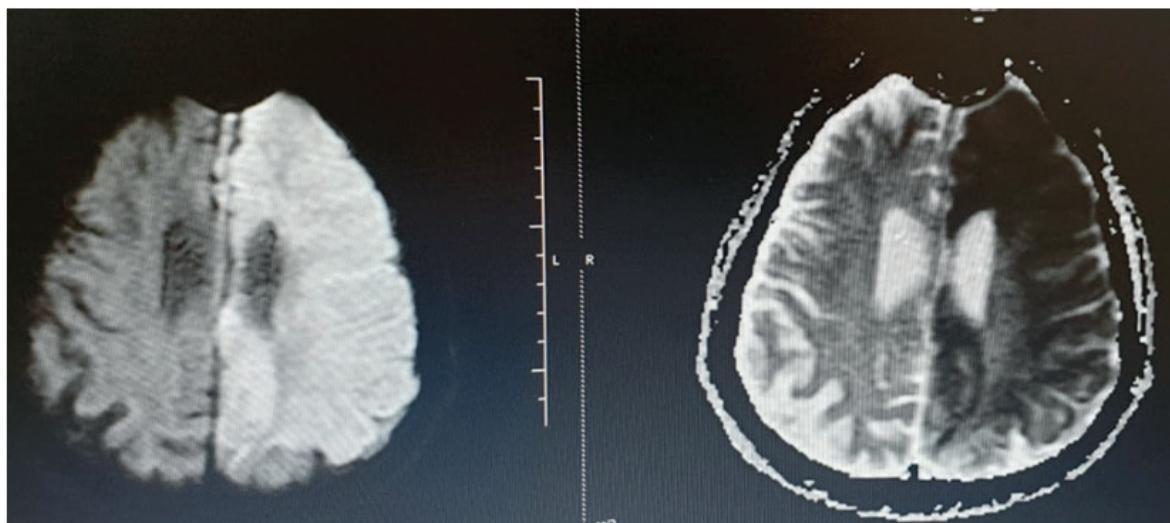
Hastalıkla ilgili yapılan ilk çalışmalarda anosmi, miyalji, baş ağrısı, bilinc bulanıklığı gibi nons-

pesifik nörolojik başlangıçlar bildirilmiştir. Ancak ilk nörolojik vakaların yayınlanmasından sonra nörolojik belirti ve bulguların raporlanması artış göstermiştir. [4-8].

SARS-CoV-2 spike (S) proteini, hücre tropizmi ile ilgili olan konak hücresel anjiotensin konverting enzim-2 (ACE-2) reseptörüne bağlanır. S proteininin transmembran proteaz serin 2 (TMPRSS2) tarafından işlenip ve hazır hale getirilmesi, virüs ve konak hücre zar füzyonunun SARS-CoV-2'nin hücreye girmesi için gerekli olduğu gösterilmiştir [9].

Koronavirüsler, ACE-2 reseptörlerine bağlanarak hücre içine girer ve beyne farklı yollardan ulaşabilir. Bunlardan ilki; kan beyin bariyerinde (KBB) ve beyin omurilik sıvısı (BOS) endotel ve epitel hücrelerini enfekte etmesi ya da lökositler aracılığıyla beyne ulaşmasıdır. İkincisi ise virüsün retrograd aksonal transport yoluyla beyne ulaşmasıdır; bu ulaşım genellikle kranial veya periferik sinirler aracılığı ile gerçekleşmektedir. Kas

<sup>1</sup> Doç. Dr. Türkan ACAR, Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi Nöroloji AD, tdeniz38@hotmail.com



**Figür 4:** COVID-19 hastasında büyük damar tıkanıklığına bağlı, difüzyon ağırlıklı MR görüntülemede, supraganglionik aksiyel kesitte, sol orta serebral arter (MCA) ve sol anterior serebral arter (ACA) sulama alanlarının etkilentiği b-1000 hiperintens, ADC karşılığı hipointens akut enfarkt ile uyumlu difüzyon kısıtlılığı.

## Sonuç

COVID-19 nörolojisi geniş bir otoimmun-trombotik bozukluk yelpazesine sahiptir. Bu olağanüstü zamanlarda, nörologların ön saflarda yer almaları ve COVID-19'un nörolojik komplikasyonlarına karşı tetikte olmaları gerekmektedir. Nörolojik bozuklukları olan hastalar, özellikle immünomodülatör tedaviler alan hastalar, yakından izlenmelidir.

## Akılda kalması gerekenler

- Klinisyenler, nörolojik tutulum ve COVID-19'un olası nörolojik belirtileri için tetikte olmalıdır.
- Klinisyenler, özellikle yaşlı hastalarda, bilişsel bozukluğu ve/veya psikiyatrik komorbiditesi olan hastalarda COVID-19 sonrası olası nörolojik ve bilişsel yakınmaların farkında olmalıdır.
- Birçok nörolojik belirtinin, virüsün başlangıç semptomu olabileceği ve atipik-akut başlangıçta COVID-19 birlikteliği akılda tutulmalıdır.
- Nörolojik tutulum sırasında tedavi protokolünün gözden geçirilmesi ve etkileşim açısından dikkatli olunması gerekmektedir.

## KAYNAKÇA

1. TC Sağlık Bakanlığı. Covid-19-Sars-Cov-2 Enfeksiyonu Rehberi (Bilim Kurulu Çalışması) 14.4.2020.
2. Acar T, Demirel EA, Afşar N, Akçali A, Demir GA, Alagöz AN, et al. Nörolojik Bakış Açısından COVID-19. Turk J Neurol. 2020;26: 56-106.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China. N Engl J Med. 2020;382:727-733
4. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77:1-9.
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.
6. Romoli M, Jelcic I, Bernard-Valnet R, García Azorín D, Mancinelli L, Akhvlediani T, et al. A systematic review of neurological manifestations of SARS-CoV-2 infection: the devil is hidden in the details. Eur J Neurol 2020;10.1111/ene.14382.
7. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: A systematic review. J Neurol Sci 2020;413:116832.
8. Romero-Sanchez CM, Diaz-Maroto I, Fernandez-Diaz E, Sanchez-Larsen A, Layos-Romero A, Garcia-Garcia J, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBA COVID registry. Neurology 2020;95(8):1060-1070.

9. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol.* 2020;94:e00127-e220
10. To KF, Tong JH, Chan PK, Au FW, Chim SS, Chan KA, et al. Tissue and cellular tropism of the coronavirüs associated with severe acute respiratory syndrome: an in-situ hybridization study of fatal cases. *J Pathol.* 2004;202:157-63.
11. Muus C, Luecken MD, Eraslan G, Waghraj A, Heimberg G, Sikkema L, et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells. *BioRxiv.* 2020. doi. org/10.1101/2020.04.19.049254
12. Chen R, Wang K, Yu J, Chen Z, Wen C, Xu Z. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. *Neuroscience.* 2020. doi. org/10.1101/2020.04.07.030650
13. Qi J, Zhou Y, Hua J, Zhang L, Bian J, Liu B, et al. The scRNA-seq expression profiling of the receptor ACE2 and the cellular protease TMPRSS2 reveals human organs susceptible to COVID-19 infection. *Bioinformatics.* 2020. doi. org/10.1101/2020.04.16.045690
14. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med.* 2005;202:415-424
15. Kabbani N, Olds JL. Does COVID19 infect the brain? If so, smokers might be at a higher risk. *Mol Pharmacol.* 2020;97:351-353
16. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol.* 2020; doi.org/10.1001/jamaneurol.2020.2065
17. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci.* 2020;11:995-998
18. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* 2020;92:552-555
19. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol.* 2008;82:7264-7275
20. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dube M, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses.* 2019;12(1):14
21. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. *2020 medRxiv.*
22. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirüs. *Emerg Infect Dis* 2004;10:342-344.
23. Jin H HC, Chen S, Zhou Y, Wang Y, Mao L, et al. Consensus for prevention and management of coronavirüs disease 2019 (COVID-19) for neurologists *Stroke & Vascular Neurology* 2020. doi:10.1136/svn-2020-000382.
24. Ozturk S. COVID-19 ve Nöroloji. *Turk J Neurol* 2020.
25. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J et al. A first case of meningitis/encephalitis associated with SARS-Coronavirüs-2. *Int J Infect Dis* 2020;94:55-58.
26. Baig AM. Neurological manifestations in COVID-19 caused by SARSCoV-2. *CNS Neurosci Ther.* 2020;26:499-501.
27. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. *Radiology.* 2020;201187
28. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis* 2020;71:189-190.
29. Fitzgerald S. Loss of Smell as an Early Symptom of COVID-19: What Research Is Uncovering: American Academy of Neurology. (2020). Available online at: <https://journals.lww.com/neurotodayonline/blog/breakingnews/> pages/post.aspx?PostID=928 (accessed April 12, 2020)
30. Steardo L, Steardo L Jr., Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiol (Oxf).* 2020;229(30):e13473. doi: 10.1111/apha.13473.
31. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun.* 2020;87:18-22.
32. Bostancılioğlu M. SARS-CoV2 entry and spread in the lymphatic drainage system of the brain. *Brain Behav Immun.* 2020;87:122-123.
33. Li Z, Liu T, Yang N, Han D, Mi X, Li Y, et al. Neurological manifestations of patients with COVID-19: potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain. *Front Med.* 2020. doi: 10.1007/s11684-020-0786-5

34. Needham EJ, Chou SH, Coles AJ, Menon DK. Neurological implications of COVID-19 infections. *Neurocrit Care.* 2020; 32(3):667-671.
35. Bolay H, Güll A, Baykan B. COVID-19 is a Real Headache, Headache. 2020. doi.org/10.1111/head.13856
36. Vacchiano V, Riguzzi P, Volpi L, Tappata M, Avoni P, Rizzo G, et al. Early neurological manifestations of hospitalized COVID-19 patients. *Neurological Sciences.* 2020;41(8):2029-2031.
37. MaassenVanDenBrink A, De Vries T, Danser AJ. Headache medication and the COVID-19 pandemic. *The Journal of Headache and Pain.* 2020;21(1), 1-4.
38. Ellul MA, Benjamin L, Singh B, Lant S, Michael, B, Kneen R, et al. Neurological associations of COVID-19. *Lancet Neurol.* 2020. doi:10.1016/S1474-4422(20)30221-0
39. Laurendon T, Radulesco T, Mugnier J, Gerault M, Chagnaud C, ElAhmadi AA, et al. Bilateral transient olfactory bulb edema during COVID-19 related anosmia. *Neurology* 2020;95:224-225.
40. Politi LS, Salsano E and Grimaldi M. Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and anosmia. *JAMA Neurol.* 2020;77:1028-1029
41. Held P, Seitz J, Fründ R, Nitz WR, Haffke T, Hees H and Bonkowsky V: MRI detection of olfactory bulb and tract. *J Neuroradiol* 2000;27:112-118.
42. Kirchdoerfer RN, Wang N, Pallesen J, Wrapp D, Turner HL, Cottrell CA, et al. Stabilized coronavirus spikes are resistant to conformational changes induced by receptor recognition or proteolysis. *Scientific reports.* 2018;8(1):1-11.
43. Finsterer J, Stollberger C. Causes of hypogeusia/hyposmia in SARS-CoV2 infected patients. *J Med Virol* 2020. doi:10.1002/jmv.25903.
44. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence?. *The Lancet Neurology.* 2020;19(5):383-384.
45. Jacobs BC, Rothbarth P H, VanderMeche FGA, Herbrink P, Schmitz PIM, De Klerk MA, et al. The spectrum of antecedent infections in Guillain-Barre syndrome: a case-control study. *Neurology.* 1998;51(4):1110-1115.
46. Haber P. Guillain-Barre syndrome following influenza vaccination. *JAMA.* 2004;292:2478.
47. Cao-Lormeau VM, Blake AMS, Lastere SRC, Vanhomwegen J, Ghawche F. Guillain-Barre Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *The Lancet.* 2016;387(10027):1531-1539.
48. Fantini J, Chahinian H, Yahi N. Synergistic antiviral effect of hydroxychloroquine and azithromycin in combination against SARS-CoV-2: what molecular dynamics studies of virus-host interactions reveal. *IntJ Antimicrob Agents.* 2020;106020:1-9
49. Vaduganathan M, Vardeny O, Michel T, McMurray J JV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med.* 2020;382:1653-1659.
50. Dalakas MC. Guillain-Barre syndrome: the first documented COVID-19-triggered autoimmune neurologic disease: more to come with myositis in the offing. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:5.
51. Hartung HP, Toyka KV. T-cell and macrophage activation in experimental autoimmune neuritis and Guillain-Barre syndrome. *Ann Neurol.* 1990;27(1):57-63.
52. Pilotto A, Odolini S, Masciocchi S, Comelli A, Volonighi I, Gazzina S, et al. Steroid-responsive encephalitis in COVID-19 disease. *Ann Neurol.* 2020; doi: 10.1002/ana.25783.
53. Bernard-Valnet, Pizzarotti B, Anichini A, Demars Y, Russo E, Schmidhauser M, et al. Two patients with acute meningo-encephalitis concomitant to SARS-CoV-2 infection. *Eur J Neurol.* 2020; doi: 10.1111/ene.14298.
54. Liu K, Pan M, Xiao Z, Xu X. Neurological manifestations of the coronavirus (SARS-CoV-2) pandemic 2019-2020. *J Neurol Neurosurg Psychiatry.* 2020; 91(6):669-670. doi: 10.1136/jnnp2020-323177.
55. Leonardi M, Padovani A, McArthur JM. Neurological manifestations associated with COVID19: a review and a call for action. *J Neurol.* 2020; 1573-1576.
56. Wong AM, Simon EM, Zimmerman RA, Wang HS, Toh CH, Ng SH. Acute Necrotizing Encephalopathy of Childhood: Correlation of MR Findings and Clinical Outcome AJNR Am J Neuroradiol. 2006;27(9):1919-23.
57. Zhang T, Rodricks MB, Hirsh E. COVID-19-Associated Acute Disseminated Encephalomyelitis – A Case Report. 2020; medRxiv preprint doi: doi.org/10.1101/2020.04.16.20068148.
58. Toscano G, Palmerini F, Ravalia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-Barre Syndrome Associated with SARS-CoV-2. *N. Engl. J. Med.* 2020; doi.org/10.1056/NEJMc2009191.
59. Hirano T, Murakami M. COVID-19: A new virus, but a familiar receptor and cytokine release syndrome. *Immunity.* 2020; doi.org/10.1016/j.imuni.2020.04.003.
60. Hartung HP, Aktas O. COVID-19 and management of neuroimmunological disorders. *Nature Reviews Neurology.* 2020;1-2.
61. Leung TW, Wong KS, Hui AC, To KF, Lai ST, Ng WF, et al. Myopathic changes associated with severe acute respiratory syndrome: a postmortem case series. *Arch Neurol* 2005;62:1113-1117

62. Markus HS, Brainin M. COVID-19 and stroke-A global World Stroke Organization perspective. International journal of stroke, 2020;15(4):361-364.
63. Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost. 2019;17(11):1989–94. doi.org/10.1111/jth.14578.
64. Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA, et al. Tissue plasminogen activator (tPA) treatment for COVID19 associated acute respiratory distress syndrome (ARDS): a case series. J Thromb Haemost. 2020. doi.org/10.1111/jth. 14828.
65. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med. 2020;382(20):60.
66. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry. 2020.
67. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. Rev Neurol. 2020;70(9):311-22.
68. Franceschi AM, Ahmed O, Giliberto L, Castillo M. Hemorrhagic posterior reversible encephalopathy syndrome as a manifestation of COVID-19 infection. AJNR Am J Neuroradiol. 2020.
69. Yaghi S, Ishida K, Torres J, Grory BM, Raz E, Humbert K, et al. SARS-CoV-2 and stroke in a New York healthcare system. Stroke. 2020;51(7):2002-11.
70. Qureshi AI, Abd-Allah F, Alsenani F, Aytac E, Borhani-Haghghi A, Ciccone A, et al. Management of acute ischemic stroke in patients with COVID-19 infection: Report of an international panel. International Journal of Stroke, 2020; doi.org/10.1177/1747493020923234.