

Bölüm 2

COVID 19 ve İlişkili Nörolojik Bulgulara Güncel Yaklaşım

Neslihan EŞKUT¹

GİRİŞ

2019 Aralık ayında Çin' in Wuhan kentinde benzer klinik bulgulara sahip çok sayıda atipik pnömoni olgusunun görülmüşsinirdindan yeni tip korona virüs hastalığı (COVID 19) tanımlandı ¹. Dünya Sağlık Örgütü (DSÖ), 11 Mart 2020' de COVID 19' un 100 den fazla ülkeye yayılmasının ardından global pandemi ilan etti ². COVID 19 semptomlarının 2002' de görülen 'severe acute respiratory syndrome coronavirus' (SARS-CoV) ve 2012' deki 'Middle East respiratory syndrome coronavirus' (MERS-CoV) ile ortaya çıkan enfeksiyonla benzerlik gösterdiği ve aynı zamanda etkenin genomik olarak SARS-CoV ve MERS-CoV gibi betakoronavirüs olduğu saptandı ³⁻⁵. Virüsün konak hücreye giriş reseptörünün de SARS-CoV gibi anjiotensin converting enzim 2 (ACE2) olması nedeniyle SARS-CoV 2 olarak adlandırıldı.

Tüm Dünyayı etkisi altına alan SARS-CoV ve COVID 19 hakkında hala çok fazla bilinmeyen olsa da literatüre her geçen gün yeni bilgiler eklenmektedir. DSÖ' nün WEB sayfasında da SARS-CoV ve COVID 19 ile ilgili hasta yönetimi ve laboratuvar testleridahil çok yönlü bilgilendirme yapılmaktadır ⁶.

Bu yazında SARS-COV2'nin genel özelliklerinin ardından COVID 19'un tanı basamakları ve klinik bulguları kısaca gözden geçirilerek COVID 19 ile ilişkili nörolojik semptom, bulgu ve komplikasyonlar sunulacaktır.

Korona Virus Patogenezi

Korona virüsler, koronaviridea ailesi, Orthocoronavirinae altailesinden, küresel yapıda, zarflı, pozitif polariteli, tek sarmallı RNA virusleridir. Yüzeyinde yer alan çıkışları nedeniyle Latincede 'corona' yani 'taç' kelimesinden yola çıkılarak koronavirüs (taçlı virüs) olarak isimlendirilmiştir. Viral RNA, yapısal proteinleri (S,E,M,N,HE) kodlayan 5 gen ile yapısal olmayan proteinleri kodlayan genleri içerir ⁷. Yapısal proteinlerden Spike (S) glukoprotein konağa tutunmada dominant rol oynamaktadır ⁸.

¹ Uzman doktor, Başasistan, Sağlık Bilimleri Üniversitesi İzmir Bozyaka Eğitim ve Araştırma Hastanesi, Nöroloji Kliniği, nespur@hotmail.com

Italian Society of Neurology öncülüğünde İtalya'da retrospektif-prospektif olarak planlanan ve COVID 19 hastalarında hem tanı ve taburculuk hem de 3-6 aylık izlem sürecindeki nörolojik semptom ve bulguların dökümante edilmesinin amaçlandığı çalışmanın sonuçları yayınlandığında COVID 19-nöroloji ilişkisinin anlaşmasına ve uzun dönem sonuçların derlenmesine büyük katkı sağlayacaktır⁶².

SONUÇ

Dünya çapında konuya ilgili yapılan çalışmalarдан elde edilen veriler arttıkça COVID 19 ile ilişkili gelişen nörolojik semptom ve bulguların önemi anlaşılmıştır. Klinisyenler hem acil servislerde hem de polikliniklerde bilinc değişikliğinden kranial sinir tutulumuna, akut serebrovasküler hastalıktan otoimmün bozukluklara kadar çeşitli nörolojik semptom ve hastalıkların COVID 19 ile ilişkili olabileceğini akılda bulundurmmalıdır. Nazal semptomlar olmadan ani koku ve tat kaybı gelişmesinin COVID19 açısından önemli semptomlar olduğu artık bilinmektedir. Nörolojik semptom ve hastalıkların etiyopatogenezinde direkt nörolojik invazyon, indirekt nöroinflamasyon ya da otoimmün süreçlerin rol aldığı düşünülmektedir. COVID19 tanısı ile takip edilen hastalarda meydana gelen hızlı klinik kötüleşmelerde de hekimler ensefalit, inme gibi acil nörolojik durumları göz önünde bulundurmalıdır. COVID19 ile ilgili uzun dönem etki ve komplikasyonların anlaşılması için prospektif çalışmalar yapılması yol gösterici olacaktır.

KAYNAKÇA

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.
2. Pang J, Wang MX, Ang IYH, et al. Potential Rapid Diagnostics, Vaccine and Therapeutics for 2019 Novel Coronavirus (2019nCoV): A Systematic Review. J Clin Med 2020;9:623 doi.org/10.3390/jcm9030623
3. Kristl Vonck, Ieme Garrez, Veerle De Herdt, et al. Neurological manifestations and neuro-invasive mechanisms of the severe acute respiratory syndrome coronavirus type 2. Eur J Neurol 2020. Doi: 10.1111/ene.14329
4. Zaki AM, va Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012;367:1814-1820
5. Song Z, Xu Y, Bao L, et al. From SARS to MERS, Trusting Coronavirus into the spotlight. Viruses 2019; 11:doi:10.3390/v11010059
6. World Health Organization. Novel coronavirus (2019-nCoV) technical guidance. 2020. https://www.who.int/emergencies_diseases/novel-coronavirus-2019/technical-guidance
7. Iroegbu JD, Ifenatuoha CW, Ijomone OM. Potential neurological impact of coronaviruses: implications for the novel SARS-CoV-2. Neurol Sci 2020; 10.1007/s10072-020-04469-4
8. Hamming I, Timens W, Bulthuis ML, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203:631-7.
9. Masters PS, Perlman S. Coronaviridae. In: Fields Virology, 6th edition, Knipe DM, Howley PM (Eds), Lippincott Williams & Wilkins, Philadelphia, 2013

10. Drexler JF, Gloza-Rausch F, Glende J, et al. Genomic Characterization of Severe Acute Respiratory Syndrome-Related Coronavirus in European Bats and Classification of Coronaviruses Based on Partial RNA-Dependent RNA Polymerase Gene Sequences. *J Virol* 2010; ;84:11336-11349
11. Rabi FA, Al Zoubi MS, Kasasbeh GA, et al. SARS-CoV-2 and Coronavirüs Disease 2019: What We Know So Far. *Pathogens* 2020;99(3):231. doi: 10.3390/pathogens9030231
12. Zhao Y, Zhao Z, Wang Y, et al. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. *bioRxiv* 2020; doi.org/10.1101/2020.01.26.919985
13. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers; France: European Society of Cardiology; 2020. [https://www.escardio.org/Councils/Council-on-Hypertension-\(CHT\)](https://www.escardio.org/Councils/Council-on-Hypertension-(CHT))
14. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü. COVID-19 (Sars-Cov-2 Enfeksiyonu) Rehberi Bilim Kurulu Çalışması. Ankara: T.C. Sağlık Bakanlığı; 1 haziran 2020
15. Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Ann Intern Med* 2020 172(9):577-582
16. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVIS 19 in 391 cases and 1286 of their close contacts in Shenzhen, China: A retrospective chorth study. *Lancet Infect Dis* 2020;Doi:10.1016/S1473.3099(20)30357-1
17. He JL, Luo L, Luo ZD, Lyu JX, Ng MY, Shen XP, et al. Diagnostic performance between CT and initial real-time RT-PCR for clinically suspected 2019 coronavirus disease (COVID-19) patients outside Wuhan, China. *Respir Med* 2020;168:105980
18. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382(18): doi: 10.1056/NEJMoa2002032
19. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W, Hao P. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci.* 2020; 63: 457-60.
20. Kanne JP, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for Radiologists on COVID-19: An Update-Radiology Scientific Expert Panel. *Radiology.* 2020: 200527
21. Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection: A Narrative Review. *Ann Intern Med.* 2020;soi:10.7326/M20-3012
22. Calgagno N, Colombo E, Maranzano A, et al. Rising evidence for neurological involvement in COVID-19 pandemic. *Neurol Sci* 2020; 41:1339–1341
23. Yu P, Zhu J, Zhang Z, et al. A Familial Cluster of Infection Associated With the 2019 Novel Coronavirus Indicating Possible Person-to-Person Transmission During the Incubation Period. *J infect Dis* 2020; Doi:10.1093/infdis/jia077
24. Desforges M, Favreau DJ, Brison É, et al. Human Coronaviruses: Respiratory Pathogens Revisited as Infectious Neuroinvasive, Neurotropic, and Neurovirulent Agents. In: Singh SK, Ruzek D, editors. 1st ed. Boca Raton, FL: CRC Press; 2013.93–122.
25. Netland J, Meyerholz DK, Moore S, et al. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol [Internet].* 2008;82:7264–7275.
26. Desforges M, Le Coupanec A, Dubeau P, et al. Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? *Viruses* 2020;12:14 doi: 10.3390/v12010014
27. Bohmwald K, Galvez NMS, Ríos M, Kalergis AM. Neurologic alterations Due to Respiratory Virus Infections. *Front Cell Neurosci* 2018;12: 386. doi: 10.3389/fncel.2018.00386.
28. Natoli S, Oliveira V, Calabresi P, Maia LF, Pisani A. Does SARS-Cov-2 invade the brain? Translational lessons from animal models. *Eur J Neurol* 2020. doi: 10.1111/ene. 14277
29. Nath A. Neurologic Complications of Coronavirus Infections. *Neurology* 2020. [Epub ahead of print]

30. Koyuncu OO, Hogue I B, Enquist L W. Virus infections in the nervous system. *Cell Host Microbe* 2013; 13, 379–393
31. Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2). *J Med Virol* 2020. doi: 10.1002/jmv. 25915
32. Mucha SR, Dugar S, McCrae K, et al. Coagulopathy in COVID-19. *Cleve Clin J Med* 2020. doi: 10.3949/ccjm. 87a.ccc024
33. Jose RJ, Manuel A. COVID-19 cytokine storm: The interplay between inflammation and coagulation. *Lancet Respir Med* 2020;S2213-2600(20)30216-2. doi: 10.1016/S2213-2600(20)30216-2.
34. Yang F, Shi S, Zhu J, et al. Analysis of 92 deceased patients with COVID-19. *J Med Virol* 2020. doi: 10.1002/jmv. 25891.
35. Hung EC, Chim SS, Chan PK, et al. Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. *Clin Chem* 2003;49:2108–2109
36. Kim JE, Heo JH, Kim HO, et al. Neurological complications during treatment of Middle East respiratory syndrome. *J Clin Neurol* 2017;13:227–233.
37. Garg RK. Spectrum of Neurological Manifestations in COVID-19: A Review. *Neurol India* 2020;68:560-72
38. Lechien JR, Chiesa-Estomba CM, De Santi DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): A multicenter European study. *Eur Arch Otorhinolaryngol* 2020;1-11. doi: 10.1007/s00405-020-05965-1
39. Liguori C, Pierantozzi M, Spanetta M, et al. Subjective neurological symptoms frequently occur in patients with SARS-CoV2 infection. *Brain Behav Immun* 2020: doi: 10.1016/j.bbi. 2020.05.037
40. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID19 and other coronaviruses. *Brain Behav Immun* 2020;doi: <https://doi.org/10.1016/j.bbi.2020.03.031>
41. Moriguchi T, Harii N, Goto J, et al. A First Case of Meningitis/Encephalitis Associated with SARSCoronavirus-2. *Int J Infect Dis* 2020;94:55–58
42. Bernard-Valnet R, Pizzarotti B, Anichini A, et al. Two patients with acute meningo-encephalitis concomitant to SARS-CoV-2 infection. *Eur J Neurol* 2020. doi: 10.1111/ene. 14298
43. Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. *Brain Behav Immun* 2020: 10.1007/s11481-020-09924-9
44. Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. *Brain Behav Immun* 2020: 88:945–946
45. Li Z, Huang Y, Guo X. The brain, another potential target organ, needs early protection from SARS-CoV-2 neuroinvasion. *Sci China Life Sci* 2020;63:771-773
46. Karimi N, Sharifi Razavi A, Rouhani N. Frequent Convulsive Seizures in an Adult Patient with COVID-19: A Case Report, *Iran Red Crescent Med J*. 2020;22:e102828 doi: 10.5812/ircmj.102828
47. Wei H, Yin H, Huang M, Guo Z. The 2019 novel coronoavirus pneumonia with onset of oculomotor nerve palsy: A case study. *J Neurol* 2020;267:1550-3
48. Fotuhi M, Mian A, Meysami S, Raji CA. Neurobiology of COVID-19. *J Alzheimers Dis*. 2020;76:3-19
49. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med* 2020;382:2268-70
50. Kaya Y, Kara S, Akinci C, Kocaman AS. Transient cortical blindness in COVID-19 pneumonia; a PRES-like syndrome: A case report. *J Neurol Sci* 2020;413:116858
51. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683-690
52. Talan J. COVID-19: Neurologists in Italy to Colleagues in US: Look for PoorlyDefined Neurologic Conditions in Patients with the Coronavirus; *Neurology Today* 2020, American Academy

- of Neurology. <https://journals.lww.com/neurotodayonline/blog/breakingnews/pages/post.aspx?PostID=920>
- 53. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;doi: <https://doi.org/10.1001/jama.2020.1585>
 - 54. Beyrouti R, Adams ME, Benjamin L, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry 2020;doi: 10.1136/jnnp-2020-323586
 - 55. Li Y, Wang M, Zhou Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke & Vascular Neurology 2020; doi:10.1136/svn-2020-000431
 - 56. Kremer S, Lersy F, de Sèze J, et al. Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. Radiology 2020; doi.org/10.1148/radiol.2020202222
 - 57. Zhao H, Shen D, Zhou H, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection: Causality or coincidence? Lancet Neurol 2020;19:383-384
 - 58. Camdessanche JP, Morel J, Pozzetto B, et al. COVID-19 may induce Guillain-Barré syndrome. Rev Neurol (Paris) 2020;176:516-518.
 - 59. Toscano G, Palmerini F, Ravaglia S, et al. Guillain-Barré syndrome associated with SARS-CoV-2. N Engl J Med 2020. doi: 10.1056/NEJMc2009191
 - 60. Virani A, Rabold E, Hanson T, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection. IDCases 2020:e00771. doi: 10.1016/j.idcr. 2020.e00771
 - 61. Gutiérrez-Ortiz C, Méndez A, Rodrigo-Rey S, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. Neurology 2020;doi: 10.1212/WNL.00000000000009619
 - 62. Ferrarese C, Silani V, Priori A, et al, on behalf of Italian Society of Neurology (SIN). An Italian multicenter retrospective-prospective observational study on neurological manifestations of COVID-19 (NEUROCOVID). Neurol Scie 2020; 41:1355–1359