

Disputes & Debates: Editors' Choice

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Editors' Note: CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series

In "CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series," Edén et al. describe CSF results in 6 patients with neurologic symptoms in the setting of COVID-19 infection. Three patients had a positive CSF SARS-CoV-2 PCR initially, although the cycle threshold was elevated (>35), indicating a low viral load. It is important that SARS-CoV-2 RNA was undetectable in all 3 samples when reanalyzed. All patients had elevated CSF neopterin and β 2-microglobulin. Kumar and Lall comment that these findings are consistent with nonspecific inflammation and emphasize the fact that neuropathogenesis in COVID-19 is multifactorial because of systemic inflammation, hypoxemia, hypercoagulability, and potentially unidentifiable mechanisms. Brenner agrees that these findings suggest COVID-19 does not directly invade the CNS, but that it can cause an autoimmune or immune-mediated meningoencephalitis. He proposes that treatment with steroids, IVIG, and/or plasmapheresis may be considered. Edén agrees that a number of different mechanisms may contribute to the development of neurologic symptoms in patients with COVID-19 and reinforces the need for ongoing research to evaluate potential interventions.

Ariane Lewis, MD, and Steven Galetta, MD
Neurology® 2021;97:508. doi:10.1212/WNL.00000000000012526

Reader Response: CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series

Anand Kumar (Varanasi, India) and Neha Lall (Varanasi, India)
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We read with interest the article by Edén et al.¹ assessing the CSF biomarkers of intrathecal inflammation (CSF white blood cell counts, neopterin, β 2-microglobulin [β 2M], and immunoglobulin G index), blood-brain barrier integrity (albumin ratio), and axonal injury (CSF neurofilament light chain protein [NfL]) in COVID-19 patients with neurologic symptoms. The results illustrate evidence of significant CSF inflammation with raised soluble markers without any cellular response, unlike other viral CNS infections. As far as intrathecal markers such as neopterin and β 2M are concerned, these are nonspecific and are produced by macrophages during the activation of cell-mediated immune response. These are often found significantly raised in various conditions such as HIV infection,² relapsing-remitting or chronic progressive multiple sclerosis,³ and head trauma,⁴ putting forth questions about its value as a disease-specific marker.

NfL being a component of axonal and dendritic cytoskeleton, it is considered as a biomarker of axonal injury. It is raised in the CSF in diseases such as amyotrophic lateral sclerosis, Parkinson disease, multiple sclerosis, head trauma, and Alzheimer disease, making it a very low specific marker.⁵

Neuropathogenesis in COVID-19 is still unknown and is considered multifactorial. Systemic inflammation, hypoxemia, hypercoagulability, and some unidentifiable mechanisms may all contribute to specific neurologic condition, and this warrants further study.

1. Edén A, Kanberg N, Gostner J, et al. CSF biomarkers in patients with COVID-19 and neurological symptoms: a case series. *Neurology*. 2021;96(2):e294-e300.
2. Bogner JR, Junge-Hülsing B, Kronawitter U, Sadri I, Matuschke A, Goebel FD. Expansion of neopterin and beta 2-microglobulin in cerebrospinal fluid reaches maximum levels early and late in the course of human immunodeficiency virus infection. *Clin Investig*. 1992; 70(8):665-669.
3. Ott M, Demisch L, Engelhardt W, Fischer PA. Interleukin-2, soluble interleukin-2-receptor, neopterin, L-tryptophan and beta 2-microglobulin levels in CSF and serum of patients with relapsing-remitting or chronic-progressive multiple sclerosis. *J Neurol*. 1993; 241(2):108-114.
4. Lenzlinger PM, Hans VHJ, Joller-Jemelka HI, Trentz O, Morganti-Kossmann MC, Kossmann T. Markers for cell-mediated immune response are elevated in cerebrospinal fluid and serum after severe traumatic brain injury in humans. *J Neurotrauma*. 2001;18(5): 479-489.
5. Peng L, Bi C, Xia D, Mao L, Qian H. Increased cerebrospinal fluid neurofilament light chain in central nervous system inflammatory demyelinating disease. *Mult Scler Relat Disord*. 2019;30:123-128.

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Reader Response: CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series

Steven R. Brenner (University City, MO)

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I read the article by Edén et al. regarding COVID-19 patients with neurologic symptoms with interest.¹ It appears the adults with neurologic symptoms, primarily of encephalopathy, are similar to those of children with influenza experiencing encephalopathy—CSF neopterin elevation being a common feature, whereas CSF pleocytosis was only present in a third of patients.² Influenza-related encephalopathy is believed to primarily be mediated through inflammatory or immune-mediated mechanisms.²

CSF examination in a series of 6 patients with COVID-19, who were agitated or failed to regain consciousness after decrease in sedation following ventilation treatment of acute respiratory distress syndrome, revealed high protein, no pleocytosis, and negative PCR for SARS-CoV-2.³ MRI findings appeared either normal or consistent with meningoencephalitis, indicating likely autoimmune encephalitis.³ Plasmapheresis resulted in dramatic improvement—most patients regaining consciousness, with improvement in serum ferritin. In addition, MRI findings were reversible in those cases consistent with meningoencephalitis.

It appears likely COVID-19 triggers an autoimmune or immune-mediated meningoencephalitis, rather than direct viral invasion and infection. Immunomodulatory treatments such as corticosteroids,² IVIG,² and/or plasmapheresis^{2,3} are considerations, having been used in these circumstances.

1. Edén A, Kanberg N, Gostner J, et al. CSF Biomarkers in patients with COVID-19 and neurologic symptoms: a case series. *Neurology*. 2021;96(2):e294-e300.
2. Macdonald-Laurs E, Koirala A, Britton PN, et al. CSF neopterin, a useful biomarker in children presenting with influenza associated encephalopathy? *Eur J Paediatr Neurol*. 2019;23(1):204-213.
3. Dogan L, Kaya D, Sarikaya T, et al. Plasmapheresis treatment in COVID-19-related autoimmune meningoencephalitis: case series. *Brain Behav Immun*. 2020;87:155-158.

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Author Response: CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series

Arvid Edén (Gothenburg, Sweden)

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We thank Dr. Brenner for his interest in our report¹ and for emphasizing CSF neopterin results. Indeed, marked CSF immune activation indicating microglial activation is a universal feature in all patients with neurologic manifestations that we have examined in our clinic during the acute phase of COVID-19. Of interest, other typical signs of CNS infections—CSF pleocytosis, blood-brain barrier injury, and intrathecal IgG synthesis—are usually mild or absent, and viral RNA is almost never detected. These features clearly distinguish COVID-19 from typical CNS-invasive infections but are similar to processes seen in other CNS encephalitides² and, as suggested, may well resemble influenza-encephalitis that is also a consequence of a respiratory viral infection.

Likely, the CNS pathology observed during COVID-19 is a consequence of several contributing factors, where direct viral interaction with olfactory mucosal cells, indirect effects of the systemic inflammatory response, and potentially viral interaction with cells of the vasculature can all contribute to the immune response observed within the CNS. Autoimmune mechanisms may well be triggered as part of the immune response, as is suggested in some early reports.³ However, therapeutic efforts directed toward CNS manifestations are still anecdotal, and it is vital that proposed interventions are studied in properly designed, preferably controlled, clinical trials.

1. Edén A, Kanberg N, Gostner J, et al. CSF Biomarkers in patients with COVID-19 and neurologic symptoms: a case series. *Neurology*. 2021;96(2):e294-e300.
2. Pilotto A, Masciocchi S, Volonghi I, et al. SARS-CoV-2 encephalitis is a cytokine release syndrome: evidences from cerebrospinal fluid analyses. *Clin Infect Dis*. 2021:ciaa1933. doi: 10.1093/cid/ciaa1933.
3. Franke C, Ferse C, Kreye J, et al. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. *Brain Behav Immun*. 2020;93:415-419.

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Editors' Note: Dietary Antioxidants and the Risk of Parkinson Disease: The Swedish National March Cohort

In “Dietary Antioxidants and the Risk of Parkinson Disease: The Swedish National March Cohort,” Hantikainen et al. surveyed dietary intake through a food frequency questionnaire from 1997 to 2016 and found that higher dietary vitamin E and vitamin C were associated with a lower risk of Parkinson disease. They found no relationship between beta-carotene intake or nonenzymatic antioxidant capacity and Parkinson disease. Kawada notes that a previous study found beta-carotene and vitamin E intake was inversely associated with a risk of Parkinson disease, but there was no significant relationship between intake of vitamin C and nonenzymatic antioxidant capacity and Parkinson disease. They suggest that sex differences may be relevant to these findings. Hantikainen et al. acknowledge that there are discrepancies across studies, but they did not find any sex differences. Both authors agree more research is needed to evaluate the relationship between antioxidants and Parkinson disease and whether there are sex differences that might play a role.

Ariane Lewis, MD, and Steven Galetta, MD

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Reader Response: Dietary Antioxidants and the Risk of Parkinson Disease: The Swedish National March Cohort

Tomoyuki Kawada (Tokyo)

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Hantikainen et al. examined the associations of high baseline dietary antioxidants and total nonenzymatic antioxidant capacity (NEAC) with Parkinson disease. The adjusted hazard ratios (HRs)—95% confidence intervals (CIs)—of dietary vitamin E and vitamin C for Parkinson disease were 0.68 (0.52–0.90) and 0.68 (0.52–0.89), respectively.¹ By contrast, there was no significant association of estimated intake of dietary beta-carotene or NEAC with Parkinson disease.

However, according to a study by Yang et al.,² the associations of dietary antioxidant vitamins C, E, beta-carotene, and NEAC with Parkinson disease were examined. The adjusted HRs (95% CIs) of dietary intake of beta-carotene for Parkinson disease in women and men were 0.86 (0.78–0.95) and 0.91 (0.84–0.99), respectively.² In addition, the adjusted HRs (95% CIs) of dietary intake of vitamin E for Parkinson disease in women and men were 0.87 (0.79–0.96) and 0.93 (0.88–0.99), respectively.² By contrast, dietary intake of vitamin C and NEAC were not significantly associated with PD.

As such, discrepancy exists regarding the effect of vitamin C and beta-carotene on Parkinson disease in these studies.^{1,2} As the risk reduction of dietary antioxidants for Parkinson disease was stronger in women, sex difference might be proposed with caution as a related factor. In any case, further prospective studies are needed to verify the association.

1. Hantikainen E, Trolle Lagerros Y, Ye W, et al. Dietary antioxidants and the risk of Parkinson disease: the Swedish National March Cohort. *Neurology*. 2021;96(6):e895–e903.
2. Yang F, Wolk A, Håkansson N, Pedersen NL, Wirdefeldt K. Dietary antioxidants and risk of Parkinson's disease in two population-based cohorts. *Mov Disord*. 2017;32(11):1631–1636.

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Author Response: Dietary Antioxidants and the Risk of Parkinson Disease: The Swedish National March Cohort

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We are grateful for Dr. Kawada's interest in our paper.¹ There are indeed discrepancies between findings on vitamin C, beta-carotene, and the risk of Parkinson disease, while the evidence for vitamin E is consistent when considering findings by Yang et al.² and those in our study.¹ Furthermore, 2 meta-analyses reported that a higher intake of vitamin E was found to protect against Parkinson disease,³ whereas no such association was seen with vitamin C³ or beta-carotene.^{3,4} A recent publication from the Nurses' Health Study and the Health Professionals Follow-up Study reported an inverse association between dietary vitamin C and Parkinson disease, although the results were nonsignificant after excluding cases occurring during the first 4 years of follow-up. No association was seen between vitamin E and beta-carotene.⁵

Given the stronger effect of dietary antioxidants on Parkinson disease risk in women reported by Yang et al.,² possible sex differences might exist. We investigated potential effect modification by sex—however, we did not find any evidence for such an interaction. Nevertheless, more research is needed to confirm findings on different antioxidants and the risk of Parkinson disease and potential sex differences of such an effect.

Author disclosures are available upon request (journal@neurology.org).

1. Hantikainen E, Trolle Lagerros Y, Ye W, et al. Dietary antioxidants and the risk of Parkinson disease: the Swedish National March Cohort. *Neurology*. 2021;96(6):e895-e903.
2. Yang F, Wolk A, Håkansson N, Pedersen NL, Wirdefeldt K. Dietary antioxidants and risk of Parkinson's disease in two population-based cohorts. *Mov Disord*. 2017;32(11):1631-1636.
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4. Takeda A, Nyssen OP, Syed A, Jansen E, Bueno-de-Mesquita B, Gallo V. Vitamin A and carotenoids and the risk of Parkinson's disease: a systematic review and meta-analysis. *Neuroepidemiology*. 2014;42(1):25-38.
5. Hughes KC, Gao X, Kim IY, et al. Intake of antioxidant vitamins and risk of Parkinson's disease. *Mov Disord*. 2016;31(12):1909-1914.

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CORRECTIONS

Low-Dose vs Standard-Dose Alteplase in Acute Lacunar Ischemic Stroke

The ENCHANTED Trial

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In the article “Low-Dose vs Standard-Dose Alteplase in Acute Lacunar Ischemic Stroke: The ENCHANTED Trial” by Zhou et al.,¹ the first sentence under Methods in the Abstract should read “In a cohort of 3,297 ENCHANTED participants, we identified those with lacunar or non-lacunar AIS with different levels of confidence (definite/probable/possible) according to prespecified definitions based on clinical and adjudicated imaging findings.” The publisher regrets the error.

Reference

1. Zhou Z, Delcourt C, Xia C, et al. Low-dose vs standard-dose alteplase in acute lacunar ischemic stroke: the ENCHANTED trial. *Neurology*. 2021;96(11):e1512-e1526.

In Defense of the AAN Position on Lawful Physician-Hastened Death

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In the special editorial “In Defense of the AAN Position on Lawful Physician-Hastened Death” by Vucic et al.,¹ the author contributions should read:

J.A.R. is the principal author of this editorial and of “Lawful physician-hastened death: AAN position statement.”²

L.G.E., R.J.B., R.C., W.D.G., M.K., J.A.K., D.L., R.M.P., M.R., J.A.S., Z.S., L.T., and M.A.W., coauthors of “Lawful physician-hastened death: AAN position statement,”² reviewed relevant literature and were actively involved in editing multiple iterations of this editorial.

A.T., coauthor of “Lawful physician-hastened death: AAN position statement,” elected not to contribute to this editorial.

The publisher regrets the error.

Reference

1. Russell JA, Epstein LG, Bonnie RJ, et al. In defense of the AAN position on lawful physician-hastened death. *Neurology*. 2020;94(15):641-643.

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Low-Dose vs Standard-Dose Alteplase in Acute Lacunar Ischemic Stroke: The ENCHANTED Trial

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