Cell Reports Medicine

CellPress
OPEN ACCESS

Commentary

Potential role of neurofilament in COVID-19 and preeclampsia

Athina Samara,[1,2,*] Eric Herlenius,[1,2] Patrick O' Brien,[3,4] and Asma Khalil[5,6,7,*]
[1]Division of Clinical Paediatrics, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
[2]Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden
[3]The Royal College of Obstetricians and Gynaecologists, London, UK
[4]University College London Hospitals NHS Foundation Trust, London, UK
[5]Fetal Medicine Unit, St George's Hospital, St George's University of London, London, UK
[6]Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK
[7]Fetal Medicine Unit, Liverpool Women's Hospital, University of Liverpool, Liverpool, UK
*Correspondence: athina.samara@ki.se (A.S.), akhalil@sgul.ac.uk (A.K.)
https://doi.org/10.1016/j.xcrm.2021.100490

Neurofilament light (NFL) is a promising circulating biomarker in preeclampsia and COVID-19, even without evident neurological complications. Several pathways might contribute to the elevated serum NFL levels seen in both pathologies. Future studies will determine whether NFL is a long COVID marker and delineate NFL's role in COVID-19-associated preeclampsia.

Neurological markers of COVID-19

COVID-19 is primarily a respiratory disease but has also been associated with diverse neurological manifestations[1] and symptoms that range from mild, such as headaches, to more severe, including cognitive impairment, to the very rare Guillain-Barré syndrome (GBS). Elevations of neurological dysfunction biomarkers have been detected in cerebrospinal fluid (CSF) and blood of COVID-19 patients, and several studies focus on the use of serum neurofilament light (sNFL) as a marker of COVID-19-related neuronal injury.[2]

Neurofilaments are intermediate filament (IF) proteins that during neuronal development and maturation replace the IF protein nestin, which is present in progenitor cells.[3] Neurofilaments form heteropolymeric structural scaffolding networks, the integrity of which is critical for the maintenance of axonal structure. NFL is released into the CSF and blood as a result of axonal lesions/injury and is thus considered a marker of neuronal damage.

sNFL is an easily accessible age-dependent biomarker, commonly used to screen for disease severity and/or progression in several pathologies related to neuronal loss. NFL has also been detected in the CSF of critically ill[4] and the serum of hospitalized individuals[5] with COVID-19. This study demonstrated a positive correlation of sNFL with worse clinical outcomes and COVID-19 severity. Elevated sNFL has also been documented in 28 non-hospitalized healthcare workers with mild-to-moderate COVID-19.[6] Another study showed that plasma NFL levels were 3.1 times higher in 18 patients who developed severe COVID-19 compared to healthy age-matched SARS-CoV-2-negative individuals (n = 33).[7] NFL was also shown to be significantly increased in the blood of COVID-19 patients requiring ICU admission and in those who died from it.[8]

However, in most COVID-19 cases, viral central nervous system (CNS) infection or blood-brain barrier injury could not be confirmed by detection of viral RNA in CSF. Thus, direct SARS-CoV-2 CNS infection might not be driving the neurological manifestations resulting in the detection of neurological blood biomarkers.

Association between preeclampsia and COVID-19 in pregnancy

Several studies have reported an epidemiological link between COVID-19 and preeclampsia. In a recent national study from England, pregnant women with confirmed SARS-CoV-2 infection at birth had twice the risk of preeclampsia compared to those testing negative for SARS-CoV-2.[9] Similar findings were reported from Spain[10] and the INTERCOVID cohort study.[11] Preeclampsia was the only condition the INTERCOVID study assessed in which women with asymptomatic SARS-CoV-2 infection had worse outcomes than women without it. In two recent meta-analyses, a higher incidence of preeclampsia was identified in pregnant women with coronavirus-spectrum infections (including SARS-CoV-2) than in the general pregnant population.[12] SARS-CoV-2 infection during pregnancy was associated with a greater risk of severe preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome.[13] COVID-19 is thus strongly associated with preeclampsia.

Neurofilament and preeclampsia

sNFL has previously been reported as a serum marker predicting preeclampsia with an accuracy similar to that of the more established angiogenic factor markers soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF); levels of sNFL increased with maternal age (> 36 years), with a greater increase in women with preeclampsia compared to controls.[14] In another study, women with preeclampsia without clinically detectable neurological complications had increased CSF and plasma concentrations of NFL compared to women with normotensive pregnancies.[15] However, scant information is currently available regarding the origin, importance, and role of sNFL, and there are no reliable blood tests to predict eclampsia- or

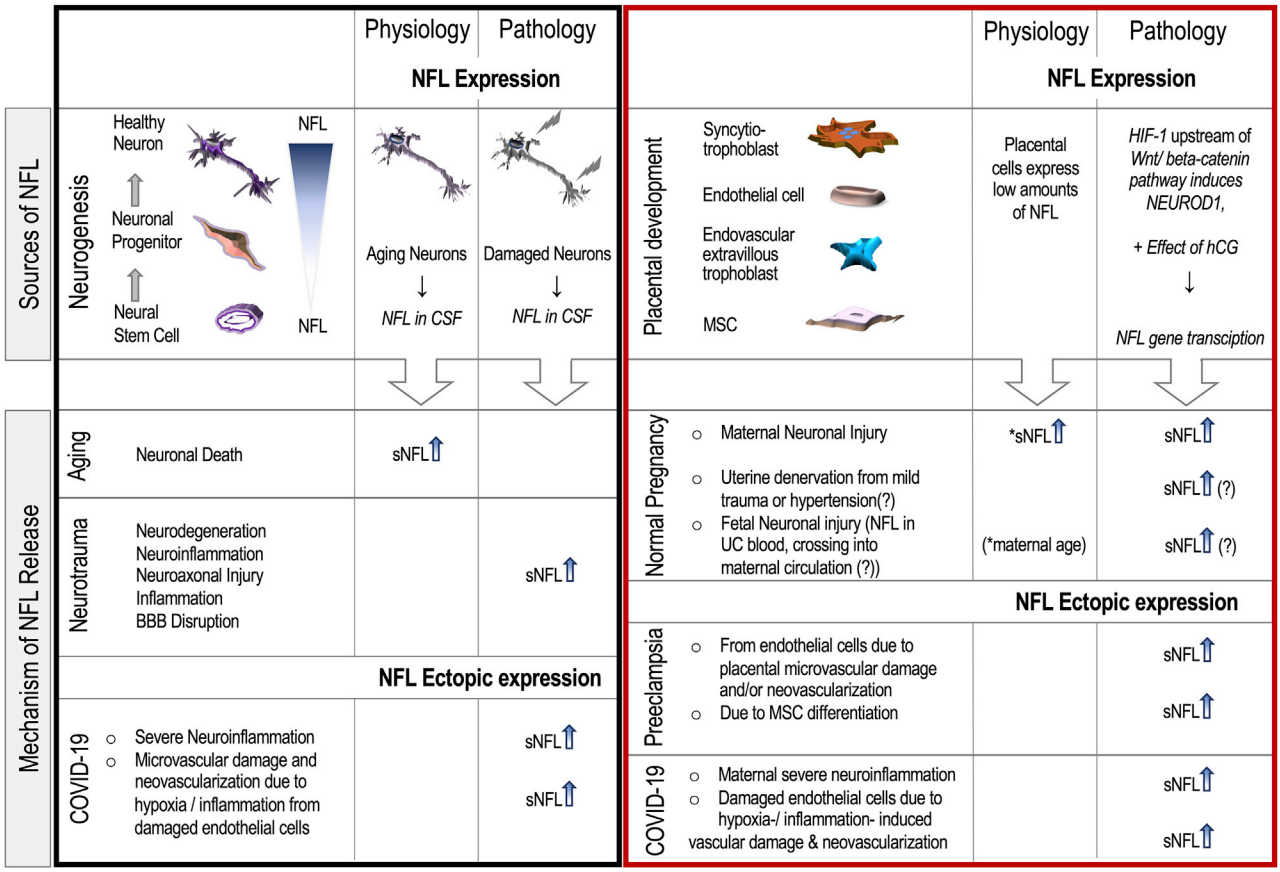

Figure 1. Published and suggested mechanisms of induction and secretion of sNFL that might be contributing to the elevated maternal levels of NFL seen in preeclampsia and COVID-19

Cellular origin of neurofilament during neurogenesis and placental development and mechanistic similarities among the two pathologies are highlighted, indicating physiological sources of sNFL and ectopic expression and release. CSF, cerebrospinal fluid; BBB, blood-brain barrier; MSC, mesenchymal stem cell; *HIF-1*, hypoxia-inducible factor 1, *NEUROD1*, neurogenic differentiation 1; hCG, human chorionic gonadotropin; UC, umbilical cord.

preeclampsia-induced cerebral edema. Furthermore, few data exist on sNFL in term and preterm infants.

Other possible sources of NFL

Early in gestation, placental tissues express various proneural and neural genes and transcription factors. The ectopic expression of one of these, neurogenic differentiation 1 (*NEUROD1*), might be key to induction of differentiation and nestin replacement by neurofilaments. Hypoxia is another mechanism that induces nestin expression in the umbilical cord, the placental and chorionic villous mesenchymal stem cells (MSCs), and the immature endothelial cells generated during angiogenesis.

As nestin expression in undifferentiated cells is transient, we hypothesize that in preeclampsia and COVID-19, nestin expression might be induced by hypoxia via vascular endothelial growth factor (*VEGF*) and hypoxia-inducible factor 1 subunit alpha (*HIF-1*α), enhanced by brain-derived neurotrophic factor (*BDNF*), and activated by *NEUROD1*. Nestin expression might later be downregulated and/or replaced in the cytoskeleton by neurofilaments.

Regarding pregnancy complications, such as preeclampsia, in which the maternal blood can be normoxic, or in cases of hypoxia, such as from COVID-19, blood flow into the intervillous space might be locally compromised. Thus, the placental villi could be exposed to a heterogeneous oxygen supply that contributes to the impairment of villous development and pathology. This hypoxia, as seen in COVID-19 pregnancies, might mimic or cause the placental pathology seen in preeclampsia.

The COVID-19 pathology, including damage to the angiotensin-converting enzyme 2 (ACE2)-bearing cells in blood vessels and wound healing neovascularization, could further add to the neurofilament pool in the pregnant woman's blood. Thus, there are several potential sources (summarized in Figure 1) that might be contributing to the elevated maternal levels of NFL seen in preeclampsia and COVID-19. Brain-derived NFL could be detected in the blood having crossed the disrupted blood-brain barrier; this NFL originates from the damaged maternal brain compartment as a result of neuroaxonal damage. NFL might also originate from uterine denervation due to mild trauma or due to hypertension. In addition, hypoxia could induce ectopic

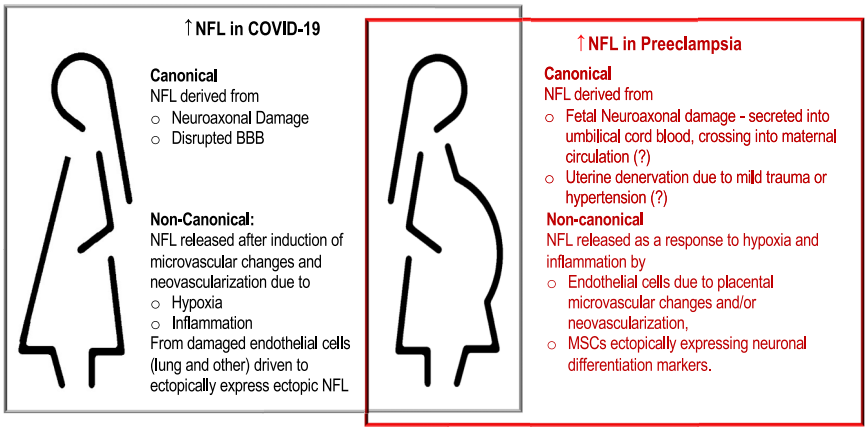

Figure 2. A summary of the known NFL release and suggested NFL ectopic expression mechanisms in COVID-19 and preeclampsia

expression of NFL after blood vessel damage.

Since preeclampsia is a generalized endothelial disease, NFL might also be released from maternal endothelial lung cells driven to express ectopic neuronal differentiation markers, due to the hypoxia-induced neovascularization. Furthermore, considering the placental neovascularization, the hypoxia-altered molecular signals affecting fetal cell development in gestation, and the abundant MSC component of the placenta, the increased nestin levels might be translated into increased levels of neurofilaments secreted into the umbilical cord blood and possibly crossing into the maternal circulation.

In conclusion, NFL is emerging as a promising circulating biomarker in both preeclampsia and COVID-19, even in the absence of clinically evident neurological complications. The emerging data suggest that sNFL is an early indicator that might help to stratify disease management among COVID-19 patients (Figure 2). Further studies are needed to verify the source(s) of NFL that contribute to the pool of NFL identified in the maternal serum and its relation to preeclampsia: the amniotic, placental, and umbilical cord-derived stem cells, the result of mild trauma to uterine innervation due to hypertension, and/or neuronal injury. Larger, longitudinal studies following uninfected and post-COVID-19 pregnancies will help identify the physiological levels of NFL in pregnancy and post partum, ultimately determining whether NFL is a potential clinical marker of long COVID.

REFERENCES

1. The Lancet Neurology (2021). Long COVID: understanding the neurological effects. Lancet Neurol. *20*, 247.
2. Paterson, R.W., Benjamin, L.A., Mehta, P.R., Brown, R.L., Athauda, D., Ashton, N.J., Leckey, C.A., Ziff, O.J., Heaney, J., Heslegrave, A.J., et al.; UCLH Queen Square COVID-19 Biomarker Study Group (2021). Serum and cerebrospinal fluid biomarker profiles in acute SARS-CoV-2-associated neurological syndromes. Brain Commun *3*, b099.
3. Frederiksen, K., and McKay, R.D. (1988). Proliferation and differentiation of rat neuroepithelial precursor cells in vivo. J. Neurosci. *8*, 1144–1151.
4. Garcia, M.A., Barreras, P.V., Lewis, A., Pinilla, G., Sokoll, L.J., Kickler, T., Mostafa, H., Caturegli, M., Moghekar, A., Fitzgerald, K.C., and Pardo, C.A.; Hopkins Neuro-COVID-19 Group (2021). Cerebrospinal fluid in COVID-19 neurological complications: Neuroaxonal damage, anti-SARS-Cov2 antibodies but no evidence of cytokine storm. J. Neurol. Sci. *427*, 117517.
5. Prudencio, M., Erben, Y., Marquez, C.P., Jansen-West, K.R., Franco-Mesa, C., Heckman, M.G., White, L.J., Dunmore, J.A., Cook, C.N., Lilley, M.T., et al. (2021). Serum neurofilament light protein correlates with unfavorable clinical outcomes in hospitalized patients with COVID-19. Sci. Transl. Med. *13*, eabi7643.
6. Ameres, M., Brandstetter, S., Toncheva, A.A., Kabesch, M., Leppert, D., Kuhle, J., and Wellmann, S. (2020). Association of neuronal injury blood marker neurofilament light chain with mild-to-moderate COVID-19. J. Neurol. *267*, 3476–3478.
7. Kanberg, N., Ashton, N.J., Andersson, L.M., Yilmaz, A., Lindh, M., Nilsson, S., Price, R.W., Blennow, K., Zetterberg, H., and Gisslén, M. (2020). Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. Neurology *95*, e1754–e1759.
8. De Lorenzo, R., Loré, N.I., Finardi, A., Mandelli, A., Cirillo, D.M., Tresoldi, C., Benedetti, F., Ciceri, F., Rovere-Querini, P., Comi, G., et al. (2021). Blood neurofilament light chain and total tau levels at admission predict death in COVID-19 patients. J. Neurol. *268*, 4436–4442.
9. Gurol-Urganci, I., Jardine, J.E., Carroll, F., Draycott, T., Dunn, G., Fremeaux, A., Harris, T., Hawdon, J., Morris, E., Muller, P., et al. (2021). Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. Am. J. Obstet. Gynecol. *225*, 522.e1–522.e11.
10. Cruz Melguizo, S., de la Cruz Conty, M.L., Carmona Payán, P., Abascal-Saiz, A., Pintando Recarte, P., González Rodríguez, L., Cuenca Marín, C., Martínez Varea, A., Oreja Cuesta, A.B., Rodríguez, P.P., et al. (2021). Pregnancy Outcomes and SARS-CoV-2 Infection: The Spanish Obstetric Emergency Group Study. Viruses *13*, 853.
11. Villar, J., Ariff, S., Gunier, R.B., Thiruvengadam, R., Rauch, S., Kholin, A., Roggero, P., Prefumo, F., do Vale, M.S., Cardona-Perez, J.A., et al. (2021). Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study. JAMA Pediatr. *175*, 817–826.
12. Di Mascio, D., Buca, D., Berghella, V., Khalil, A., Rizzo, G., Odibo, A., Saccone, G., Galindo, A., Liberati, M., and D'Antonio, F. (2021). Counseling in maternal-fetal medicine: SARS-CoV-2 infection in pregnancy. Ultrasound Obstet. Gynecol. *57*, 687–697.
13. Conde-Agudelo, A., and Romero, R. (2021). SARS-CoV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. Am. J. Obstet. Gynecol. *226* (*1*), P68–P89. S0002-9378(21)00795-X. Published online July 21, 2021. In press. https://doi.org/10.1016/j.ajog.2021.07.009.
14. Evers, K.S., Atkinson, A., Barro, C., Fisch, U., Pfister, M., Huhn, E.A., Lapaire, O., Kuhle, J., and Wellmann, S. (2018). Neurofilament as Neuronal Injury Blood Marker in Preeclampsia. Hypertension *71*, 1178–1184.
15. Andersson, M., Oras, J., Thörn, S.E., Karlsson, O., Kälebo, P., Zetterberg, H., Blennow, K., and Bergman, L. (2021). Signs of neuroaxonal injury in preeclampsia-A case control study. PLoS ONE *16*, e0246786.