NfL value is a well-established marker for neuronal injury. Corroborating our results, recent reports have shown low to intermediate NfL levels in COVID-19 patients as compared to other infectious diseases, for example, bacterial pneumonia and sepsis.[2, 3] Thus, with respect to changes of NfL levels, our own data and current evidence do not indicate commonly occurring neuronal damage in COVID-19. However, differences in cohort composition, such as incidence of delirium or acute kidney injury, could explain the observations made by Sutter and colleagues. As recently reported, delirium itself is associated with NfL elevation and cognitive impairment independent of infection.[4] Furthermore, renal dysfunction might also have influenced NfL levels.[5]

In conclusion, we agree with the authors' statement that prospective studies testing the cognitive outcome of COVID-19 patients are needed to evaluate the prognostic value of NfL levels for neuronal injury during acute SARS-CoV-2 infection. Nonetheless, at this stage, we caution against interpreting the NfL data shown by Sutter *et al.* as indicating COVID-19–specific neuronal damage.

Acknowledgments

Plasma from a subgroup of an ongoing single-center prospective cohort study was employed for analyses (NCT03620409; https://doi.org/10.1136/bmjopen-2019-036527). The clinical study was funded by the Federal Ministry of Education and Research (grant 03Z22JN12 to S.M.C.). This work was further supported by the Center for Sepsis Control and Care (FKZ 01EO1502), the Interdisciplinary Center of Clinical Research of the Jena Medical Faculty, and the Schilling foundation.

We thank the other members of the research group Translational Septomics for their support.

Potential Conflicts of Interest

Nothing to report.

[1]*Section Translational Neuroimmunology, Department of Neurology, Jena University Hospital, Jena, Germany*
[2]*Center for Sepsis Control and Care, Jena University Hospital, Jena, Germany*
[3]*Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany*
[4]*Septomics Research Center, Jena University Hospital, Jena, Germany*
[5]*Neuroimmunology, Institute of Clinical Chemistry, University Hospital Schleswig-Holstein, Kiel, Germany*

[†]H.-Y.C. and C.N. share first authorship.

References

1. Sutter R, Hert L, De Marchis GM, et al. Serum neurofilament light chain levels in the intensive care unit: comparison between severely ill patients with and without coronavirus disease 2019. Ann Neurol 2021;89:610–616.
2. Kanberg N, Ashton NJ, Andersson LM, et al. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. Neurology 2020;95:e1754–e1759.
3. Ehler J, Petzold A, Wittstock M, et al. The prognostic value of neurofilament levels in patients with sepsis-associated encephalopathy—a prospective, pilot observational study. PLoS One 2019;14:e0211184.
4. Fong TG, Vasunilashorn SM, Ngo L, et al. Association of plasma neurofilament light with postoperative delirium. Ann Neurol 2020;88:984–994.
5. Akamine S, Marutani N, Kanayama D, et al. Renal function is associated with blood neurofilament light chain level in older adults. Sci Rep 2020;10:20350.

DOI: 10.1002/ana.26135

Reply to: Neurofilament Light Chain in Patients with COVID-19 and Bacterial Pneumonia

David Leppert, MD,[1,2] Raoul Sutter, MD,[2,3] and Jens Kuhle, MD, PhD[1,2]

Dear Editor

We read with great interest the letter of Chung HY et al[1] in which they refer to our recent publication in the Annals of Neurology on "Serum Neurofilament Light Chain Levels in the Intensive Care Unit: Comparison between Severely Ill Patients with and without Coronavirus Disease 2019."[2]

The authors compared plasma neurofilament light chain (pNfL) levels in patients with bacterial and coronavirus disease 2019 (COVID-19) pneumonia; pNfL levels in bacterial pneumonia 3 days after onset of sepsis were considerably higher than those in COVID-19 pneumonia at days 3 and 7.

Chung and colleagues concluded that their results are corroborated by those of others[3,4] showing "low to intermediate NfL levels in COVID-19 patients as compared to other infectious diseases…" and that their "own data and current evidence do not indicate commonly occurring neuronal damage in COVID-19." Noteworthy, the clinical severity of patients with COVID-19 pneumonia by Chung HY et al were lower with a mean Sequential Organ Failure Assessment (SOFA) score of 4, whereas in our cohort it was 7; 86% of the critically ill patients in our study were ventilated and 17% died (no data are provided about eg, ventilation, comorbidities, intensive care unit [ICU] admission, oxygenation indexes, and outcome in patients with COVID-19 in the cohort of Chung HY et al). In contrast to our cohort, which was analyzed after disease progression that led to an admission to the ICU (ie, representing a later stage of the disease), the patients presented by Chung HY et al were analyzed within the first few days after onset of pneumonia. In fact, the patients with COVID-19 described by us match better with the subgroup categorized as "severe" by Kanberg et al[3] where the median pNfL level was 32.7 pg/ml, very similar to our finding of 36.1 pg/ml in serum (vs approximately 5–10 pg/ml in Fig 1C of Chung HY et al). We consider these levels not as "low to intermediate" as they are in the range of patients with bacterial pneumonia presented by Chung HY et al.

Patients with sepsis-associated encephalopathy show radiological signs of brain damage and neuropsychological signs of brain dysfunction,[4] pNfL levels were strongly increased compared to patients without brain dysfunction; further, they correlated with a poorer long-term neurofunctional outcome. Neuronal damage can be

assumed as the cause for the elevation of serum neurofilament light chain (sNfL) observed by Chung et al in their cohort with bacterial pneumonia. Important in our view is the observation that neuronal damage occurs in the course of both COVID-19 and sepsis-associated encephalopathy (ie, also in absence of overt infection of the central nervous system).[4,5] We agree that neuronal damage is not specific for COVID-19, but seems likely a generic consequence in severe infectious disease of various etiologies. We agree as well that the role of renal dysfunction and other metabolic changes as factors modulating NfL levels during infectious diseases needs to be explored.

Potential Conflicts of Interest

The authors declared no conflict of interest.

[1]*Neurologic Clinic and Policlinic, MS Center and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), University Hospital Basel, Basel, Switzerland*
[2]*Medical Faculty, University of Basel, Basel, Switzerland*
[3]*Intensive Care Unit, University Hospital Basel, Basel, Switzerland*

References

1. Chung HY, Neu C, Wickel J, et al. Neurofilament light chain in patients with COVID-19 and bacterial pneumonia. Ann Neurol 2021. (Online ahead of print) https://doi.org/10.1002/ana.26135.
2. Sutter R, Hert L, De Marchis GM, et al. Serum neurofilament light chain levels in the intensive care unit: comparison between severely ill patients with and without coronavirus disease 2019. Ann Neurol 2021;89:610–616.
3. Kanberg N, Ashton NJ, Andersson LM, et al. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. Neurology 2020;95:e1754–e1759.
4. Ehler J, Petzold A, Wittstock M, et al. The prognostic value of neurofilament levels in patients with sepsis-associated encephalopathy - a prospective, pilot observational study. PLoS One 2019;14:e0211184.
5. Thakur T, Miller EH, Glendinning MD, et al. COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. Brain 2021;awab148. (Online ahead of print) https://doi.org/10.1093/brain/awab148.

DOI: 10.1002/ana.26132

Concerns Regarding Therapeutic Implications of Very Low-Level Dystrophin

Eric P. Hoffman, PhD,[1] and Paula R. Clemens, MD[2]

De Feraudy et al[1] present an elegant study correlating low levels of dystrophin in muscle biopsy with clinical symptoms in dystrophinopathy patients. They selected for subjects who have *DMD* gene mutations with a higher likelihood of showing leaky (non-null) dystrophin protein. They found 48 of 90 subjects (53%) to show detectable (residual) dystrophin on muscle biopsy (34 Group B = >0% but <5% dystrophin; 14 Group C = ≥5% normal dystrophin levels); the remaining 42 subjects showed no detectable dystrophin (Group A). Clinical findings in Group A were consistent with extensive published studies of Duchenne muscular dystrophy (DMD), where undetectable levels of dystrophin are consistent with a typical DMD phenotype. Likewise, Group C findings were consistent with previous studies where dystrophin levels greater than 5% are associated with a milder DMD or Becker muscular dystrophy (BMD) phenotype.

The main focus of the authors was the 34 subjects in Group B with very low dystrophin levels (>0% but <5%). Of these 34, 28 (82%) showed splice site or pseudoexon mutations; these types of mutations are expected to result in residual levels of biochemically normal dystrophin protein.

The authors note that "Very low residual dystrophin protein quantity can cause a shift in disease phenotype from DMD toward BMD" (Abstract). The authors note that their data has implications for therapeutic approaches to dystrophin replacement, such as gene therapy, CRISPR gene editing, and exon skipping.

Unfortunately, there is a key limitation to this interpretation of their data that is not noted by the authors. Namely, the large majority of subjects studied (82%) were likely producing low levels of biochemically normal dystrophin (full-length, 427kDa) from birth. In contrast, there are no current or envisioned therapeutic approaches to DMD that seek to introduce biochemically normal dystrophin. Instead, gene therapy, exon skipping, and envisioned CRISPR approaches aim to introduce biochemically abnormal, semifunctional dystrophin. Although very low levels of biochemically normal dystrophin, especially when present from birth, may mitigate clinical symptoms, this cannot be assumed for biochemically abnormal dystrophin introduced later in life. The study results, although interesting for a genotype–phenotype correlation, should not be extrapolated to being informative in a dystrophin-restoring therapeutic context.

By not making the distinction of biochemically normal versus biochemically abnormal dystrophin, the authors may inadvertently heighten the expectations of patients, families, physicians, and regulatory agencies regarding anticipated clinical benefit from very low levels of semifunctional dystrophin.

[1]*School of Pharmacy and Pharmaceutical Sciences, Binghamton University–State University of New York, Binghamton, NY*
[2]*Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA*

© 2021 The Authors. Annals of Neurology published by Wiley Periodicals LLC on behalf of American Neurological Association.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

[Correction added on May 27, 2021, after first online publication: Copyright statement was updated.]

Reference

1. de Feraudy Y, Ben Yaou R, Wahbi K, et al. Very low residual dystrophin quantity is associated with milder dystrophinopathy. Ann Neurol 2021;89:280–292.

DOI: 10.1002/ana.26097