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

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We read with great interest the recent article by Sutter and colleagues reporting increased serum neurofilament light chain (NfL) levels in COVID-19 patients compared to non–COVID-19 intensive care unit (ICU) patients without infectious disease.[1] They postulated that infection with SARS-CoV-2 leads to neuronal injury in ICU-patients and that NfL might be used to identify patients at risk for neurological complications.

We evaluated these findings in the broader context of infectious disorders by comparing the plasma NfL levels of critically ill patients with similar disease severity and pneumonia induced by SARS-CoV-2 versus bacterial pathogens. We excluded patients with neurological comorbidities or trauma and matched the study population investigated by Sutter et al for sex, age, and disease severity (COVID-19 pneumonia vs bacterial pneumonia: mean age = 65 years, range = 42–89, 78% male, Sequential Organ Failure Assessment [SOFA] score = 4, range = 2–11 vs mean age = 67 years, range = 50–89, 90% male, SOFA score = 3, range = 0–5). Most notably, we observed that patients with COVID-19 pneumonia had considerably lower NfL levels compared to patients with bacterial pneumonia at day 3 ± 1 after onset of sepsis (defined as infection-related acute change in total SOFA score ≥ 2 points), which did not significantly increase over time (Fig A). Consistently with previous reports, we found a positive correlation between NfL levels and age as well as SOFA score in COVID-19 patients (see Fig B, C).

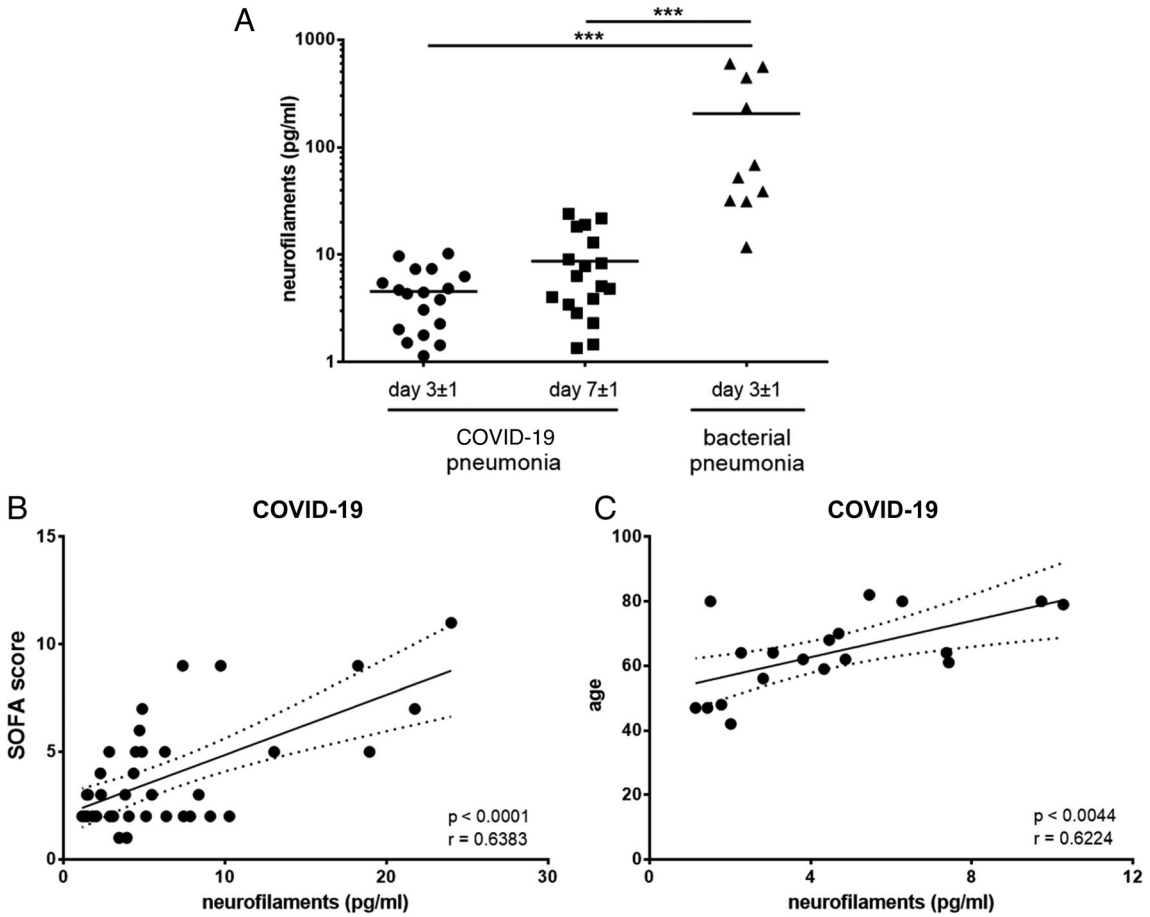

FIGURE: Neurofilament light chain (NfL) assay by Quanterix (Billerica, MA) HD-X was used to measure NfL levels according to manufacturer's instructions. (A) Comparison of NfL levels in patients with COVID-19 pneumonia at day 3 ± 1 and day 7 ± 1 (n = 18) and bacterial pneumonia at day 3 ± 1 (scatter dot blot with mean; n = 10) after onset of sepsis (analysis of variance on ranks, $p < 0.001$; Dunn multiple comparison test, ***$p < 0.001$). (B, C) Pearson correlation was used to assess correlations between neurofilaments and Sequential Organ Failure Assessment (SOFA) score (n = 36; day 3 ± 1 and 7 ± 1) or age (n = 18; day 3 ± 1) in COVID-19 patients.

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.

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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.

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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.

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[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