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*

[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