Association of Neuronal Injury Blood Marker Neurofilament light chain with mild-to-moderate COVID-19

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Research Article

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Abstract

The coronavirus disease 2019 (COVID-19) affects primarily the respiratory system but neurologic manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are possible. Serum neurofilament light chain (sNfL) has recently been considered as a specific biomarker to quantitate neuro-axonal damage. Concentrations of sNfL were determined in a prospective cohort study of 100 health care workers (84 females, 16 males) following a COVID-19 outbreak in a large hospital by using the single molecule array (Simoa) NF-light advantage kit. Twenty eight health care workers contracted mild-to-moderate COVID-19, recovered after 1-3 weeks without hospitalization and showed no or only minor neurological symptoms such as anosmia, fatigue or headache. sNfL levels were consistently higher in older persons and multivariable linear regression analysis revealed COVID-19 status as an independent predictor of sNfL (p=.005). In conclusion, increased sNfL levels in mild-to-moderate COVID-19 patients points towards a more general neuro-destructive capability of SARS-CoV-2.

Introduction

Even though the coronavirus disease 2019 (COVID–19) affects primarily the respiratory system some reports describe nervous system involvement as well.[1–3] Headache and anosmia have been frequently described as neurological symptoms of mild-to-moderate COVID–19 but a direct impact of COVID–19 on neuronal integrity has not been clarified yet.[4] Therefore, a neuronal biomarker would be extremely useful to elucidate neuro-axonal injury during an infection with Severe Acute Respiratory Syndrome Coronavirus–2 (SARS-CoV–2) and in the post-infection follow up period. Serum neurofilament light chain (sNfL) has recently been considered as a specific biomarker to quantitate neuro-axonal damage in several disorders of the peripheral and central nervous system.[5] Hence, sNfL might also serve as a sensitive screening and follow-up marker for neuronal injury in COVID–19 patients.

Methods

We conducted a prospective cohort study in 100 health care workers (84 females, 16 males) following a COVID–19 outbreak in a major German children's and women's hospital.[6] The Ethics Committee of the University of Regensburg approved the study (file-number: 20–1767–101), and written informed consent was obtained from all study participants. They were categorized according to their SARS-CoV–2 infection status, n = 28 tested positive, n = 72 negative in PCR based viral RNA amplification from nasopharyngeal swabs (Xpert© Xpress SARS-CoV–2, Cepheid).[5] To preserve anonymity of study participants, age was assessed in three categories (18–35 years n = 33, 36–50 years n = 37 and 51–65 years n = 30).[7] sNfL concentrations were measured using the single molecule array (Simoa) NF-light® kit on the HD-X Analyzer (Quanterix, Lexington, MA).[5] A multivariable linear regression model was fitted with sNfL as dependent variable with sex, age and COVID–19 status as independent variables.

Results

All COVID–19 patients had mild-to-moderate symptoms and recovered after 1–3 weeks and showed no or only minor neurological symptoms, including anosmia and headache. First sNfL measurement was done in COVID–19 patients 23 days (median, IQR 21–26) after onset of disease. Whereas sNfL levels did not differ in the youngest age group between COVID–19 patients (median NfL 4.5 pg/ml [IQR 3.7–5.7] n = 13) and controls (4.4 [3.5–5.5], n = 20) in older COVID–19 patients sNfL levels were consistently higher than in age matched controls (36–50 years: 9.6 [6.5–11.3], n = 9 vs controls 6.8 [5.6–8.8], n = 28; 51–65 years: 11.6 [8.4–18.3], n = 6 vs controls 9.6 [8.2–11.2] n = 24). Multivariable linear regression analysis revealed COVID–19 status as an independent predictor of sNfL (p =.005) (Table). In COVID–19 patients with two sNfL measurements (n = 16, time span between the measurements was median 35 days, range 29 to 36 days) sNfL levels were highly correlated (r = 0.96).

Discussion

NfL is a highly specific structural protein of neurons and elevated levels of sNfL are recognized as measures of acute or chronic neuro-axonal damage.[5] Our results from a study in health care workers without known co-morbidities indicate that mild-to-moderate COVID–19 is associated with increased sNfL levels. Neurologic symptoms and complications in patients with SARS-CoV–2 infection have been reported by the first available studies during SARS-CoV–2 pandemic.[1,2] However, these studies are restricted to hospitalized patients and therefore represent a population more likely to have severe neurological manifestations for a variety of reasons. Our results indicate for the first time that COVID–19 may affect the neuro-axonal integrity also in adults with a mild-to-moderate course of the disease. This new evidence for a more general neuro-destructive capability of SARS-CoV–2 also in mild-to-moderate COVID–19 patients should raise awareness for potential long-term neurologic sequelae following COVID–19. Of note, our study includes only a limited number of patients. To draw any further conclusions additional studies on sNfL and COVID–19 are needed.

Table

Table

A) Baseline Characteristics of study participants stratified by COVID-19 status

	Non COVID-19 (n=72)	COVID-19 (n=28)
Female (N, %)	59 (81.9)	25 (89.3)
Male (N, %)	13 (18.1)	3 (10.7)
Age group 18-35 years (N, %)	20 (27.7)	13 (46.4)
Age group 36-50 years (N, %)	28 (38.9)	9 (32.14)
Age group 51-65 years (N, %)	24 (33.3)	6 (21.4)
Respiratory symptoms (N, %)		17 (60.7)
Neurological symptoms (N, %)		21 (75.0)

Notes: Respiratory symptoms included cough and shortness of breath; neurological symptoms included headache and anosmia

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B) Multivariable linear regression analysis of sex, age and COVID-19 status on sNfL

	b	SE B	β	*p*
Sex (female)	-0.02	0.84	-0.00	*.981*
Age group 18-35 years	*Reference category*			
Age group 36-50 years	3.38	0.72	0.44	*<.001*
Age group 51-65 years	6.10	0.74	0.76	*<.001*
COVID-19	1.87	0.65	0.23	*.005*

Notes: n=100. Nagelkerke's R^2=.45; b: regression coefficient; SE B: standard error (regression coefficient); β: standardized regression coefficient; *p*: significance value.

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Declarations

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Conflicts of interest: Nothing to disclose

Availability of data and material: On request

Ethics approval: The Ethics Committee of the University of Regensburg approved the study (file-number: 20–1767–101)

Author contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Markus Ameres, Susanne Brandstetter, Antoaneta A. Toncheva, David Leppert and Jens Kuhle. The first draft of the manuscript was written by Markus Ameres and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Figures

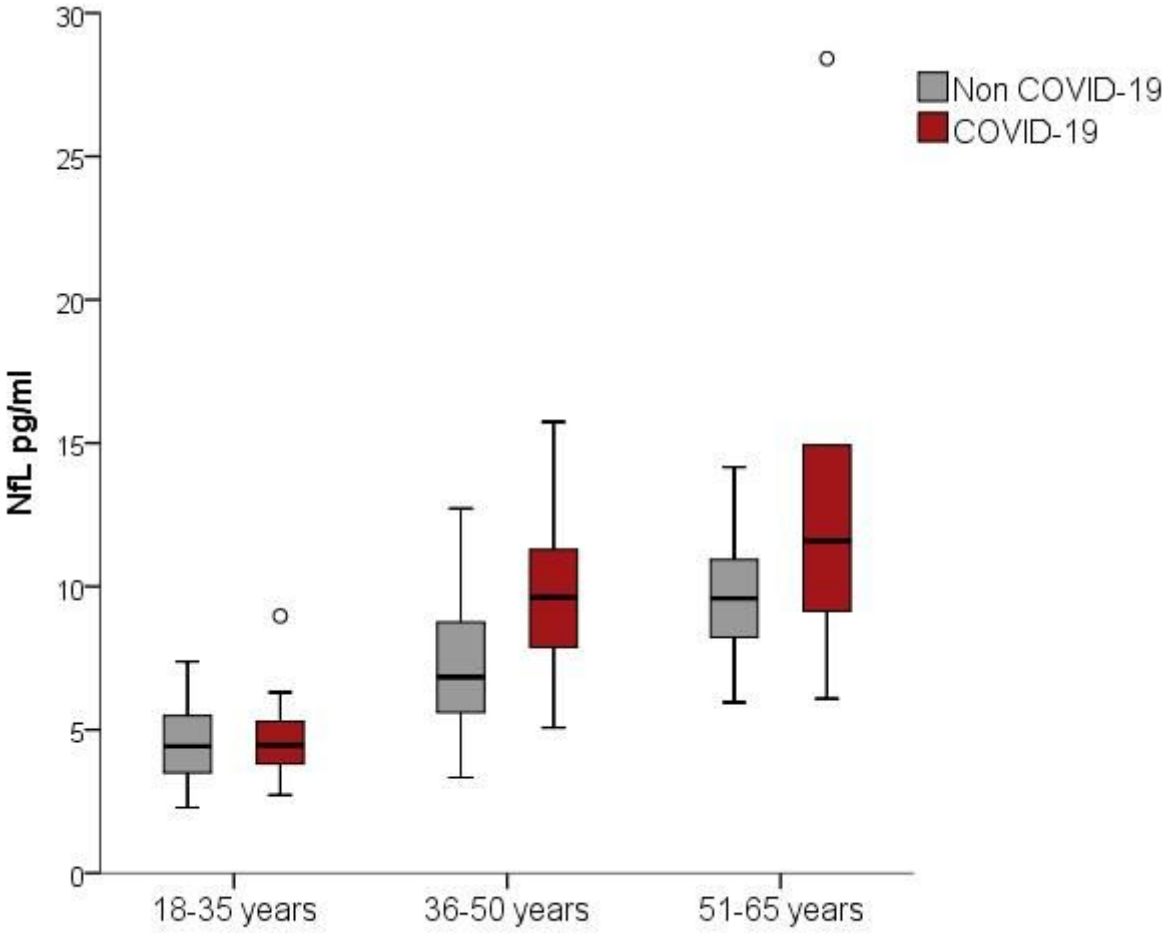

Figure 1

Boxplots of sNfL concentrations in COVID-19 and control cases stratified by age group. Of note, COVID-19 status (p=0.005) and age group (p<0.001) are significantly associated with sNfL values in a multivariable linear regression analysis of sex, age and COVID-19 status.