

Comparison of Simoa(TM) and Ella(TM) to assess serum neurofilament-light chain in multiple sclerosis

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BRIEF COMMUNICATION

Comparison of Simoa™ and Ella™ to assess serum neurofilament-light chain in multiple sclerosis

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Abstract

We compared Simoa™ and Ella™ immunoassays to assess serum neurofilament-light chain levels in 203 multiple sclerosis patients from the OFSEP HD study. There was a strong correlation ($\rho = 0.86$, $p < 0.0001$) between both platforms. The Ella™ instrument overestimated values by 17%, but as the data were linear ($p = 0.57$), it was possible to apply a correction factor to Ella™ results. As for Simoa™, serum neurofilament-light chain levels measured by Ella™ were correlated with age and EDSS and were significantly higher in active multiple sclerosis, suggesting that these assays are equivalent and can be used in routine clinical practice.

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[b]OFSEP Investigators list is in Appendix (5.5 Co-investigators).

Introduction

Neurofilaments (Nf) are major components of the neuronal cytoskeleton, consisting predominantly of three subunits: Nf-light (NfL), Nf-medium and Nf-heavy chains.[1] Upon neuro-axonal damage of the central nervous system (CNS), NfL is released into the extracellular space and is detectable in the cerebrospinal fluid and blood.[2] Thus, NfL levels are increased proportionally to the degree of damage,[2] making serum NfL levels a useful biomarker for diagnosing and predicting disease progression of a variety of CNS disorders, including multiple sclerosis (MS).[3] In MS, serum NfL is correlated with several factors including age, Expanded Disability Status Scale (EDSS), disease activity and disease-modifying treatments.[4]

Several ultrasensitive immunoassay technologies are available for quantification of serum NfL. The current reference method is the Single Molecular Array (Simoa™, Quanterix)[5] using an antibody developed by Uman Diagnostics. Recently, several companies have acquired this antibody, allowing NfL quantification using the Simple Plex™ Ella (Ella™) microfluidic platform (ProteinSimple). The Ella™ instrument allows rapid and ultra-sensitive measurement of biomarkers.[6] This platform allows quantitation of an analyte from 72 samples in a single disposable microfluidic cartridge, within 90 minutes (ProteinSimple, 2020). However, the comparability of the two technologies in measuring serum NfL levels in patients with MS remains to be determined.

The objective of this study was to compare the NfL values obtained using the Simoa™ platform with Ella™ instrument in MS patients and healthy controls (HCs). Correlations of the serum NfL measures were performed to evaluate whether Ella™ had good clinical performance in reflecting age, EDSS and disease activity, and could be routinely used to monitor MS patients in clinical practice.

Materials and methods

Serum samples

Anonymized serum samples were taken from 203 of the 1800 anticipated patients ≥15 years old with MS according to the revised McDonald diagnosis criteria included in the OFSEP "High Definition" cohort (NCT03981003), and from 30 HCs. Ethics approvals were obtained, and all patients and controls participated voluntarily in the study and provided written informed consent (Details in Supplementary materials and methods).

Simoa™ and Ella™ NfL assay

Serum NfL concentrations were prospectively determined in parallel with the Simoa™ Human Neurology 4-Plex "A" kit (Quanterix Corp, Boston, MA) on Simoa™ HD-1 analyzer and Simple Plex™ NfL Assay (ProteinSimple, CA, USA) on Ella™ instrument, according to the manufacturers' instructions. Ella™ was calibrated using the in-cartridge factory standard curve and Simoa™ using the provided standards. All samples were measured in simplicate, on the same day, after a single thaw, with a 1:2 dilution for Ella™ and 1:4 for Simoa™. In each run, the HC, one control patient with active relapsing remitting MS (RRMS), and one high and one low concentration control sample provided with the kits were assayed. The lower limit of quantification is 0.241 pg/ml for Simoa™ and 2.70 pg/ml for Ella™.

Statistical analysis

The intra-assay coefficients of variation (CV) of manufacturer-provided controls were automatically calculated in duplicate (Simoa™) or internal triplicate (Ella™). Repeatability tests were performed with samples at high (RRMS patient) and low (HC) concentrations by repeated measures for Simoa™ (30 times each) and for Ella™ (28 times and 25 times, respectively). Intra-assay CV was calculated from the standard deviation of the average concentrations divided by the overall mean of the average concentrations.

Median NfL values obtained by each platform were compared using the Wilcoxon–Mann–Whitney test. Spearman correlation coefficients were calculated to assess the association between concentrations obtained by each platform, presented with 95% confidence interval (95% CI). The Bland–Altman method[7] was used to measure mean difference and 95% limit of agreement between log-transformed concentrations obtained by each platform. The regression relationship between the two platforms was evaluated using Passing–Bablok.[8] Finally, correlations of serum NfL levels with clinical parameters were analyzed using linear regression (age, EDSS) or Wilcoxon–Mann–Whitney (e.g. RRMS *vs.* progressive MS).

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Statistical analyses were performed on Prism 8.3.0.538 (GraphPad). A p-value <0.05 was considered statistically significant.

Data availability statement

Anonymized data will be shared by request from any qualified investigator.

Results

Repeatability tests were performed by measuring 25-30 times one sample at low concentration (HC) and one sample at high concentration (RRMS patient) and showed similar CVs with both platforms (Supplementary Figure A). The mean [min-max] intra-assay CVs on Ella™ technology was 2.12% [1.53-2.70] vs 3.78% [2.93-4.63] on Simoa™ platform. The mean [min-max] inter-assay CV of the three runs was 12.93% [7.59-18.27] on Ella™ and 5.54% [5.08-6.00] on Simoa™. In MS patients, median serum NfL levels [interquartile range] measured by Ella™ were higher than by Simoa™ (13.90 pg/ml [10.73-18.48] for Ella™ *vs.* 9.46 pg/ml [6.94-12.9] for Simoa™, $p < 0.001$) (Figure 1A). Serum NfL levels were strongly correlated between the two technologies in MS patients (Spearman r = 0.86, 95% CI [0.821-0.895]) (Figure 1B) and in HCs (Spearman r = 0.76, 95%CI [0.533-0.882], Supplementary Figure B).

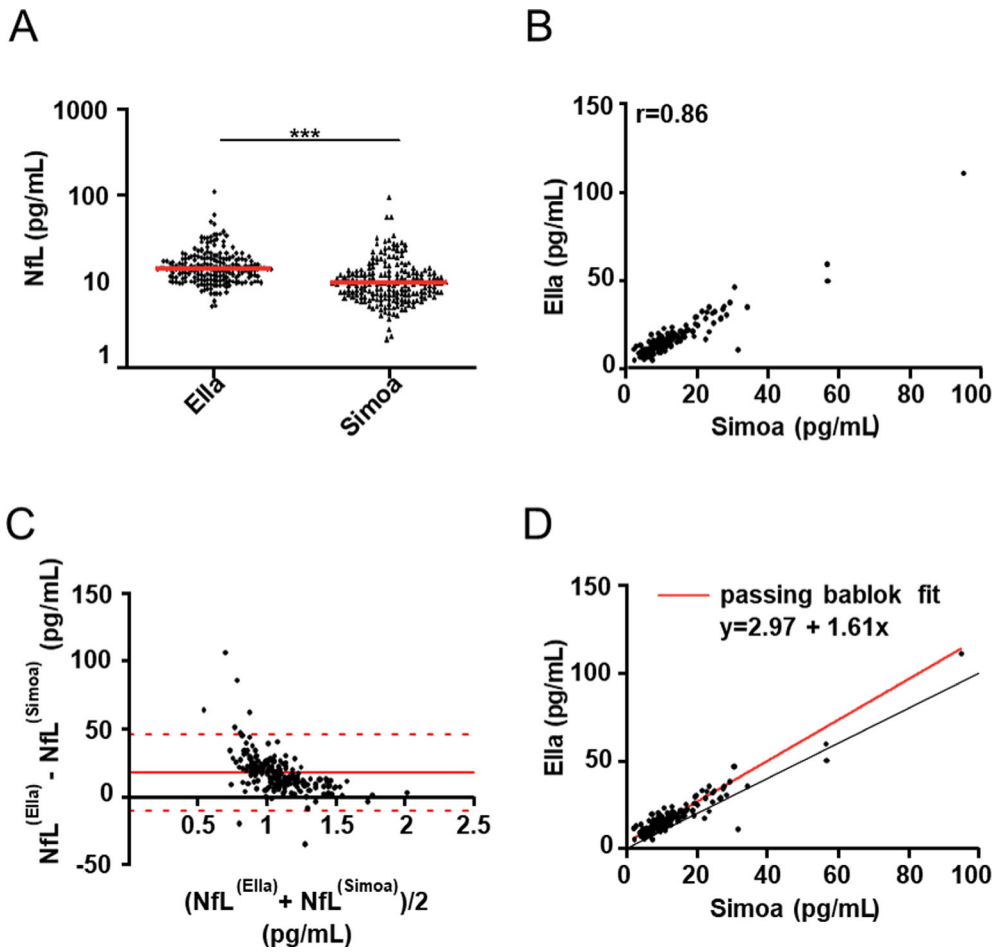


Figure 1. Properties of serum NfL values measured by the Simoa™ and Ella™ platforms. A, Quantitation of NfL concentration (pg/ml) in serum with Ella™ and Simoa™ platforms shown in logarithmic scale. Red lines represent median NfL level. The statistical difference was evaluated by Wilcoxon–Mann–Whitney with 203 samples. ***$p < 0.001$. B, Spearman correlation (r) between NfL concentration values obtained by the Ella™ compared to the Simoa™ instruments ($p < 0001$). C, Bland–Altman plots comparing agreement between NfL concentrations determined using the Simoa™ and Ella™ platforms. The solid red line represents the bias between assays (17.6%), the dashed red lines represent 95% limits of agreement (−10.61% to 45.81%). D, Passing–Bablok regression analysis of NfL concentration calculated on 203 samples by the Ella™ compared to the Simoa™ platform. It shows the value of slope (1.161) and intercept (2.917). Solid gray line: Passing–Bablok regression line; solid red line: identity line (x = y).

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The Bland–Altman method depicted a mean bias of 17.6% for the NfL concentrations between the assays performed with the two technologies. Thus, Ella™ showed a 17.6% "overestimation" compared with Simoa™. Overall, 95% of observations were within the limit of agreement (Figure 1C). The slope of the Passing–Bablok regression line was 1.161 (95% CI [1.091-1.240], $p < 0.0001$) and the intercept was 2.917 pg/ml (95% CI [2.132-3.676], $p < 0.0001$). The 95% CI of intercept and slope values differ from zero and one, respectively, indicating a method agreement and allowing application of a correction coefficient.[9] Moreover, the linearity test demonstrated no significant deviation from linearity between the two datasets ($p = 0.57$), suitable for concluding on method agreement (Figure 1D).

Both platforms exhibited significant correlations of serum NfL with age, EDSS and disease form (Figure 2). Especially, serum NfL levels were higher in RRMS patients than in age-matched HCs, higher in active MS than in inactive MS, higher during relapses than in patients with a stable disease and higher in PMS than in RRMS patients with both platforms (Figure 2B). The last comparison was no longer significant in a multivariate model including age.

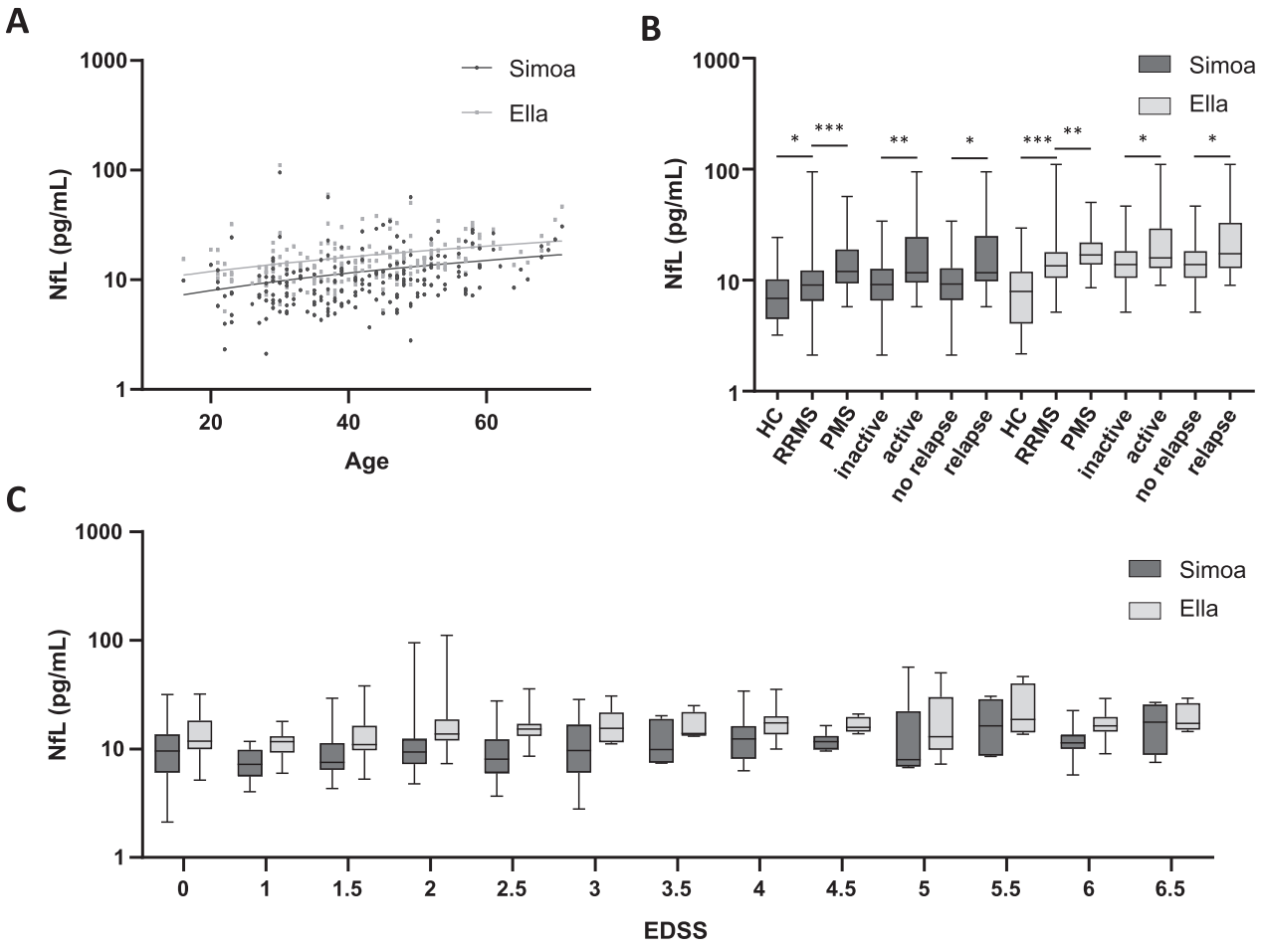


Figure 2. Comparison of serum NfL values measured by the Simoa™ and Ella™ platforms. A, Association of age with NfL concentration (pg/ml, shown in logarithmic scale) in serum determined by Ella™ (light gray) and Simoa™ (dark gray) platforms were estimated using the linear regression with 203 samples (b = 0.18, $p = 0.002$, $r^2 = 0.045$ in Simoa™ and b = 0.21, $p < 001$, $r^2 = 0.057$ in Ella™). B: Comparison of NfL levels (pg/ml, shown in logarithmic scale) in serum for HCs and MS patients, obtained by the Simoa™ (dark gray, left) and the Ella™ (light gray, right) instruments. Serum NfL levels were higher in RRMS patients than in HCs ($p = 0.021$ and $p < 0001$, respectively), higher in active MS than in inactive MS ($p = 0.0080$ and $p = 0.0356$, respectively), higher during relapses than in patients with a stable disease ($p = 0.0153$ and $p = 0.0373$, respectively), and lower in RRMS than in PMS patients ($p = 0.0007$ and $p = 0.0021$, respectively) (*$p < 05$, **$p < 01$, ***$p < 001$, ****$p < 0001$). C: Association of EDSS with NfL concentration (pg/ml, shown in logarithmic scale) in serum determined by Simoa™ (left, dark gray boxplots) and Ella™ (right, light gray boxplots) platforms were estimated using linear regression with 203 samples (b = 0.83, $p = 0.026$, $r^2 = 0.026$ in Simoa™ and b = 0.96, $p = 0.015$, $r^2 = 0.031$ in Ella™).

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Discussion

Blood NfL is a biomarker associated with several clinical parameters in MS.[10] We showed that both Ella™ and Simoa™ platforms offer excellent sensitivity, detecting serum NfL concentrations in the picogram range, Simoa™ platform offering the lowest inter-assay imprecision at low analyte levels. A limitation of our study was restricting the analysis to three runs, making the inter-assay CV harder to accurately define. The two systems use different methods to determine intra-assay CV, using technical duplicate or triplicate readings, preventing direct comparison. However, Simple Plex™ runs the samples in parallel at the same time, assuring the exact same conditions for replicate analysis, an advantage over the Simoa™ platform that processes serial measures. Moreover, calibrators are directly integrated in the Simple Plex™ cartridges, providing best calibration for each run.

The main finding of this study is the demonstration of a concordance between NfL levels measured using both platforms, even at low levels in the HC group. This is potentially the result of using the same anti-NfL antibody and of heterophilic blockers limiting potential cross-reaction between anti-NfL antibody and antibodies in the serum for both platforms. However, we observed significant differences in absolute biomarker concentrations between these two instruments. Using different calibrators (naturally derived bovine NfL for Ella™ and a recombinant human NfL for Simoa™) has been associated with differences in NfL measure and could explain the differences in absolute values obtained by both assays.[2] The NfL raw concentrations measured by Simoa™ were globally lower vs Ella™, as confirmed by the Bland–Altman plot. The "spike recovery" reported in the data sheet of the two assays is 68% for Simoa™ NfL kit and 108% for Simple Plex™ NfL, suggesting that Simoa™ could underestimate the values of NfL by 17% compared to Ella™ due to a greater effect of the serum matrix than in the Simple Plex™ method. Passing–Bablok allowed the bias to be evaluated over the entire measurement range and the linear test shows that the data are linear ($p = 0.57$). Thus, it is possible to apply a correction factor 2.917. Therefore, Ella™ technology, with the advantage of small footprint and a robust and cheaper platform, represents a reliable substitute for Simoa™ to measure serum NfL.

Moreover, we demonstrate that serum NfL levels determined by Ella™ show the same properties, concerning correlation of serum NfL with age, EDSS and disease activity. This is crucial, since future studies with Ella™ can directly resume previous results already published using Simoa™. However, NfL cannot be used in combination with other brain biomarkers that remain unavailable on this platform, such as glial fibrillary acidic protein, available on the Simoa™ platform which currently has a larger range of biomarkers.

Although the Ella™ platform showed a greater inter-assay variation compared to Simoa™, it seems an attractive choice for routine quantification of serum NfL considering the reduced cost, high performance and small footprint while maintaining a high concordance with Simoa™. Serum NfL biomarker can be quantified using automated Ella™ instrument to reliably and rapidly monitor disease activity and treatment in MS as well as in many other CNS pathological conditions, thus optimizing quality of care.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Audrey Gauthier: nothing to disclose; Sébastien Viel: nothing to disclose; Magali Perret: nothing to disclose; Sabine Laurent-Chabalier: nothing to disclose; Marc Debouverie: nothing to disclose; Gilles Edan: consultancy and lecturing fees from Bayer-Schering, Biogen, LFB, Merck, Novartis, Roche, Sanofi; research grants from Bayer, Biogen, Genzyme, Mercks, Novartis, Roche, Teva, and the ARSEP foundation. He has been principal investigator in phase 2 and 3 clinical studies conducted by Bayer, Biogen, Merck, Novartis, Sanofi-Aventis Teva, and 4 academic programs (programmes hospitaliers de recherche clinique, PHRC) on MS sponsored by Rennes University Hospital; Sandra Vukusic: grants, personal fees and non-financial support from Biogen, grants and personal fees from Geneuro, grants, personal fees and non-financial support from Genzyme, grants and personal fees from Medday, grants, personal fees and non-financial support from Merck-Serono, grants, personal fees and non-financial support from Novartis, grants, personal fees and non-financial support from Roche, grants, personal fees and nonfinancial support from Sanofi, personal fees from Teva; Christine

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Figure S1. Comparison of Simoa™ and Ella™ platforms at low serum NfL levels. A: Repeatability tests of both platforms using samples from one HC and from one RRMS patient tested 30 times. For Simoa™, average NfL concentrations were 6.55 pg/ml and 14.22 pg/ml and CVs were 11.3% and 8.1%, respectively. For Ella™, average serum NfL concentrations were 8.60 pg/ml and 38.38 pg/ml and CVs were 12.8% and 8.9%, respectively, as indicated on the graph. B: Spearman correlation (r) between NfL concentration values obtained by the Ella™ compared to the Simoa™ instruments in a cohort of 29 HCs ($r = 0.76$, $p < 0.0001$).
Supplementary Material and Methods. Origin of serum samples.

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