Plasma glial fibrillary acidic protein and neurofilament light chain are measures of disease severity in semantic variant primary progressive aphasia

Authors

Carolin Heller BSc[1], Elise Chan MSc[1], Martha S. Foiani PhD[1], Emily Todd MRes[2], Lucy Russell PhD[2], Caroline V. Greaves BSc[2], Amanda Heslegrave PhD[1], Jason D. Warren FRACP PhD[2], Henrik Zetterberg PhD[1,3,4], Martina Bocchetta PhD[2], Jonathan D. Rohrer FRCP PhD[2]

Affiliations

[1]UK Dementia Research Institute, [2]Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, UK. [3]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden. [4]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden.

Corresponding author

Dr Jonathan Rohrer, Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, j.rohrer@ucl.ac.uk

Word count: 863

INTRODUCTION

Semantic variant primary progressive aphasia (svPPA) is a neurodegenerative disorder characterised by loss of conceptual knowledge, commonly presenting with word-finding difficulties, impaired single word comprehension and focal atrophy of the temporal lobe[1]. It is a subtype of frontotemporal dementia (FTD) and usually associated with TDP-43 type C pathology. Whilst much progress has been made in the last twenty years in understanding the cognitive and biological nature of svPPA, there have been limited studies of fluid biomarkers[2]. In this study, we investigated the role of plasma glial fibrillary acidic protein (GFAP) and neurofilament light-chain (NfL) as biomarkers for astroglial activation and neurodegeneration in svPPA, as well as their association with disease severity in svPPA.

METHODS

Participants

Plasma samples were collected from 64 consecutively recruited participants from the University College London FTD cohort studies: 28 participants meeting diagnostic criteria for svPPA[1] and 36 age- and sex-matched healthy controls (t-test, p=0.934 and Fisher's exact test, p>1.000, respectively). Participants underwent a standardized clinical and cognitive assessment (Table) including two measures of semantic knowledge, Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary subtest and the British Picture Vocabulary Scale (BPVS, a word-picture matching task). They also underwent a 3D T1-weighted magnetic resonance imaging (MRI) of the brain on either a Siemens Trio or Prisma 3T scanner with 55 scans passing initial quality control for cross-sectional analysis (21 participants with svPPA and 34 healthy controls): temporal lobe grey matter volumes (combined left and right hemisphere) were calculated using a previously described automated segmentation technique[3,4]. The local ethics committee approved the study and all participants provided written informed consent at enrolment.

Plasma GFAP and NFL measurement

Plasma was collected, processed and stored in aliquots at -80°C according to standardised procedures. GFAP and NfL were measured using the Neurology 4-Plex A kit on the SIMOA HD-1 Analyzer (Quanterix, Billerica, MA), as previously described[4]. All samples were measured in duplicates (all CVs below 15%), except for nine samples that only had a single measurement available. The measurements were performed in one round of experiments using one batch of reagents and the analyst was blinded to clinical data.

Statistical analysis

Histograms and Shapiro-Wilk tests were used to investigate normality distribution of all variables. If data followed a normal distribution, two-sample t-tests were used to compare groups; alternatively, a two-sample Wilcoxon rank-sum test was performed. Spearman correlations were performed to investigate relationships between continuous variables. All p-values were two-tailed and significance was set at $p < 0.05$. Analysis was performed in Stata (v.14; Texas, USA).

RESULTS

Consistent with the clinical diagnosis, the svPPA group were significantly impaired on both tests of semantic knowledge (WASI Vocabulary, z=6.20, p<0.001; BPVS, z=6.35, p<0.001) and had lower temporal lobe volumes (t=12.79, p<0.001) than the control group (Table).

Both GFAP and NfL concentrations were significantly higher in the svPPA group compared to controls (z=-2.77, p=0.006; z=-6.50, p<0.001 respectively).

GFAP and NfL levels were significantly correlated with each other in both the svPPA (rho=0.53, p=0.004) and the control group (rho=0.51, p=0.002).

Increased NfL but not GFAP concentrations correlated with the extent of semantic impairment in the svPPA group (NfL: WASI Vocabulary, rho=-0.55, p=0.004; BPVS, rho=-0.56, p=0.003; GFAP: WASI Vocabulary, rho=-0.22, p=0.291; BPVS, rho=-0.26, p=0.204).

Both NfL and GFAP concentrations were negatively correlated with temporal lobe volume (NfL, rho=-0.47, p=0.033; GFAP, rho=-0.58, p=0.006).

DISCUSSION

Plasma GFAP and NfL levels were increased in svPPA compared to controls with both having a negative correlation with temporal lobe volumes, suggesting that they are markers of disease severity in this subtype of FTD.

GFAP, a marker of astrogliosis or astrocytic activation, has previously been shown to be increased in the plasma of people with progranulin-related FTD[4], and in the serum of people with behavioural variant FTD and nonfluent variant PPA, as well as those with svPPA[5], consistent with the findings in this study. However, in this prior study, no analysis was performed of the relationship of svPPA with specific measures of disease severity[5]. Here we found increased GFAP levels with lower temporal lobe volumes suggesting that as the disease progresses the concentration of GFAP rises. Future studies would benefit from measuring longitudinal levels of GFAP in individual patients with svPPA.

Little is known about the underlying molecular mechanisms that lead to the development of svPPA, a usually sporadic TDP-43 proteinopathy. However, a prior study has suggested a possible inflammatory component, with raised plasma TNF-alpha concentrations and an increased rate of systemic autoimmune disease[6]. Raised GFAP is commonly seen in neuroinflammatory disorders and therefore would be consistent with this thesis for the underpinnings of svPPA. More work on neuroinflammatory markers is needed in this group of patients.

Multiple studies have now identified NfL as a marker of neuronal damage or axonal injury across different neurological disorders. Prior studies of svPPA have shown it is raised in CSF[2] and serum[7], and one previous study showed an association with impaired naming and with lower amount of parahippocampal gyrus grey matter, consistent with the findings here of an association with semantic impairment and temporal lobe volume. As with GFAP, this suggests that NfL rises with progression of temporal lobe volume loss, although unlike GFAP, NfL concentrations more closely match with worsening of clinical impairment.

In summary, GFAP and NfL can both identify the extent of disease severity of svPPA, and aligned with other neurodegenerative diseases a decrease in their levels may well prove useful to show therapeutic benefit in future clinical trials.

Conflicts of interest

HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

REFERENCES

1. Gorno-Tempini ML, Hillis AE, Weintraub S *et al.* Classification of primary progressive aphasia and its variants. *Neurology* 2011;76(11):1006–1014.

2. Meeter LHH, Steketee RME, Salkovic D *et al.* Clinical value of cerebrospinal fluid neurofilament light chain in semantic dementia. *J Neurol Neurosurg Psychiatry*. 2019;90(9):997-1004.

3. Cardoso MJ, Modat M, Wolz r, *et al*. Geodesic information flows: Spatially-Variant graphs and their application to segmentation and fusion. *IEEE Trans Med Imaging* 2015;34:1976–88.

4. Heller C, Foiani MS, Moore K *et al.* Plasma glial fibrillary acidic protein is raised in progranulin-associated frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2020;91(3):263–270.

5. Benussi AJ, Ashton NJ, Karikari TK *et al.* Serum Glial Fibrillary Acidic Protein (GFAP) Is a Marker of Disease Severity in Frontotemporal Lobar Degeneration. *J. Alzheimer's Dis.* 2020 [Epub ahead of print].

6. Miller ZA, Rankin KP, Graff-Radford NR et al. TDP-43 frontotemporal lobar degeneration and autoimmune disease. *J Neurol Neurosurg Psychiatry.* 2013;84(9):956-62.

7. Rohrer JD, Woollacott IO, Dick KM et al. Serum neurofilament light chain protein is a measure of disease intensity in frontotemporal dementia. *Neurology.* 2016;87(13):1329-36.

Table. Demographics and clinical characteristics of the controls and semantic variant primary progressive aphasia group.

	Controls	svPPA	Test statistic	p-value
Number of participants	36	28		
Sex: number (%) of male participants	18 (50.0)	14 (50.0)		>1.000
Mean (SD) age at assessment (years)	65.65 (6.90)	65.50 (6.99)	t = 0.08	0.934
Mean (range) age at onset (years)	-	60.4 (51 - 75)		
Mean (SD) disease duration (years)	-	5.1 (2.5)		
WASI Vocabulary (standard score)	65 (62 - 67)	20 (20 - 40)	z = 6.20	< 0.001
BPVS (T score)	120 (120 - 127)	41 (41 - 70)	z = 6.35	< 0.001
Mean (SD) temporal lobe volume (as a % of TIV)	8.4 (0.4)	6.6 (0.7)	t = 12.79	< 0.001
GFAP (pg/mL)	109.10 (83.21 - 136.26)	148.33 (109.63 - 197.42)	z = -2.77	0.006
NfL (pg/mL)	15.19 (12.11 - 18.43)	39.33 (32.08 - 53.23)	z = -6.50	< 0.001

Values are median (interquartile range) unless stated. svPPA = semantic variant PPA. SD = standard deviation. WASI = Wechsler Abbreviated Scale of Intelligence. BPVS = British Picture Vocabulary Scale. GFAP = Glial fibrillary acidic protein. NfL = Neurofilament light chain protein. 25 svPPA and 34 controls completed the WASI Vocabulary and BPVS tests.

Figure. A) Glial fibrillary acidic protein (GFAP) and B) neurofilament light chain (NfL) in pg/mL in controls and semantic variant primary progressive aphasia. Median designated by blue line; interquartile ranges indicated by orange error bars. * = significant differences.