June + July 2022 Simoa Publications

Title	Lead Author	Lead Author Affiliation	Journal	Area of Focus	Technology Platform
Serum neurofilament as a predictor of 10-year grey matter atrophy and clinical disability in multiple sclerosis: a longitudinal study	Lie, I	University of Bergen, Bergen, Norway	J Neurol Neurosurg Psychiatry	MS	Bead
Quantification of SNAP-25 with mass spectrometry and Simoa: a method comparison in Alzheimer's disease	Nilsson, J	University of Gothenburg, SE-43180 Mölndal, Gothenburg	Alzheimers Res Ther	Alzheimer's disease	Bead
Modulation of the Thrombin Pathway Restores LTP in a Pilocarpine Mice Model of Status Epilepticus	Shavit-Stein, E	Tel Aviv University, Tel Aviv, Israel	Front Cell Neurosci	status epilepticus	Bead
A combination model of AD biomarkers revealed by machine learning precisely predicts Alzheimer's dementia: China Aging and Neurodegenerative Initiative (CANDI) study	Gao, F	University of Science and Technology of China, Hefei, People's Republic of China	Alzheimers Dement	Alzheimer's disease	Bead
Serum neurofilament light chain concentration predicts disease worsening in multiple sclerosis	Brune, S	University of Oslo, Oslo, Norway	Mult Scler	MS	Bead
Validation of Plasma and CSF Neurofilament Light Chain as an Early Marker for Sporadic Creutzfeldt-Jakob Disease	Schmitz, M	German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany	Mol Neurobiol	Sporadic Creutzfeldt-Jakob disease	Bead
Neurofilament light chain: a new marker for neuronal decay in the anterior chamber fluid of patients with glaucoma	Woltsche, N	Medical University of Graz, Graz, Austria	Br J Ophthalmol	Glaucoma	Bead
Repeated neurofilament light chain measurements did not capture Riluzole therapeutic effect in amyotrophic lateral sclerosis patients	Esselin, F	INSERM, Montpellier, France	CNS Neurosci Ther	ALS	Bead
Detecting ongoing disease activity in mildly affected multiple sclerosis patients under first-line therapies	Masanneck, L	Medical Faculty University Hospital Düsseldorf, Düsseldorf, Germany	Multiple Sclerosis and Related Disorders	MS	Bead
High Fat High Sucrose Diet Modifies Uterine Contractility and Cervical Resistance in Pregnant Rats: The Roles of Sex Hormones, Adipokines and Cytokines	Gáspár, Róbert	University of Szeged, 6720 Szeged, Hungary	Life	cervical resistance	planar
Neurofilament light chain and total tau in the differential diagnosis and prognostic evaluation of acute and chronic inflammatory polyneuropathies	Kmezic, Ivan	Karolinska Institutet, Stockholm, Sweden	European Journal of Neurology	inflammatory polyneuropathies	Bead

Recent Advances in Frontotemporal Dementia	Tartaglia, Maria	University of Toronto, Toronto, ON	Canadian Journal of Neurological Sciences	Frontotemporal dementia	Bead
The utility of SARS-CoV-2 nucleocapsid protein in laboratory diagnosis	Li, X	Medical School of Zhengzhou University, Zhengzhou, China	J Clin Lab Anal	Covid-19	Bead
Factors associated with mortality in early stages of parkinsonism	van Rumund, Anouke	Radboud University Medical Center, Nijmegen, The Netherlands	npj Parkinson's Disease	Parkinson's disease	Bead
Increased Neurofilament Light Chain Is Associated with Increased Risk of Long-Term Mortality in Cerebral Small Vessel Disease	Jacob, M	Radboud University Medical Center, Nijmegen, The Netherlands	J Stroke	Stroke	Bead
Sex influences clinical phenotype in frontotemporal dementia	Pengo, Marta	University of Brescia, Brescia, Italy	Neurological Sciences	frontotemporal dementia	Bead
Novel App knock-in mouse model shows key features of amyloid pathology and reveals profound metabolic dysregulation of microglia	Xia, Dan	Denali Therapeutics, Inc., South San Francisco, California	Molecular Neurodegeneration	Alzheimer's disease	Bead
Factor VII, EPCR, aPC Modulators: novel treatment for neuroinflammation	Golderman, Valery	The Chaim Sheba Medical Center, 52621 Ramat Gan, Israel	Journal of Neuroinflammation	neuroinflammation	Bead
Interferon-α-mediated therapeutic resistance in early rheumatoid arthritis implicates epigenetic reprogramming	Cooles, F	Newcastle University, Newcastle Upon Tyne, UK	Ann Rheum Dis	rheumatoid arthritis	Bead
Plasma and serum alpha-synuclein as a biomarker in Parkinson's disease: A meta-analysis	Zubelzu, Maider	University of the Basque Country (UPV/EHU), Leioa, Bizkaia, Spain	Parkinsonism & Related Disorders	Parkinson's disease	Bead
Identification of bronchoalveolar and blood immune-inflammatory biomarker signature associated with poor 28-day outcome in critically ill COVID-19 patients	Voiriot, Guillaume	Sorbonne Université, 75020 Paris, France	Scientific Reports	COVID-19	Bead & planar
The effect of the probiotic consortia on SARS-CoV-2 infection in ferrets and on human immune cell response in vitro	Lehtinen, M	IFF, Kantvik 02460, Finland	iScience	COVID-19	planar
Plasma neurofilament light and its association with all-cause mortality risk among urban middle-aged men and women	Beydoun, M	NIA/NIH/IRP, Baltimore, MD	BMC Med	all-cause mortality	Bead
Plasma Markers of Neurologic Injury and Inflammation in People With Self-Reported Neurologic Postacute Sequelae of SARS-CoV-2 Infection	Peluso, M	University of California, San Francisco, CA	Neurol Neuroimmunol Neuroinflamm	COVID-19	Bead

Glycerophosphoinositol is Elevated in Blood Samples From CLN3Δex7-8 pigs, Cln3Δex7-8 Mice, and CLN3-Affected Individuals	Brudvig, Jon	Sanford Research, Sioux Falls, SD	Biomarker Insights	CLN3 Batten disease	Bead
Diffusion tensor imaging (DTI) and plasma p-tau 181 in Alzheimer's disease	Nabizadeh, Fardin	Iran University of Medical Sciences, Tehran, Iran	Neurology Letters	Alzheimer's disease	Bead
Enhancing clinical value of serum neurofilament light chain measurement	Kosa, P	NIAD/NIH, Bethesda, MD	JCI Insight	MS	Bead
Elevated Plasma Soluble ST2 Levels are Associated With Neuronal Injury and Neurocognitive Impairment in Children With Cerebral Malaria	Fernander, E	Indiana University School of Medicine, Indianapolis, IN	Pathog Immun	malaria	Bead
Brain disconnectome mapping derived from white matter lesions and serum neurofilament light levels in multiple sclerosis: A longitudinal multicenter study	Rise, H	University of Oslo, Oslo, Norway	Neuroimage Clin	MS	Bead
Acute OSA Impacts Diurnal Alzheimer's Biomarkers Through Nocturnal Hypoxemia and State Transitions	Kam, K	Critical Care and Sleep Medicine, New York, New York	Am J Respir Crit Care Med	Obstructive sleep apnea	Bead
Glymphatic dysfunction correlates with severity of small vessel disease and cognitive impairment in cerebral amyloid angiopathy	Xu, J	Fudan University, Shanghai, China	Eur J Neurol	Cerebral amyloid angiopathy	Bead
Variability in primary Sjögren's syndrome is driven by interferon alpha, and genetically associated with the class II HLA DQ locus	Trutschel, D	Université Paris Cité, F-75015, Paris, France	Arthritis Rheumatol	Sjögren's syndrome	Bead
Association between obstructive sleep apnea and Alzheimer's disease-related blood and cerebrospinal fluid biomarkers: A meta-analysis	Kang, J	The First Hospital of Jilin University, Changchun, Jilin 130021, China	J Clin Neurosci	Obstructive sleep apnea	Bead
Investigating the use of plasma pTau181 in retired contact sports athletes	Vasilevskaya, A	University of Toronto, Toronto, ON	J Neurol	TBI	Bead
Clinical and Blood Biomarker Trajectories after Concussion: New Insights from a Longitudinal Pilot Study of Professional Flat-Track Jockeys	McDonald, S	Monash University, Melbourne, Victoria, Australia	J Neurotrauma	TBI	Bead
A Method to Combine Neurofilament Light Measurements From Blood Serum and Plasma in Clinical and Population-Based Studies	Rübsamen, Nicole	University of Münster, Münster, Germany	Frontiers in Neurology		Bead

Association of Plasma Neurofilament Light Chain With Glycaemic Control and Insulin Resistance in Middle-Aged Adults	Thota, R	Macquarie University, North Ryde, NSW, Australia	Front Endocrinol	type 2 Diabetes	Bead
Linking Plasma Amyloid Beta and Neurofilament Light Chain to Intracortical Myelin Content in Cognitively Normal Older Adults	Fernandez-Alvarez, M	Pablo de Olavide University, Seville, Spain	Front Aging Neurosci	Alzheimer's Disease	Bead
Serum neurofilament light chain levels in Covid-19 patients without major neurological manifestations	Verde, F	IRCCS Istituto Auxologico Italiano, Piazzale Brescia, 20, 20149, Milan, Italy	J Neurol	Covid-19	Bead
Ultrasensitive multiplexed chemiluminescent enzyme-linked immunosorbent assays in 384-well plates	Chen, T	Quanterix Corporation, Billerica, MA	J Immunol Methods		planar
P-tau subgroups in AD relate to distinct amyloid production and synaptic integrity profiles	Wesenhagen, K	Amsterdam UMC location VUmc, Amsterdam, The Netherlands	Alzheimers Res Ther	Alzheimer's disease	Bead
Sarm1 knockout modifies biomarkers of neurodegeneration and spinal cord circuitry but not disease progression in the mSOD1(G93A) mouse model of ALS	Collins, J	University of Tasmania, Hobart, Tas, 7001, Australia	Neurobiol Dis	ALS	Bead
Amyloid-beta misfolding and GFAP predict risk of clinical Alzheimer's disease diagnosis within 17 years	Beyer, L	Ruhr-University Bochum, Bochum, Germany	Alzheimers Dement	Alzheimer's disease	Bead
Hepatic and renal function impact concentrations of plasma biomarkers of neuropathology	Berry, K	University of California, San Francisco, California	Alzheimers Dement	cirrhosis	Bead
Sex differences in plasma p-tau181 associations with Alzheimer's disease biomarkers, cognitive decline, and clinical progression	Tsiknia, A	University of California, San Diego, La Jolla, CA	Mol Psychiatry	Alzheimer's disease	Bead
Titrating the Translational Relevance of a Low-Level Repetitive Head Impact Model	Boucher, M	Boston Children's Hospital, Boston, MA	Front Neurol	TBI	Bead
Comparative analytical performance of multiple plasma Aβ42 and Aβ40 assays and their ability to predict positron emission tomography amyloid positivity	Zicha, S	Takeda, Pharmaceutical Company Ltd., Cambridge, Massachusetts	Alzheimers Dement	Alzheimer's disease	Bead
Biochemical and clinical biomarkers in adult SMA 3-4 patients treated with nusinersen for 22 months	De Wel, B	University Hospitals Leuven, Leuven, Belgium	Ann Clin Transl Neurol	spinal muscular atrophy	Bead
Establishment of reference values for plasma neurofilament light based on healthy individuals aged 5-90 years	Simrén, J	University of Gothenburg, 41345 Gothenburg, Sweden	Brain Commun	healthy reference values	Bead

Detection of Brain Tau Pathology in Down Syndrome Using Plasma Biomarkers	Janelidze, S	Lund University, Lund, Sweden	JAMA Neurol	Alzheimer's disease	Bead
Plasma Neurofilament Light Chain Is Associated with Cognitive Impairment after Posterior Circulation Stroke	Jiang, Lianyan	Chengdu University of Traditional Chinese Medicine, Chengdu, China	Evidence-Based Complementary and Alternative Medicine	Stroke	Bead
Promising Blood Biomarkers for Clinical Use in Alzheimer's Disease: A Focused Update	Park, S	Ajou University School of Medicine, Suwon, Korea	J Clin Neurol	Alzheimer's disease	Bead
Potential association of bone mineral density loss with cognitive impairment and central and peripheral amyloid-β changes: a cross-sectional study	Zhang, P	Xiangyang Central Hospital, Xiangyang, 441021, China	BMC Musculoskelet Disord	Cognitive impairment	Bead
Epitope alteration by small molecules and applications in drug discovery	Zhu, Biyue	Massachusetts General Hospital/Harvard Medical School, Charlestown, Boston, Massachusetts, USA	Chemical Science		Bead
A point-prevalence study on community and inpatient Clostridioides difficile infections (CDI): results from Combatting Bacterial Resistance in Europe CDI (COMBACTE-CDI), July to November 2018	Viprey, V	University of Leeds, Leeds, United Kingdom	Euro Surveill	*C. difficile*	Bead
Phase 3, multicentre, randomised, placebo-controlled study evaluating the efficacy and safety of ustekinumab in patients with systemic lupus erythematosus	van Vollenhoven, R	Amsterdam Rheumatology and Immunology Center, Amsterdam, The Netherlands	Ann Rheum Dis	systemic lupus erythematosus	Bead
Improved prediction of early cognitive impairment in multiple sclerosis combining blood and imaging biomarkers	Brummer, T	University Medical Center of the Johannes Gutenberg University Mainz, Mainz 55131, Germany	Brain Commun	MS	Bead
Association of Plasma and Electroencephalography Markers With Motor Subtypes of Parkinson's Disease	Yang, X	Tianjin Medical University General Hospital, Tianjin, China	Front Aging Neurosci	Parkinson's disease	Bead
Serum glial fibrillary acidic protein (GFAP) predicts outcome after intracerebral and subarachnoid hemorrhage	Gyldenholm, T	Aarhus University Hospital, Aarhus N, Denmark	Neurol Sci	subarachnoid hemorrhage	Bead
Serum assessment of traumatic axonal injury: the correlation of GFAP, t-Tau, UCH-L1, and NfL levels with diffusion tensor imaging metrics and its prognosis utility	Castaño-Leon, A	Universidad Complutense de Madrid	J Neurosurg	TBI	Bead
Lifestyle factors in multiple sclerosis disability progression and silent brain damage: A cross-sectional study	Van Hijfte, Liesbeth	Ghent University Hospital, Ghent 9000, Belgium	Multiple Sclerosis and Related Disorders	MS	Bead

Stool Toxin Concentration Does Not Distinguish Clostridioides difficile Infection from Colonization in Children Less Than 3 Years of Age	Sandora, Thomas	Harvard Medical School, Boston, Massachusetts,	Journal of the Pediatric Infectious Diseases Society	*C. difficile*	Bead
Blood-based Aβ42 increases in the earliest pre-pathological stage before decreasing with progressive amyloid pathology in preclinical models and human subjects: opening new avenues for prevention	Botella Lucena, Pablo	Hasselt University, 3590 Diepenbeek, Belgium	Acta Neuropathologica	Alzheimer's disease	Bead
Inflammatory biomarkers, multi-morbidity, and biologic aging	St. Sauver, Jennifer	Mayo Clinic, Rochester, Minnesota	Journal of International Medical Research	aging	Bead
Abnormal prion protein, infectivity and neurofilament light-chain in blood of macaques with experimental variant Creutzfeldt-Jakob disease	Yakovleva, Oksana	US Food and Drug Administration, Silver Spring, MD	Journal of General Virology	Creutzfeldt-Jakob disease	Bead
Association of plasma neurofilament light chain with disease activity in chronic inflammatory demyelinating polyradiculoneuropathy	Kapoor, Mahima	University College London Queen Square Institute of Neurology, London, UK	European Journal of Neurology	chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Bead
Systematic Review on Saliva Biomarkers in Patients Diagnosed with Morbus Alzheimer and Morbus Parkinson	Wolgin, M	Danube Private University, 3500 Krems an der Donau, Austria	Biomedicines	Alzheimer's disease & Parkinson's disease	Bead
A review on comparative studies addressing exosome isolation methods from body fluids	Martins, Tânia	University of Aveiro, 3810-193 Aveiro, Portugal	Analytical and Bioanalytical Chemistry	exosomes	Bead
FutureMS cohort profile: a Scottish multicentre inception cohort study of relapsing-remitting multiple sclerosis	Kearns, P	The University of Edinburgh Centre for Clinical Brain Sciences, Edinburgh, UK	BMJ Open	MS	Bead
Plasma biomarkers for prognosis of cognitive decline in patients with mild cognitive impairment	Kivisäkk, P	Massachusetts General Hospital, Boston, MA	Brain Commun	Alzheimer's disease	Bead
Phenotypic Heterogeneity of Fulminant COVID-19--Related Myocarditis in Adults	Barhoum, P	Sorbonne Université, Paris, France	J Am Coll Cardiol	Covid-19 & multisystem inflammatory syndrome	Bead & planar
The relationship between plasma biomarkers and amyloid PET in dementia with Lewy bodies	Donaghy, P	Newcastle University, UK	Parkinsonism Relat Disord	Dementia with Lewy bodies	Bead
Reactive astrogliosis is associated with higher cerebral glucose consumption in the early Alzheimer's continuum	Salvadó, G	Pasqual Maragall Foundation, C/ Wellington, 30, 08005, Barcelona, Spain	Eur J Nucl Med Mol Imaging	Alzheimer's disease	Bead

A randomized controlled pilot trial of anakinra for hemodialysis inflammation	Dember, L	University of Pennsylvania, Philadelphia, PA	Kidney Int	hemodialysis patients	Bead
Findings of (18) F-PI-2620 tau PET imaging in patients with Alzheimer's disease and healthy controls in relation to the plasma P-tau181 levels in a Japanese sample	Bun, S	Keio University School of Medicine, Tokyo, Japan	Neuropsychopharmacol Rep	Alzheimer's disease	Bead
The TAS Test project: a prospective longitudinal validation of new online motor-cognitive tests to detect preclinical Alzheimer's disease and estimate 5-year risks of cognitive decline and dementia	Alty, J	University of Tasmania, Hobart, Australia	BMC Neurol	Alzheimer's disease	Bead
Minocycline treatment in clinically isolated syndrome and serum NfL, GFAP, and metalloproteinase levels	Camara-Lemarroy, C	University of Calgary, Calgary, AB	Mult Scler	Multiple sclerosis & Clinically Isolated Syndrome	Bead
Plasma Aβ42/40 ratio, p-tau181, GFAP, and NfL across the Alzheimer's disease continuum: A cross-sectional and longitudinal study in the AIBL cohort	Chatterjee, Pratishtha	Macquarie University, North Ryde, New SouthWales, Australia	Alzheimer's & Dementia	Alzheimer's disease	Bead
Evaluation of in vivo staging of amyloid deposition in cognitively unimpaired elderly aged 78-94	Michalowska, M	University of Manchester, Manchester, UK	Mol Psychiatry	cognitively unimpaired	Bead
Biomarkers of Neurodegenerative Diseases: Biology, Taxonomy, Clinical Relevance, and Current Research Status	Koníčková, D	Palacky University and University Hospital Olomouc, 77900 Olomouc, Czech Republic	Biomedicines	neurodegenerative diseases	Bead
No increase of serum neurofilament light in relapsing-remitting multiple sclerosis patients switching from standard to extended-interval dosing of natalizumab	Johnsson, Magnus	University of Gothenburg, Gothenburg, Sweden	Multiple Sclerosis Journal	MS	Bead
Dendrimer nanotherapy for severe COVID-19 attenuates inflammation and neurological injury markers and improves outcomes in a phase2a clinical trial	Gusdon, A	McGovern Medical School, Memorial Hermann Hospital, Houston, TX	Sci Transl Med	COVID-19	Bead
Neurofilament light increases over time in severe COVID-19 and is associated with delirium	Smeele, Patrick	Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands	Brain Communications	COVID-19	Bead
Association of Cerebrospinal Fluid Neurofilament Heavy Protein Levels With Clinical Progression in Patients With Parkinson Disease	Wang, L	Fudan University, Shanghai, China	JAMA Netw Open	Parkinson’s Disease	Bead

Portable Vertical Graphene@Au-Based Electrochemical Aptasensing Platform for Point-of-Care Testing of Tau Protein in the Blood	Liu, Y	Longgang District Central Hospital of Shenzhen, Shenzhen 518116, China	Biosensors	Alzheimer's disease	Bead
Serum neurofilament light reflects cognitive dysfunctions in children with obstructive sleep apnea	Shi, Y	The Second Affiliated Hospital of Xi'an Jiaotong University, Shaanxi, People's Republic of China	BMC Pediatr	obstructive sleep apnea	Bead
Functional validation of novel variants in B4GALNT1 associated with early-onset complex hereditary spastic paraplegia with impaired ganglioside synthesis	Alecu, J	Harvard Medical School, Boston, Massachusetts	Am J Med Genet A	hereditary spastic paraplegia	Bead
Pathophysiology of neurodegenerative diseases: An interplay among axonal transport failure, oxidative stress, and inflammation?	Tesco, G	Tufts University School of Medicine, Boston, MA	Semin Immunol		Bead
Extracellular vesicle biomarkers for cognitive impairment in Parkinson's disease	Blommer, J	National Institute on Aging, Baltimore, MD	Brain	Parkinson's disease	Bead
Alzheimer's disease: a scoping review of biomarker research and development for effective disease diagnosis	Faldu, K	Nirma University, Ahmedabad, India	Expert Rev Mol Diagn	Alzheimer's disease	Bead
Association of Plasma Biomarkers of Amyloid and Neurodegeneration with Cerebrovascular Disease and Alzheimer's Disease	Graff-Radford, Jonathan	Mayo Clinic, Rochester, MN	Neurobiology of Aging	Alzheimer's disease	Bead
Imaging of White Matter Injury Correlates with Plasma and Tissue Biomarkers in Pediatric Porcine Model of Traumatic Brain Injury	Shin, S	University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania	J Neurotrauma	TBI	Bead
Lower White Matter Volume and Worse Executive Functioning Reflected in Higher Levels of Plasma GFAP among Older Adults with and Without Cognitive Impairment	Asken, B	University of California, San Francisco, CA	J Int Neuropsychol Soc	cognitive unimpairment	Bead

(Please click on the title (it is a hyperlink) for further details and information on the publication.

Title: Serum neurofilament as a predictor of 10-year grey matter atrophy and clinical disability in multiple sclerosis: a longitudinal study
Journal: J Neurol Neurosurg Psychiatry
Year: 2022
Epub Date: 20220601

Author: Lie, I. A., Kaçar, S., Wesnes, K., Brouwer, I., Kvistad, S. S., Wergeland, S., Holmøy, T., Midgard, R., Bru, A., Edland, A., Eikeland, R., Gosal, S., Harbo, H. F., Kleveland, G., Sørenes, Y. S., Øksendal, N., Varhaug, K. N., Vedeler, C. A., Barkhof, F., Teunissen, C. E., Bø, L., Torkildsen, Ø, Myhr, K. M. and Vrenken, H.

Keywords: Research article
Neurology
Multiple sclerosis
Simoa Bead
serum NfL
kit

Abstract: BACKGROUND: The predictive value of serum neurofilament light chain (sNfL) on long-term prognosis in multiple sclerosis (MS) is still unclear. OBJECTIVE: Investigate the relation between sNfL levels over a 2-year period in patients with relapsing-remitting MS, and clinical disability and grey matter (GM) atrophy after 10 years. METHODS: 85 patients, originally enrolled in a multicentre, randomised trial of ω-3 fatty acids, participated in a 10-year follow-up visit. sNfL levels were measured by Simoa quarterly until month 12, and then at month 24. The appearance of new gadolinium-enhancing (Gd+) lesions was assessed monthly between baseline and month 9, and then at months 12 and 24. At the 10-year follow-up visit, brain atrophy measures were obtained using FreeSurfer. RESULTS: Higher mean sNfL levels during early periods of active inflammation (Gd+ lesions present or recently present) predicted lower total (β=-0.399, p=0.040) and deep (β=-0.556, p=0.010) GM volume, lower mean cortical thickness (β=-0.581, p=0.010) and higher T2 lesion count (β=0.498, p=0.018). Of the clinical outcomes, higher inflammatory sNfL levels were associated with higher disability measured by the dominant hand Nine-Hole Peg Test (β=0.593, p=0.004). Mean sNfL levels during periods of remission (no Gd+ lesions present or recently present) did not predict GM atrophy or disability progression. CONCLUSION: Higher sNfL levels during periods of active inflammation predicted more GM atrophy and specific aspects of clinical disability 10 years later. The findings suggest that subsequent long-term GM atrophy is mainly due to neuroaxonal degradation within new lesions.

Title: Quantification of SNAP-25 with mass spectrometry and Simoa: a method comparison in Alzheimer's disease
Journal: Alzheimers Res Ther
Year: 2022
Epub Date: 20220604

Author: Nilsson, J., Ashton, N. J., Benedet, A. L., Montoliu-Gaya, L., Gobom, J., Pascoal, T. A., Chamoun, M., Portelius, E., Jeromin, A., Mendes, M., Zetterberg, H., Rosa-Neto, P., Brinkmalm, A. and Blennow, K.

Keywords: Research article
Neurology
Alzheimer's disease
Simoa Bead
CSF, plasma SNAP-25
HD-X

Abstract: BACKGROUND: Synaptic dysfunction and degeneration are central to Alzheimer's disease (AD) and have been found to correlate strongly with cognitive decline. Thus, studying cerebrospinal fluid (CSF) biomarkers reflecting synaptic degeneration, such as the presynaptic protein synaptosomal-associated protein 25 (SNAP-25), is of importance to better understand the AD pathophysiology. METHODS: We compared a newly developed Single molecule array (Simoa) immunoassay for SNAP-25 with an in-house immunoprecipitation mass spectrometry (IP-MS) method in a well-characterized clinical cohort (n = 70) consisting of cognitively unimpaired (CU) and cognitively impaired (CI) individuals with and without Aβ pathology (Aβ+ and Aβ-). RESULTS: A strong correlation (Spearman's rank correlation coefficient (r(s)) > 0.88; $p < 0.0001$) was found between the Simoa and IP-MS methods, and no statistically significant difference was found for their clinical performance to identify AD pathophysiology in the form of Aβ pathology. Increased CSF SNAP-25 levels in CI Aβ+ compared with CU Aβ- (Simoa, $p \leq 0.01$; IP-MS, $p \leq 0.05$) and CI Aβ- (Simoa, $p \leq 0.01$; IP-MS, $p \leq 0.05$) were observed. In independent blood samples (n = 32), the Simoa SNAP-25 assay was found to lack analytical sensitivity for quantification of SNAP-25 in plasma. CONCLUSIONS: These results indicate that the Simoa SNAP-25 method can be used interchangeably with the IP-MS method for the quantification of SNAP-25 in CSF. Additionally, these results confirm that CSF SNAP-25 is increased in relation to amyloid pathology in the AD continuum.

Title: Modulation of the Thrombin Pathway Restores LTP in a Pilocarpine Mice Model of Status Epilepticus
Journal: Front Cell Neurosci
Year: 2022
Epub Date: 20220524

Author: Shavit-Stein, E., Berkowitz, S., Davidy, T., Fennig, U., Gofrit, S. G., Dori, A. and Maggio, N.

Keywords: Research article
Neurology
status epilepticus
Simoa Bead
mouse plasma TNFa
mouse plasma NfL
kit
SR-X

Abstract: BACKGROUND: Status epilepticus (SE) leads to memory impairment following a seizure, attributed to long-term potentiation (LTP) reduction. Thrombin, a coagulation factor that activates protease-activated receptor 1 (PAR1) is involved in cognitive impairment following traumatic brain

injury by reducing hippocampal LTP and in seizures as seen in a SE pilocarpine-induced mice model. Thrombin pathway inhibition prevents this cognitive impairment. We evaluated the effect of thrombin pathway inhibition in the pilocarpine-induced SE mice model, on LTP, hippocampal, and serum markers for inflammation, the PAR1 pathway, and neuronal cell damage. METHODS: SE was induced by injecting C57BL/6J mice with pilocarpine. Before pilocarpine injection, mice were injected with either the specific thrombin inhibitor α-NAPAP [Nα-(2-naphthalene-sulfonylglycyl)-4-amidino-DL-phenylalaninepiperidide], the PAR1 antagonist SCH79797, or vehicle-only solution. Recordings of excitatory postsynaptic potentials (EPSP) were conducted from hippocampal slices 24 h following pilocarpine injection. Hippocampal real-time PCR for the quantification of the PAR1, prothrombin, and tumor necrosis factor α (TNF-α) mRNA expression levels was conducted. Serum levels of neurofilament light chain (NfL) and TNF-α were measured by a single molecule array assay. RESULTS: The EPSP was reduced in the pilocarpine-induced SE mice ($p < 0.001$). This reduction was prevented by both NAPAP and SCH79797 treatments ($p < 0.001$ for both treatments). Hippocampal expression of TNF-α was elevated in the pilocarpine-induced SE group compared to the control ($p < 0.01$), however, serum levels of TNF-α were not changed. NfL levels were elevated in the pilocarpine-induced SE group ($p = 0.04$) but not in the treated groups. CONCLUSIONS: Pilocarpine-induced SE reduces LTP, in a thrombin PAR1-related mechanism. Elevation of serum NfL supports neuronal damage accompanying this functional abnormality which may be prevented by PAR1 pathway modulation.

Title: A combination model of AD biomarkers revealed by machine learning precisely predicts Alzheimer's dementia: China Aging and Neurodegenerative Initiative (CANDI) study
Journal: Alzheimers Dement
Year: 2022
Epub Date: 20220606

Author: Gao, F., Lv, X., Dai, L., Wang, Q., Wang, P., Cheng, Z., Xie, Q., Ni, M., Wu, Y., Chai, X., Wang, W., Li, H., Yu, F., Cao, Y., Tang, F., Pan, B., Wang, G., Deng, K., Wang, S., Tang, Q., Shi, J. and Shen, Y.

Keywords: Research article
Neurology
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CSF, plasma N3PA, pTau181
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China

Abstract: INTRODUCTION: To test the utility of the "A/T/N" system in the Chinese population, we study core Alzheimer's disease (AD) biomarkers in a newly established Chinese cohort. METHODS: A total of 411 participants were selected, including 96 cognitively normal individuals, 94 patients with mild cognitive impairment (MCI) patients, 173 patients with AD, and 48 patients with non-AD dementia. Fluid biomarkers were measured with single molecule array. Amyloid beta (Aβ) deposition was determined by (18) F-Flobetapir positron emission tomography (PET), and brain atrophy was quantified using magnetic resonance imaging (MRI). RESULTS: Aβ42/Aβ40 was decreased, whereas levels of phosphorylated tau (p-tau) were increased in cerebrospinal fluid (CSF) and plasma from patients with AD. CSF Aβ42/Aβ40, CSF p-tau, and plasma p-tau showed a high concordance in discriminating between

AD and non-AD dementia or elderly controls. A combination of plasma p-tau, apolipoprotein E (APOE) genotype, and MRI measures accurately predicted amyloid PET status. DISCUSSION: These results revealed a universal applicability of the "A/T/N" framework in a Chinese population and established an optimal diagnostic model consisting of cost-effective and non-invasive approaches for diagnosing AD.

Title: Serum neurofilament light chain concentration predicts disease worsening in multiple sclerosis
Journal: Mult Scler
Year: 2022
Epub Date: 20220604

Author: Brune, S., Høgestøl, E. A., de Rodez Benavent, S. A., Berg-Hansen, P., Beyer, M. K., Leikfoss, I. S., Bos, S. D., Sowa, P., Brunborg, C., Andorra, M., Pulido Valdeolivas, I., Asseyer, S., Brandt, A., Chien, C., Scheel, M., Blennow, K., Zetterberg, H., Kerlero de Rosbo, N., Paul, F., Uccelli, A., Villoslada, P., Berge, T. and Harbo, H. F.

Keywords: Research article
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serum NfL
kit

Abstract: BACKGROUND: Serum neurofilament light (sNfL) chain is a promising biomarker reflecting neuro-axonal injury in multiple sclerosis (MS). However, the ability of sNfL to predict outcomes in real-world MS cohorts requires further validation. OBJECTIVE: The aim of the study is to investigate the associations of sNfL concentration, magnetic resonance imaging (MRI) and retinal optical coherence tomography (OCT) markers with disease worsening in a longitudinal European multicentre MS cohort. METHODS: MS patients (n = 309) were prospectively enrolled at four centres and re-examined after 2 years (n = 226). NfL concentration was measured by single molecule array assay in serum. The patients' phenotypes were thoroughly characterized with clinical examination, retinal OCT and MRI brain scans. The primary outcome was disease worsening at median 2-year follow-up. RESULTS: Patients with high sNfL concentrations (⩾8 pg/mL) at baseline had increased risk of disease worsening at median 2-year follow-up (odds ratio (95% confidence interval) = 2.8 (1.5-5.3), p = 0.001). We found no significant associations of MRI or OCT measures at baseline with risk of disease worsening. CONCLUSION: Serum NfL concentration was the only factor associated with disease worsening, indicating that sNfL is a useful biomarker in MS that might be relevant in a clinical setting.

Title: Validation of Plasma and CSF Neurofilament Light Chain as an Early Marker for Sporadic Creutzfeldt-Jakob Disease
Journal: Mol Neurobiol
Year: 2022
Epub Date: 20220618

Author: Schmitz, M., Canaslan, S., Espinosa, J. C., Fernández-Borges, N., Villar-Piqué, A., Llorens, F., Varges, D., Maass, F., Torres, J. M., Hermann, P. and Zerr, I.

Keywords: Research article
Neurology
Sporadic Creutzfeldt-Jakob disease
Simoa Bead
CSF NfL
plasma NfL

Abstract: Biomarkers are becoming increasingly important for the differential diagnosis of neurodegenerative diseases. Previous observations indicated neurofilament light chain (NfL) as a potential blood-based biomarker for sporadic Creutzfeldt-Jakob disease (sCJD). Here, we investigated the stability, inter-assay/intra-assay variation and the regulation of NfL levels in CSF and plasma in a large cohort of sCJD patients by using a single-molecule array (SIMOA). We defined cutoffs for an accurate diagnosis and measured plasma NfL level in prion-infected mice models at different time points to identify the potential dynamics throughout the disease. Our analyses confirmed CSF and plasma NfL as stable and consistent marker for sCJD. Receiver operating characteristic (ROC) curve analysis showed an AUC of 0.92-0.93 to distinguish sCJD from control groups. Newly defined cutoffs revealed good diagnostic accuracies of CSF and plasma NfL, indicated by a sensitivity of 80-83.5% and a specificity of 87.4-91%. Studies on two humanized prion-infected mice lines (Tg340-PRNP 129MM and Tg361-PRNP 129VV) revealed increased plasma NfL levels in a late pre-clinical or very early clinical stage between 120-150 days post-inoculation. In conclusion, our work supports the potential use of CSF and plasma NfL as a very early biomarker in sCJD diagnostic with good diagnostic accuracies.

Title: Neurofilament light chain: a new marker for neuronal decay in the anterior chamber fluid of patients with glaucoma
Journal: Br J Ophthalmol
Year: 2022
Epub Date: 20220624

Author: Woltsche, N., Valentin, K., Hoeflechner, L., Guttmann, A., Horwath-Winter, J., Schneider, M. R., Ivastinovic, D., Lindner, M., Schmetterer, L., Singh, N., Riedl, R., Buchmann, A., Khalil, M. and Lindner, E.

Keywords: Research article
Neurology
Glaucoma
Simoa Bead
serum NfL
anterior chamber fluid NfL
SR-X

Abstract: BACKGROUND/AIMS: Neurofilament light chain (NfL) levels in cerebrospinal fluid and serum are reliable indicators for neuroaxonal damage in a broad spectrum of neurodegenerative diseases. Herein, we investigate NfL levels in serum and anterior chamber fluid of patients with glaucoma. METHODS: Patients scheduled for routine glaucoma or cataract surgery were recruited for this study. Retinal nerve fibre layer thickness was measured by optical coherence tomography (OCT, Heidelberg Spectralis). NfL levels in serum and in anterior chamber fluid were analysed with Simoa SR-X Analyzer (Quanterix; NFLIGHT, Lexington, Massachusetts, USA). T-test was used for parametric data and

Mann-Whitney-U test for nonparametric data. Spearman's rank-order correlation was used to investigate correlations. P values<0.05 were considered as statistically significant. RESULTS: Sixty patients with glaucoma and 58 controls were enrolled. Serum NfL concentration of patients with glaucoma was similar to serum NfL concentration in controls (median (IQR); 22.7 (18.9) pg/mL vs 22.5 (24.0) pg/mL; p=0.763). A positive correlation of serum NfL with age was observed in both patients with glaucoma (r=0.77; p<0.001) and in the control group (r=0.82, p<0.001). In the anterior chamber fluid, the NfL concentration was substantially increased in patients with glaucoma compared with controls (20.7 (101.3) pg/mL vs 3.1 (2.9) pg/mL; p<0.001). Furthermore, we found a positive correlation of anterior chamber fluid NfL with preoperative intraocular pressure (r=0.39, p=0.003) and with retinal nerve fibre layer thickness (r=0.58, p<0.001). CONCLUSION: NfL levels in anterior chamber fluid are elevated in patients with glaucoma and correlate with intraocular pressure and retinal nerve fibre layer thickness. The presented data strongly support anterior chamber fluid NfL as a new marker for glaucoma.

Title: Repeated neurofilament light chain measurements did not capture Riluzole therapeutic effect in amyotrophic lateral sclerosis patients
Journal: CNS Neurosci Ther
Year: 2022
Epub Date: 20220625

Author: Esselin, F., De la Cruz, E., Hirtz, C., Tiers, L., Alphandery, S., Baudesson, L., Taieb, G., Camu, W. and Lehmann, S.

Keywords: Research article
Neurology
ALS
Simoa Bead
serum NfL
kit

Abstract: BACKGROUND: Little is known about the influence of Riluzole on serum neurofilament light chain (sNfL) levels, a biomarker of prognosis in amyotrophic lateral sclerosis (ALS), and variations with time of sNfL concentrations are controversial. METHODS: Sera from ALS patients (n = 141) and controls (n = 33) were collected at inclusion (sNfL1) and second visit (sNfL2, mean delay 10.4 ± 8.7 months). sNfL levels, determined by single-molecule array, were compared between ALS and controls at both time points. sNfL concentration changes were compared between patients with Riluzole (w/Ril) at inclusion in the study and those who were treated by Riluzole following inclusion (w/o Ril). The factors influencing sNfL concentrations and changes were studied using linear regression and multivariate analysis. RESULTS: sNfL levels were higher in ALS patients than in controls at the two time points (p < 0.00001). In ALS patients, sNfL concentrations were higher in females for both sNfL1 (p = 0.014) and sNfL2 (p < 0.001). In the whole ALS group, sNfL levels were higher at sNfL2 than at sNfL1 (p < 0.001). sNfL1 and sNfL2 concentrations were similar between the two ALS subgroups (w/ and w/o Ril). ALS functional rating scale-revised rate of decline and gender were the two main factors significantly influencing both sNfL1 and sNfL2 levels (p < 0.01). However, only gender was shown to significantly influence sNfL changes with time (p = 0.003). CONCLUSIONS: In this study, sNfL levels increased with time in ALS patients and there was no difference between subjects already treated by Riluzole and those treated after sNfL1. Further studies with larger population samples and different sampling intervals are warranted to better

determine the real potential of sNfL measurement as a tool to monitor treatment response in ALS.

Title: Detecting ongoing disease activity in mildly affected multiple sclerosis patients under first-line therapies
Journal: Multiple Sclerosis and Related Disorders
Year: 2022
Date: 2022/07/01/

Author: Masanneck, Lars, Rolfes, Leoni, Regner-Nelke, Liesa, Willison, Alice, Räuber, Saskia, Steffen, Falk, Bittner, Stefan, Zipp, Frauke, Albrecht, Philipp, Ruck, Tobias, Hartung, Hans-Peter, Meuth, Sven G. and Pawlitzki, Marc

Keywords: Research article
neurology
multiple sclerosis
Simoa Bead
serum NfL
kit

Abstract: Background The current range of disease-modifying treatments (DMTs) for relapsing-remitting multiple sclerosis (RRMS) has placed more importance on the accurate monitoring of disease progression for timely and appropriate treatment decisions. With a rising number of measurements for disease progression, it is currently unclear how well these measurements or combinations of them can monitor more mildly affected RRMS patients. Objectives To investigate several composite measures for monitoring disease activity and their potential relation to the biomarker neurofilament light chain (NfL) in a clearly defined early RRMS patient cohort with a milder disease course. Methods From a total of 301 RRMS patients, a subset of 46 patients being treated with a continuous first-line therapy was analyzed for loss of no evidence of disease activity (lo-NEDA-3) status, relapse-associated worsening (RAW) and progression independent of relapse activity (PIRA), up to seven years after treatment initialization. Kaplan-Meier estimates were used for time-to-event analysis. Additionally, a Cox regression model was used to analyze the effect of NfL levels on outcome measures in this cohort. Results In this mildly affected cohort, both lo-NEDA-3 and PIRA frequently occurred over a median observational period of 67.2 months and were observed in 39 (84.8%) and 23 (50.0%) patients, respectively. Additionally, 12 out of 26 PIRA manifestations (46.2%) were observed without a corresponding lo-NEDA-3 status. Jointly, either PIRA or lo-NEDA-3 showed disease activity in all patients followed-up for at least the median duration (67.2 months). NfL values demonstrated an association with the occurrence of relapses and RAW. Conclusion The complementary use of different disease progression measures helps mirror ongoing disease activity in mildly affected early RRMS patients being treated with continuous first-line therapy.

Title: High Fat High Sucrose Diet Modifies Uterine Contractility and Cervical Resistance in Pregnant Rats: The Roles of Sex Hormones, Adipokines and Cytokines
Journal: Life
Year: 2022

Author: Gáspár, Róbert, Hajagos-Tóth, Judit, Schaffer, Annamária, Kothencz, Anna, Siska-Szabó, Lilla,

Ducza, Eszter, Csányi, Adrienn, Tábi, Tamás, Bagaméry, Fruzsina, Szökő, Éva, Kovács, Orsolya, Barna, Tamara, Samavati, Reza, Mirdamadi, Mohsen, Sztojkov-Ivanov, Anita, Szűcs, Kálmán Ferenc and Vari, Sandor G.

Keywords: Research article
Inflammation
cervical resistance
planar
plasma Rat Cytokine Panel 1 (IFNg), IL-1b, IL-2, IL-6, IL-10, keratinocytes-derived chemokine (KC), TNFa
SP-X

Abstract: Background: In obesity, the adipose tissue becomes a very significant endocrine organ producing different factors called adipokines, such as leptin, adiponectin and kisspeptin; however, no data are available about their actions on uterine contraction in obese pregnant rats. Our aim was to study the impact of obesity on pregnant uterine contraction in a rat model. Methods: Obesity was induced by the consumption of a high fat high sucrose diet (HFHSD) for 9 weeks, including pregnancy. Glucose tolerance, sex hormone, cytokine and adipokine levels were measured. Uterine contractions and cervical resistance, as well as their responses to adipokines, were tested along with the expressions of their uterine receptors. Results: HFHSD increased body weight and altered glucose tolerance and fat composition. The uterine leptin and kisspeptin pathway affect increased. The levels of proinflammatory cytokines were reduced, while the plasma level of progesterone was increased, resulting in weaker uterine contractions, and improving the uterine relaxing effects of adipokines. HFHSD reduced cervical resistance, but the core effect of adipokines is difficult to determine. Conclusions: Obesity in pregnant rats reduces uterine contractility and cytokine induced inflammatory processes, and therefore obese pregnant rat methods are partially applicable for modelling human processes.

Title: Neurofilament light chain and total tau in the differential diagnosis and prognostic evaluation of acute and chronic inflammatory polyneuropathies
Journal: European Journal of Neurology
Year: 2022

Author: Kmezic, Ivan, Samuelsson, Kristin, Finn, Anja, Upate, Zane, Blennow, Kaj, Zetterberg, Henrik and Press, Rayomand

Keywords: Research article
Neurology
inflammatory polyneuropathies
Simoa Bead
plasma NfL, tau
kit
HD-X

Abstract: Background and Purpose: To investigate the diagnostic and prognostic value of axonal injury biomarkers in patients with inflammatory polyneuropathies. Methods: Neurofilament light chain (NfL) and total tau (T-tau) were measured in the cerebrospinal fluid (CSF) and plasma in 41 patients with Guillain–Barré syndrome (GBS), 32 patients with chronic inflammatory demyelinating polyneuropathy (CIDP), 10 with paraproteinemia-related demyelinating polyneuropathy (PDN), and 8 with multifocal

motor neuropathy (MMN), in comparison with 39 disease-free controls and 59 other controls. Outcome was measured with the GBS-disability score (GBS-ds) or Inflammatory Neuropathy Cause and Treatment (INCAT) disability score. Results: Neurofilament light chain levels in CSF and plasma were higher in GBS, CIDP, and PDN vs. disease-free controls. Patients with MMN had higher NfL levels in plasma vs. disease-free controls, but lower levels in CSF and plasma vs. patients with amyotrophic lateral sclerosis (ALS). T-tau levels in plasma were higher in GBS, CIDP, PDN, and MMN vs. all control groups. Neurofilament light chain levels in CSF and plasma in patients with GBS correlated with GBS-ds, as higher levels were associated with inability to run after 6 and 12 months. NfL levels in CSF and plasma in CIDP did not correlate significantly with outcome. Conclusions: Acute and chronic inflammatory neuropathies are associated with an increase in levels of NfL in CSF and plasma, but NfL is validated as a prognostic biomarker only in GBS. NfL could be used in differentiating patients with MMN from ALS. T-tau in plasma is a novel biomarker that could be used in a diagnostic assessment of patients with acute and chronic inflammatory polyneuropathies.

Title: Recent Advances in Frontotemporal Dementia
Journal: Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques
Year: 2022
Epub Date: 2022/05/30

Author: Tartaglia, Maria Carmela and Mackenzie, Ian R. A.

Keywords: Review
neurology
Frontotemporal dementia
Simoa Bead

Abstract: Frontotemporal dementia (FTD) is a devastating neurodegenerative condition for which there is currently no effective treatment. Although it is much less common than Alzheimer's disease, the impact of FTD is increased by its relatively early onset and high heritability. Clinical heterogeneity and overlap with other neurodegenerative and psychiatric syndromes complicate diagnosis. However, recent advances in our understanding of the molecular basis of FTD provide a foundation for the development of much-needed biomarkers and targeted therapies. This review provides a summary of the recently revised clinical criteria for FTD, highlights diagnostic challenges, briefly summarizes recent molecular discoveries and then focuses on promising developments in biomarkers and clinical trials.

Title: The utility of SARS-CoV-2 nucleocapsid protein in laboratory diagnosis
Journal: J Clin Lab Anal
Year: 2022
Epub Date: 20220603

Author: Li, X., Xiong, M., Deng, Q., Guo, X. and Li, Y.

Keywords: Review
Infectious disease
Covid-19
Simoa Bead

China

Abstract: BACKGROUND: The Coronavirus Disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has now become a global pandemic owing to its high transmissibility. The SARS-CoV-2 nucleocapsid protein tests are playing an important role in screening and diagnosing patients with COVID-19, and studies about the utility of SARS-CoV-2 nucleocapsid protein tests are increasing now. METHODS: In this review, all the relevant original studies were assessed by searching in electronic databases including Scopus, Pubmed, Embase, and Web of Science. "SARS-CoV-2", "COVID-19", "nucleocapsid protein", and "antigen detection" were used as keywords. RESULTS: In this review, we summarized the utility of SARS-CoV-2 nucleocapsid protein in laboratory diagnosis. Among the representative researches, this review analyzed, the sensitivity of SARS-CoV-2 nucleocapsid protein detection varies from 13% to 87.9%, while the specificity could almost reach 100% in most studies. As a matter of fact, the sensitivity is around 50% and could be higher or lower due to the influential factors. CONCLUSION: It is well suggested that SARS-CoV-2 nucleocapsid protein is a convenient method with a short turnaround time of about half an hour, and the presence of N antigen is positively related to viral transmissibility, indicating that SARS-CoV-2 N protein immunoassays contribute to finding out those infected people rapidly and segregating them from the uninfected people.

Title: Factors associated with mortality in early stages of parkinsonism
Journal: npj Parkinson's Disease
Year: 2022
Date: 2022/06/02

Author: van Rumund, Anouke, Esselink, Rianne A. J., Berrevoets-Aerts, Marjolein B., Otto, Markus, Bloem, Bastiaan R. and Verbeek, Marcel M.

Keywords: Research article
Neurology
Parkinson's Disease
Simoa Bead
serum NfL

Abstract: Prognosis of patients with parkinsonism varies greatly between the various parkinsonian syndromes. However, it is often difficult to distinguish the different forms, particularly in early stages. We examined predictors of mortality and functional outcome in patients with recent-onset parkinsonism with an initially uncertain diagnosis (n = 156). Patients were recruited between 2003 and 2006, comprehensively investigated, and followed prospectively (up to 15 years, mean 7 years). A final clinical diagnosis was established after follow-up. Independent predictors of mortality were investigated with multivariable Cox regression and combined into a simple prediction model. Model performance to predict 5- and 10-year mortality and functional outcome after 3 years was evaluated and externally validated in a second cohort of 62 patients with parkinsonism with an initially uncertain diagnosis. Ninety-one patients died (58%). Orthostatic hypotension, impaired cognition, abnormal tandem gait, and elevated neurofilament light chain concentration in serum or CSF were associated with mortality. A simple model that combined these factors showed excellent performance for prediction of functional outcome after 3 years and mortality after 5 and 10 years (c-statistic ~0.90 for all models). Model performance was confirmed after external validation: prediction of functional outcome after 3 years

(c-statistic 0.89, 95% CI 0.80–0.98) and mortality after 5 years (c-statistic 0.91, 95% CI 0.84–0.99) were comparable to the results in the discovery cohort. These findings help clinicians to estimate a patient's prognosis, irrespective of the specific diagnosis.

Title: Increased Neurofilament Light Chain Is Associated with Increased Risk of Long-Term Mortality in Cerebral Small Vessel Disease
Journal: J Stroke
Year: 2022
Epub Date: 20220531

Author: Jacob, M. A., Peters, N., Cai, M., Duering, M., Engelter, S. T., Kuhle, J., de Leeuw, F. E. and Tuladhar, A. M.

Keywords: Research article
Neurology
stroke
Simoa Bead
serum NfL

Title: Sex influences clinical phenotype in frontotemporal dementia
Journal: Neurological Sciences
Year: 2022
Date: 2022/06/08

Author: Pengo, Marta, Alberici, Antonella, Libri, Ilenia, Benussi, Alberto, Gadola, Yasmine, Ashton, Nicholas J., Zetterberg, Henrik, Blennow, Kaj and Borroni, Barbara

Keywords: Research article
Neurology
FTD
Simoa Bead
serum NfL
kit
HD-X

Abstract: Introduction: Frontotemporal dementia (FTD) encompasses a wide spectrum of genetic, clinical, and histological findings. Sex is emerging as a potential biological variable influencing FTD heterogeneity; however, only a few studies explored this issue with nonconclusive results. Objective To estimate the role of sex in a single-center large cohort of FTD patients. Methods: Five hundred thirty-one FTD patients were consecutively enrolled. Demographic, clinical, and neuropsychological features, survival rate, and serum neurofilament light (NfL) concentration were determined and compared between sex. Results: The behavioral variant of FTD was more common in men, whereas primary progressive aphasia was overrepresented in women ($p < 0.001$). While global cognitive impairment was comparable, females had a more severe cognitive impairment, namely in Trail Making Test parts A and B ($p = 0.003$), semantic fluency ($p = 0.03$), Short Story Recall Test ($p = 0.003$), and the

copy of Rey Complex Figure ($p = 0.005$). On the other hand, men exhibited more personality/behavioral symptoms (Frontal Behavior Inventory [FBI] AB, $p = 0.003$), displaying higher scores in positive FBI subscales (FBI B, $p < 0.001$). In particular, apathy ($p = 0.02$), irritability ($p = 0.006$), poor judgment ($p = 0.033$), aggressivity ($p = 0.008$), and hypersexuality ($p = 0.006$) were more common in men, after correction for disease severity. NfL concentration and survival were not statistically different between men and women ($p = 0.167$ and $p = 0.645$, respectively). Discussion: The present study demonstrated that sex is a potential factor in determining FTD phenotype, while it does not influence survival. Although the pathophysiological contribution of sex in neurodegeneration is not well characterized yet, our findings highlight its role as deserving biological variable in FTD.

Title: Novel App knock-in mouse model shows key features of amyloid pathology and reveals profound metabolic dysregulation of microglia
Journal: Molecular Neurodegeneration
Year: 2022
Date: 2022/06/11

Author: Xia, Dan, Lianoglou, Steve, Sandmann, Thomas, Calvert, Meredith, Suh, Jung H., Thomsen, Elliot, Dugas, Jason, Pizzo, Michelle E., DeVos, Sarah L., Earr, Timothy K., Lin, Chia-Ching, Davis, Sonnet, Ha, Connie, Leung, Amy Wing-Sze, Nguyen, Hoang, Chau, Roni, Yulyaningsih, Ernie, Lopez, Isabel, Solanoy, Hilda, Masoud, Shababa T., Liang, Chun-chi, Lin, Karin, Astarita, Giuseppe, Khoury, Nathalie, Zuchero, Joy Yu, Thorne, Robert G., Shen, Kevin, Miller, Stephanie, Palop, Jorge J., Garceau, Dylan, Sasner, Michael, Whitesell, Jennifer D., Harris, Julie A., Hummel, Selina, Gnörich, Johannes, Wind, Karin, Kunze, Lea, Zatcepin, Artem, Brendel, Matthias, Willem, Michael, Haass, Christian, Barnett, Daniel, Zimmer, Till S., Orr, Anna G., Scearce-Levie, Kimberly, Lewcock, Joseph W., Di Paolo, Gilbert and Sanchez, Pascal E.

Keywords: Research article
Neurology
Alzheimer's disease
Simoa Bead
CSF NfL
kit
SR-X

Abstract: Genetic mutations underlying familial Alzheimer’s disease (AD) were identified decades ago, but the field is still in search of transformative therapies for patients. While mouse models based on overexpression of mutated transgenes have yielded key insights in mechanisms of disease, those models are subject to artifacts, including random genetic integration of the transgene, ectopic expression and non-physiological protein levels. The genetic engineering of novel mouse models using knock-in approaches addresses some of those limitations. With mounting evidence of the role played by microglia in AD, high-dimensional approaches to phenotype microglia in those models are critical to refine our understanding of the immune response in the brain.

Title: Factor VII, EPCR, aPC Modulators: novel treatment for neuroinflammation
Journal: Journal of Neuroinflammation
Year: 2022
Date: 2022/06/11

Author: Golderman, Valery, Ben-Shimon, Marina, Maggio, Nicola, Dori, Amir, Gofrit, Shany Guly, Berkowitz, Shani, Qassim, Lamis, Artan-Furman, Avital, Zeimer, Talya, Chapman, Joab and Shavit-Stein, Efrat

Keywords: Research article
Neurology
neuroinflammation
Simoa Bead
mouse serum NfL
homebrew

Abstract: Background: Inflammation and coagulation are linked and pathogenic in neuroinflammatory diseases. Proteaseactivated receptor 1 (PAR1) can be activated both by thrombin, inducing increased inflammation, and activated protein C (aPC), inducing decreased inflammation. Modulation of the aPC‐PAR1 pathway may prevent the neuroinflammation associated with PAR1 over‐activation. Methods: We synthesized a group of novel molecules based on the binding site of FVII/aPC to the endothelial protein C receptor (EPCR). These molecules modulate the FVII/aPC‐EPCR pathway and are therefore named FEAMs—Factor VII, EPCR, aPC Modulators. We studied the molecular and behavioral effects of a selected FEAM in neuroinflammation models in‐vitro and in‐vivo. Results: In a lipopolysaccharide (LPS) induced in‐vitro model, neuroinflammation leads to increased thrombin activity compared to control (2.7 ± 0.11 and 2.23 ± 0.13 mU/ml, respectively, $p = 0.01$) and decreased aPC activity (0.57 ± 0.01 and 1.00 ± 0.02, respectively, $p < 0.0001$). In addition, increased phosphorylated extracellular regulated kinase (pERK) (0.99 ± 0.13, 1.39 ± 0.14, control and LPS, $p < 0.04$) and protein kinase B (pAKT) (1.00 ± 0.09, 2.83 ± 0.81, control and LPS, $p < 0.0002$) levels indicate PAR1 overactivation, which leads to increased tumor necrosis factor‐alpha (TNF‐α) level (1.00 ± 0.04, 1.35 ± 0.12, control and LPS, $p = 0.02$). In a minimal traumatic brain injury (mTBI) induced neuroinflammation in‐vivo model in mice, increased thrombin activity, PAR1 activation, and TNF‐α levels were measured. Additionally, significant memory impairment, as indicated by a lower recognition index in the Novel Object Recognition (NOR) test and Y‐maze test (NOR: 0.19 ± 0.06, ‐0.07 ± 0.09, $p = 0.03$. Y‐Maze: 0.50 ± 0.03, 0.23 ± 0.09, $p = 0.02$ control and mTBI, respectively), as well as hypersensitivity by hot‐plate latency (16.6 ± 0.89, 12.8 ± 0.56 s, control and mTBI, $p = 0.01$), were seen. FEAM prevented most of the molecular and behavioral negative effects of neuroinflammation in‐vitro and in‐vivo, most likely through EPCR‐PAR1 interactions. Conclusion: FEAM is a promising tool to study neuroinflammation and a potential treatment for a variety of neuroinflammatory diseases.

Title: Interferon-α-mediated therapeutic resistance in early rheumatoid arthritis implicates epigenetic reprogramming
Journal: Ann Rheum Dis
Year: 2022
Epub Date: 20220609

Author: Cooles, F. A. H., Tarn, J., Lendrem, D. W., Naamane, N., Lin, C. M., Millar, B., Maney, N. J., Anderson, A. E., Thalayasingam, N., Diboll, J., Bondet, V., Duffy, D., Barnes, M. R., Smith, G. R., Ng, S., Watson, D., Henkin, R., Cope, A. P., Reynard, L. N., Pratt, A. G. and Isaacs, J. D.

Keywords: Research article

Inflammation
rheumatoid arthritis
Simoa Bead
serum IFNa

Abstract: OBJECTIVES: An interferon (IFN) gene signature (IGS) is present in approximately 50% of early, treatment naive rheumatoid arthritis (eRA) patients where it has been shown to negatively impact initial response to treatment. We wished to validate this effect and explore potential mechanisms of action. METHODS: In a multicentre inception cohort of eRA patients (n=191), we examined the whole blood IGS (MxA, IFI44L, OAS1, IFI6, ISG15) with reference to circulating IFN proteins, clinical outcomes and epigenetic influences on circulating CD19+ B and CD4+ T lymphocytes. RESULTS: We reproduced our previous findings demonstrating a raised baseline IGS. We additionally showed, for the first time, that the IGS in eRA reflects circulating IFN-α protein. Paired longitudinal analysis demonstrated a significant reduction between baseline and 6-month IGS and IFN-α levels ($p<0.0001$ for both). Despite this fall, a raised baseline IGS predicted worse 6-month clinical outcomes such as increased disease activity score (DAS-28, $p=0.025$) and lower likelihood of a good EULAR clinical response ($p=0.034$), which was independent of other conventional predictors of disease activity and clinical response. Molecular analysis of CD4+ T cells and CD19+ B cells demonstrated differentially methylated CPG sites and dysregulated expression of disease relevant genes, including PARP9, STAT1, and EPSTI1, associated with baseline IGS/IFNα levels. Differentially methylated CPG sites implicated altered transcription factor binding in B cells (GATA3, ETSI, NFATC2, EZH2) and T cells (p300, HIF1α). CONCLUSIONS: Our data suggest that, in eRA, IFN-α can cause a sustained, epigenetically mediated, pathogenic increase in lymphocyte activation and proliferation, and that the IGS is, therefore, a robust prognostic biomarker. Its persistent harmful effects provide a rationale for the initial therapeutic targeting of IFN-α in selected patients with eRA.

Title: Plasma and serum alpha-synuclein as a biomarker in Parkinson's disease: A meta-analysis
Journal: Parkinsonism & Related Disorders
Year: 2022

Author: Zubelzu, Maider, Morera-Herreras, Teresa, Irastorza, Gorka, Gómez-Esteban, Juan Carlos and Murueta-Goyena, Ane

Keywords: Review
Neurology
Parkinson's disease
Simoa Bead

Abstract: Background: Reliable biomarkers for Parkinson’s disease (PD) diagnosis are urgently needed. Alpha-synuclein (α-syn) and its proteoforms play a key role in PD pathology but in vivo measurements have raised conflicting results, and whether α-syn in blood could distinguish PD patients from healthy controls is still controversial. Methods: A systematic literature search yielded 35 eligible studies for meta-analysis reporting the concentration of total, oligomeric or phosphorylated α-syn in plasma and/or serum of PD patients and healthy controls. Standardized mean differences (SMD) were pooled using multivariate/multilevel linear mixed-effects models. Meta-regression analyses were conducted to investigate possible modifiers. Results: A meta-analysis of 32 articles involving 2683 PD patients and 1838 controls showed a significant overall effect of PD on total α-syn levels (SMD = 0.85, p = 0.004).

Meta-regression showed that increased SMD of total α-syn in PD was significantly associated with lower age, shorter disease duration, mild motor impairment, and Immunomagnetic Reduction assay for protein quantification. In contrast, no significant differences were observed for oligomeric or phosphorylated α-syn between PD and controls but increased oligomeric α-syn was significantly associated with shorter disease duration. The heterogeneity among studies was high (>98%). Conclusions: These findings suggest that increased total plasma/serum α-syn levels in PD primarily occur in early phases of the disease. The evidence obtained from a small number of studies measuring plasma/serum concentrations of oligomeric and phosphorylated species of α-syn shows no difference. The clinical applicability of measuring plasma or serum α-syn species for differentiating PD from healthy control warrants further studies with better clinical profiling of PD patients.

Title: Identification of bronchoalveolar and blood immune-inflammatory biomarker signature associated with poor 28-day outcome in critically ill COVID-19 patients
Journal: Scientific Reports
Year: 2022
Date: 2022/06/09

Author: Voiriot, Guillaume, Dorgham, Karim, Bachelot, Guillaume, Fajac, Anne, Morand-Joubert, Laurence, Parizot, Christophe, Gerotziafas, Grigorios, Farabos, Dominique, Trugnan, Germain, Eguether, Thibaut, Blayau, Clarisse, Djibré, Michel, Elabbadi, Alexandre, Gibelin, Aude, Labbé, Vincent, Parrot, Antoine, Turpin, Matthieu, Cadranel, Jacques, Gorochov, Guy, Fartoukh, Muriel and Lamazière, Antonin

Keywords: Research article
Infectious disease
COVID-19
Simoa Bead
planar
BALF cell-free supernatant and serum GM-CSF, IL-2, IFNa, VEGF (bead)
BALF cell-free supernatant and serum Corplex IL-1b, IL-4, IL-5, IL-6, IL-8, IL-10, IL12p70, IL-22, IFNg, TNFa (planar)
HD-1
SP-X

Abstract: The local immune-inflammatory response elicited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is still poorly described, as well as the extent to which its characteristics may be associated with the outcome of critical Coronavirus disease 2019 (COVID-19). In this prospective monocenter study, all consecutive COVID-19 critically ill patients admitted from February to December 2020 and explored by fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) were included. Biological assays, including digital ELISA cytokine profiling and targeted eicosanoid metabolomic analysis, were performed on paired blood and BAL fluid (BALF). Clinical outcome was assessed through the World Health Organization 10-point Clinical Progression Scale (WHO-CPS) at the 28th day (D28) following the admission to intensive care unit. A D28-WHO-CPS value higher than 5 defined a poor outcome. Seventy-six patients were included, 45 (59%) had a poor day-28 outcome. As compared to their counterparts, patients with D28-WHO-CPS > 5 exhibited a neutrophil-predominant bronchoalveolar phenotype, with a higher BALF neutrophil/lymphocyte ratio, a blunted local type I interferon response, a decompartimentalized immune-inflammatory response illustrated by lower BALF/blood ratio of concentrations of IL-6 (1.68 [0.30–4.41] vs. 9.53 [2.56–19.1]; p = 0.001), IL-10, IL-5,

IL-22 and IFN-γ, and a biological profile of vascular endothelial injury illustrated by a higher blood concentration of VEGF and higher blood and/or BALF concentrations of several vasoactive eicosanoids. In critically ill COVID-19 patients, we identified bronchoalveolar and blood immune-inflammatory biomarker signature associated with poor 28-day outcome.

Title: The effect of the probiotic consortia on SARS-CoV-2 infection in ferrets and on human immune cell response in vitro
Journal: iScience
Year: 2022
Epub Date: 20220523

Author: Lehtinen, M. J., Kumar, R., Zabel, B., Mäkelä, S. M., Nedveck, D., Tang, P., Latvala, S., Guery, S. and Budinoff, C. R.

Keywords: Research article
Infectious disease
COVID-19
planar
Corplex 7-plex (IFNg, IL-1b, IL-6, IL-10, IL-12p70, TNFa)
IL23, TGFb1 (developer)
cell culture supernates

Abstract: Probiotics have been suggested as one solution to counter detrimental health effects by SARS-CoV-2; however, data so far is scarce. We tested the effect of two probiotic consortia, OL-1 and OL-2, against SARS-CoV-2 in ferrets and assessed their effect on cytokine production and transcriptome in a human monocyte-derived macrophage (Mf) and dendritic cell (DC) model. The results showed that the consortia significantly reduced the viral load, modulated immune response, and regulated viral receptor expression in ferrets compared to placebo. In the human Mf and DC model, OL-1 and OL-2-induced cytokine production and genes related to SARS-CoV-2 antiviral immunity. The study results indicate that probiotic stimulation of the ferret immune system leads to improved antiviral immunity against SARS-COV-2, and the genes and cytokines associated with anti-SARS-CoV-2 immunity are stimulated in human immune cells in vitro. The effect of the consortia against SARS-CoV-2 warrants further investigations in human clinical trials.

Title: Plasma neurofilament light and its association with all-cause mortality risk among urban middle-aged men and women
Journal: BMC Med
Year: 2022
Epub Date: 20220613

Author: Beydoun, M. A., Noren Hooten, N., Weiss, J., Beydoun, H. A., Hossain, S., Evans, M. K. and Zonderman, A. B.

Keywords: Research article
Neurology
all-cause mortality

Simoa Bead
plasma NfL
kit
HD-X

Abstract: BACKGROUND: Neurofilament light chain (NfL) is released into the blood during neuronal damage. NfL is linked to mortality in neurological disorders, remaining unexplored in population studies. We investigated whether initial (v(1)) and annualized change (δ) in plasma NfL can predict all-cause mortality in middle-aged dementia-free urban adults. METHODS: Longitudinal data were from 694 participants in the Healthy Aging in Neighborhoods of Diversity Across the Life Span study (HANDLS, mean age(v1): 47.8 years, 42% male, 55.8% African American). Plasma NfL was measured prospectively at three visits. Analyses included Cox proportional hazards models for all-cause mortality risk and 4-way decomposition testing for interaction and mediation. RESULTS: Unlike men, women exhibited a direct association between δNfL (above vs. below median) and all-cause mortality risk in both the minimally (HR = 3.91, 95% CI 1.10-13.9, p = 0.036) and fully adjusted models (HR = 4.92, 95% CI 1.26-19.2, p = 0.022), and for δNfL (per unit increase) in the full model (HR = 1.65, 95% CI 1.04-2.61, p = 0.034). In both models, and among women, 1 standard deviation of NfL(v1) was associated with an increased all-cause mortality risk (reduced model: HR = 2.01, 95% CI 1.24-3.25, p = 0.005; full model: HR = 1.75, 95% CI 1.02-2.98, p = 0.041). Only few interactions were detected for cardio-metabolic risk factors. Notably, NfL(v1) was shown to be a better prognostic indicator at normal hsCRP values among women, while HbA1c and δNfL interacted synergistically to determine mortality risk, overall. CONCLUSIONS: These findings indicate that plasma NfL levels at baseline and over time can predict all-cause mortality in women and interacts with hsCRP and HbA1c to predict that risk.

Title: Plasma Markers of Neurologic Injury and Inflammation in People With Self-Reported Neurologic Postacute Sequelae of SARS-CoV-2 Infection
Journal: Neurol Neuroimmunol Neuroinflamm
Year: 2022
Epub Date: 20220614

Author: Peluso, M. J., Sans, H. M., Forman, C. A., Nylander, A. N., Ho, H. E., Lu, S., Goldberg, S. A., Hoh, R., Tai, V., Munter, S. E., Chenna, A., Yee, B. C., Winslow, J. W., Petropoulos, C. J., Martin, J. N., Kelly, J. D., Durstenfeld, M. S., Hsue, P. Y., Hunt, P. W., Greene, M., Chow, F. C., Hellmuth, J., Henrich, T. J., Glidden, D. V. and Deeks, S. G.

Keywords: Research article
Infectious disease
COVID-19
Simoa Bead
GFAP, C3PA (IL-6, IL-10, TNFa); IFNg, IP-10, MCP-1, SARS-CoV-2 receptor-binding domain (RBD) immunoglobulin (Ig)
plasma NfL
kit
HD-X

Abstract: BACKGROUND AND OBJECTIVES: The biologic mechanisms underlying neurologic postacute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PASC) are

incompletely understood. METHODS: We measured markers of neurologic injury (glial fibrillary acidic protein [GFAP], neurofilament light chain [NfL]) and soluble markers of inflammation among a cohort of people with prior confirmed SARS-CoV-2 infection at early and late recovery after the initial illness (defined as less than and greater than 90 days, respectively). The primary clinical outcome was the presence of self-reported CNS PASC symptoms during the late recovery time point. We compared fold changes in marker values between those with and without CNS PASC symptoms using linear mixed-effects models and examined relationships between neurologic and immunologic markers using rank linear correlations. RESULTS: Of 121 individuals, 52 reported CNS PASC symptoms. During early recovery, those who went on to report CNS PASC symptoms had elevations in GFAP (1.3-fold higher mean ratio, 95% CI 1.04-1.63, p = 0.02), but not NfL (1.06-fold higher mean ratio, 95% CI 0.89-1.26, p = 0.54). During late recovery, neither GFAP nor NfL levels were elevated among those with CNS PASC symptoms. Although absolute levels of NfL did not differ, those who reported CNS PASC symptoms demonstrated a stronger downward trend over time in comparison with those who did not report CNS PASC symptoms (p = 0.041). Those who went on to report CNS PASC also exhibited elevations in interleukin 6 (48% higher during early recovery and 38% higher during late recovery), monocyte chemoattractant protein 1 (19% higher during early recovery), and tumor necrosis factor α (19% higher during early recovery and 13% higher during late recovery). GFAP and NfL correlated with levels of several immune activation markers during early recovery; these correlations were attenuated during late recovery. DISCUSSION: Self-reported neurologic symptoms present approximately 4 months after SARS-CoV-2 infection are associated with elevations in markers of neurologic injury and inflammation at earlier time points. Some inflammatory pathways seem to be involved months after acute infection. Additional work will be needed to better characterize these processes and to identify interventions to prevent or treat this condition.

Title: Glycerophosphoinositol is Elevated in Blood Samples From CLN3Δex7-8 pigs, Cln3Δex7-8 Mice, and CLN3-Affected Individuals
Journal: Biomarker Insights
Year: 2022

Author: Brudvig, Jon J, Swier, Vicki J, Johnson, Tyler B, Cain, Jacob C, Pratt, Melissa, Rechtzigel, Mitch, Leppert, Hannah, Dang Do, An N, Porter, Forbes D and Weimer, Jill M

Keywords: Research article
Neurology
CLN3 Batten disease
Simoa Bead
pig serum N4PA

Abstract: Introduction: CLN3 Batten disease is a rare pediatric neurodegenerative lysosomal disorder caused by biallelic disease-associated variants in CLN3. Despite decades of intense research, specific biofluid biomarkers of disease status have not been reported, hindering clinical development of therapies. Thus, we sought to determine whether individuals with CLN3 Batten disease have elevated levels of specific metabolites in blood. Methods: We performed an exhaustive metabolomic screen using serum samples from a novel minipig model of CLN3 Batten disease and validated findings in CLN3 pig serum and CSF and Cln3 mouse serum. We further validate biomarker candidates with a retrospective analysis of plasma and CSF samples collected from participants in a natural history study. Plasma

samples were evaluated from 22 phenotyped individuals with CLN3 disease, 15 heterozygous carriers, and 6 non-affected non-carriers (NANC). Results: CLN3 pig serum samples from 4 ages exhibited large elevations in 4 glycerophosphodiester species: glycerophosphoinositol (GPI), glycerophosphoethanolamine (GPE), glycerophosphocholine (GPC), and glycerophosphoserine (GPS). GPI and GPE exhibited the largest elevations, with similar elevations found in CLN3 pig CSF and Cln3 mouse serum. In plasma samples from individuals with CLN3 disease, glycerophosphoethanolamine and glycerophosphoinositol were significantly elevated with glycerophosphoinositol exhibiting the clearest separation (mean 0.1338 vs 0.04401 nmol/mL for non-affected non-carriers). Glycerophosphoinositol demonstrated excellent sensitivity and specificity as a biomarker, with a receiver operating characteristic area under the curve of 0.9848 (P = .0003). Conclusions: GPE and GPI could have utility as biomarkers of CLN3 disease status. GPI, in particular, shows consistent elevations across a diverse cohort of individuals with CLN3. This raises the potential to use these biomarkers as a blood-based diagnostic test or as an efficacy measure for disease-modifying therapies.

Title: Diffusion tensor imaging (DTI) and plasma p-tau 181 in Alzheimer's disease
Journal: Neurology Letters
Year: 2022

Author: Nabizadeh, Fardin and Jameie, Seyed Behnamedin

Keywords: Research article
Neurology
Alzheimer' s Disease
Simoa Bead
plasma pTau181
homebrew

Abstract: Alzheimer's Disease (AD) is characterized by cognitive impairments and memory difficulties, which cause daily activities, and personal and behavioral problems. In recent years blood-based biomarkers like plasma phosphorylated tau protein at threonine 181 (p tau 181) emerged as new tools and showed a sufficient power in detecting AD patients from healthy people. Here we investigate the correlation between p tau 181 and white matter microstructural changes in AD patients. We add 21 Alzheimer diagnosed patients with baseline plasma p tau level, CSF Amyloidβ, CSF Tau, CSF p Tau, and DTI metrics from the ADNI database. The analysis revealed that the plasma level of p tau 181 could predict changes in MD, RD, AD, and FA parameters in several regions Also, there is a significant association between white matter pathways alteration in different regions with each of the CSF biomarkers. In conclusion, our study results show that plasma p tau 181 levels are associated with microstructural changes in pathogenesis areas of Alzheimer's disease, which enhance this biomarker's diagnostic status. Longitudinal studies are also necessary to prove the efficacy of these biomarkers and predicting role in structural changes.

Title: Enhancing clinical value of serum neurofilament light chain measurement
Journal: JCI Insight
Year: 2022
Epub Date: 20220623

Author: Kosa, P., Masvekar, R., Komori, M., Phillips, J., Ramesh, V., Varosanec, M., Sandford, M. and Bielekova, B.

Keywords: Research article
Neurology
Multiple sclerosis
Simoa Bead
serum NfL
kit
HD-1

Abstract: Serum neurofilament light chain (sNFL) is becoming an important biomarker of neuroaxonal injury. Though sNFL correlates with cerebrospinal fluid (CSF) NFL (cNFL), 40-60% of variance remains unexplained. We aimed to mathematically adjust sNFL to strengthen its clinical value. We measured NFL in blinded fashion in 1,138 matched CSF and serum samples from 571 subjects. Multiple linear regression (MLR) models constructed in the training cohort were validated in an independent cohort. MLR model that included age, blood urea nitrogen (BUN), alkaline phosphatase (AP), creatinine, and weight improved correlations of cNFL with sNFL (from R2 = 0.57 to 0.67). Covariate-adjustment significantly improved the correlation of sNFL with number of contrast-enhancing lesions (from R2 = 0.18 to 0.28; 36% improvement) in the validation cohort. Unexpectedly, only sNFL, but not cNFL, weakly but significantly correlated with cross-sectional MS severity outcomes. Investigating two non-overlapping hypotheses, we show that subjects with proportionally higher sNFL to cNFL have higher clinical and radiological evidence of spinal cord (SC) injury, and likely release NFL from peripheral axons into blood, bypassing the CSF. Thus, sNFL captures two sources of axonal injury: central and peripheral; the latter reflecting SC damage, which primarily drives disability progression in MS.

Title: Elevated Plasma Soluble ST2 Levels are Associated With Neuronal Injury and Neurocognitive Impairment in Children With Cerebral Malaria
Journal: Pathog Immun
Year: 2022
Epub Date: 20220623

Author: Fernander, E. M., Adogamhe, P., Datta, D., Bond, C., Zhao, Y., Bangirana, P., Conroy, A. L., Opoka, R. O. and John, C. C.

Keywords: Research article
Infectious disease
malaria
Simoa Bead
plasma tau

Abstract: BACKGROUND: Murine experimental cerebral malaria studies suggest both protective and deleterious central nervous system effects from alterations in the interleukin-33 (IL-33)/ST2 pathway. METHODS: We assessed whether soluble ST2 (sST2) was associated with neuronal injury or cognitive impairment in a cohort of Ugandan children with cerebral malaria (CM, n=224) or severe malarial anemia (SMA, n=193). RESULTS: Plasma concentrations of sST2 were higher in children with CM than in children with SMA or in asymptomatic community children. Cerebrospinal fluid (CSF) sST2 levels were

elevated in children with CM compared with North American children. Elevated plasma and CSF ST2 levels in children with CM correlated with increased endothelial activation and increased plasma and CSF levels of tau, a marker of neuronal injury. In children with CM who were ≥5 years of age at the time of their malaria episode, but not in children <5 years of age, elevated risk factor-adjusted plasma levels of sST2 were associated with worse scores for overall cognitive ability and attention over a 2-year follow-up. CONCLUSIONS: The study findings suggest that sST2 may contribute to neuronal injury and long-term neurocognitive impairment in older children with CM.

Title: Brain disconnectome mapping derived from white matter lesions and serum neurofilament light levels in multiple sclerosis: A longitudinal multicenter study
Journal: Neuroimage Clin
Year: 2022
Epub Date: 20220625

Author: Rise, H. H., Brune, S., Chien, C., Berge, T., Bos, S. D., Andorrà, M., Valdeolivas, I. P., Beyer, M. K., Sowa, P., Scheel, M., Brandt, A. U., Asseyer, S., Blennow, K., Pedersen, M. L., Zetterberg, H., de Schotten, M. T., Cellerino, M., Uccelli, A., Paul, F., Villoslada, P., Harbo, H. F., Westlye, L. T. and Høgestøl, E. A.

Keywords: Research article
Neurology
Multiple sclerosis
Simoa Bead
serum NfL
homebrew

Abstract: BACKGROUND AND OBJECTIVES: Connectivity-based approaches incorporating the distribution and magnitude of the extended brain network aberrations caused by lesions may offer higher sensitivity for axonal damage in patients with multiple sclerosis (MS) than conventional lesion characteristics. Using individual brain disconnectome mapping, we tested the longitudinal associations between putative imaging-based brain network aberrations and levels of serum neurofilament light chain (NfL) as a neuroaxonal injury biomarker. METHODS: MS patients (n = 312, mean age 42.9 years, 71 % female) and healthy controls (HC) (n = 59, mean age 39.9 years, 78 % female) were prospectively enrolled at four European MS centres, and reassessed after two years (MS, n = 242; HC, n = 30). Post-processing of 3 Tesla (3 T) MRI data was performed at one centre using a harmonized pipeline, and disconnectome maps were calculated using BCBtoolkit based on individual lesion maps. Global disconnectivity (GD) was defined as the average disconnectome probability in each patient's white matter. Serum NfL concentrations were measured by single molecule array (Simoa). Robust linear mixed models (rLMM) with GD or T2-lesion volume (T2LV) as dependent variables, patient as a random factor, serum NfL, age, sex, timepoint for visit, diagnosis, treatment, and center as fixed factors were run. RESULTS: rLMM revealed significant associations between GD and serum NfL ($t = 2.94$, $p = 0.003$), age ($t = 4.21$, $p = 2.5 \times 10(-5)$), and longitudinal changes in NfL ($t = -2.29$, $p = 0.02$), but not for sex ($t = 0.63$, $p = 0.53$) or treatments ($t = 0.80$-0.83, $p = 0.41$-0.42). Voxel-wise analyses revealed significant associations between dysconnectivity in cerebellar and brainstem regions and serum NfL ($t = 7.03$, $p < 0.001$). DISCUSSION: In our prospective multi-site MS cohort, rLMMs demonstrated that the extent of global and regional brain disconnectivity is sensitive to a systemic biomarker of axonal damage, serum NfL, in patients with MS. These findings provide a neuroaxonal correlate of advanced disconnectome mapping and provide a platform for further investigations of the functional and potential clinical relevance of

brain disconnectome mapping in patients with brain disorders.

Title: Acute OSA Impacts Diurnal Alzheimer's Biomarkers Through Nocturnal Hypoxemia and State Transitions
Journal: Am J Respir Crit Care Med
Year: 2022
Epub Date: 20220613

Author: Kam, K., Jun, J., Parekh, A., Bubu, O. M., Mullins, A. E., Gu, C., Pham, L., Wisniewski, T. M., Rapoport, D. M., Ayappa, I., Osorio, R. S. and Varga, A. W.

Keywords: Research article
Neurology
Obstructive sleep apnea
Simoa Bead
plasma N3PA
plasma NfL
kit
HD-1

Title: Glymphatic dysfunction correlates with severity of small vessel disease and cognitive impairment in cerebral amyloid angiopathy
Journal: Eur J Neurol
Year: 2022
Epub Date: 20220617

Author: Xu, J., Su, Y., Fu, J., Wang, X., Nguchu, B. A., Qiu, B., Dong, Q. and Cheng, X.

Keywords: Research article
Neurology
Cerebral amyloid angiopathy
Simoa Bead
serum NfL kit
plasma N3PA
HD-1
China

Abstract: BACKGROUND AND PURPOSE: Cerebral amyloid angiopathy (CAA) is characterized by β-amyloid deposition in cortical and leptomeningeal arterioles, which might result from glymphatic dysfunction. The aim was to explore glymphatic function in CAA using the non-invasive diffusion tensor image analysis along the perivascular space method. METHODS: Sixty-three patients with CAA were prospectively recruited together with seventy age- and sex-matched normal controls. The Mini-Mental State Examination and Montreal Cognitive Assessment were applied to screen global cognitive status. Magnetic resonance imaging scans were conducted to calculate the index for diffusivity along the perivascular space (ALPS index), and linear regression models were used to assess its relationships with cerebral small vessel disease (CSVD) markers, cognitive status and blood biomarkers. Cox proportional

hazard models were applied to explore the role of the baseline ALPS index in disease recurrence. RESULTS: Patients with CAA exhibited a lower ALPS index than controls globally ($p < 0.001$). In addition, a lower ALPS index was related to more enlarged perivascular space in basal ganglia ($p = 0.026$), more lacunes ($p < 0.001$), higher white matter hyperintensity Fazekas score ($p = 0.049$), elevated total magnetic resonance imaging burden of CSVD ($p = 0.034$) and lower Mini-Mental State Examination ($p = 0.001$) as well as Montreal Cognitive Assessment ($p < 0.001$) in CAA. During a median follow-up of 4.1 years, a higher ALPS index was associated with lower disease recurrence ($p = 0.022$). The ALPS index was also negatively correlated with serum soluble intercellular adhesion molecule-1, neurofilament light and chitinase-3-like protein 1 in CAA. CONCLUSIONS: Patients with CAA showed impaired glymphatic function. The ALPS index was significantly related to CSVD severity, cognitive impairment and disease recurrence in CAA.

Title: Variability in primary Sjögren's syndrome is driven by interferon alpha, and genetically associated with the class II HLA DQ locus
Journal: Arthritis Rheumatol
Year: 2022
Epub Date: 20220620

Author: Trutschel, D. Dr rer nat, Bost, P., Mariette, X., Bondet, V., Llibre, A., Posseme, C., Charbit, B., Thorball, C. W., Jonsson, R. Prof, Lessard, C. J., Felten, R., Ng, W. F. Prof, Chatenoud, L. Prof, Dumortier, H., Sibilia, J., Fellay, J., Brokstad, K. A. Prof, Appel, S. Prof Dr rer nat, Tarn Dr, J. R., Murci, L. Q. Prof Dr, Mingueneau, M., Meyer, N., Duffy, D., Schwikowski, B. and Gottenberg, J. E.

Keywords: Research article
Inflammation
Sjögren's syndrome
Simoa Bead
serum INFa, IFNg homebrew

Abstract: OBJECTIVE: Primary Sjögren's syndrome (pSS) is the second most frequent systemic autoimmune disease affecting 0.1% of the general population. To characterize the molecular and clinical variability across pSS patients, we integrated transcriptomic, proteomic, cellular and genetic data with clinical phenotypes in a cohort of 351 pSS patients. METHODS: Blood transcriptomes and genotypes of 351 pSS patients from a multi-center prospective clinical cohort were analyzed. Replication of the transcriptomic results was performed using 3 independent cohorts (n=462 patients). Circulating IFN-alpha (IFNα) and IFN-gamma (IFNγ) protein concentrations were determined using digital ELISA. RESULTS: Transcriptomic analysis of the prospective cohort showed a strong IFN gene signature in more than half of the patients. This finding was replicated in three independent cohorts. As gene expression analysis did not discriminate between type I and II interferons, we applied digital ELISA to demonstrate that the IFN transcriptomic signature was driven by circulating IFNα, and not IFNγ, protein levels. IFNα protein levels, detectable in 75% of patients, were significantly associated with clinical and immunological features of disease activity at enrollment, and with increased frequency of systemic complications during the 5-year follow-up. Genetic analysis revealed a significant association between IFNα protein levels, a MHC-II haplotype and anti-SSA antibody. Additional cellular analysis revealed that a MHC-II HLA-DQ locus acts through upregulation of HLA II molecules on conventional DCs. CONCLUSIONS: The present analysis identified the predominance of IFNα as driver of pSS variability and revealed an association with HLA gene polymorphisms.

Title: Association between obstructive sleep apnea and Alzheimer's disease-related blood and cerebrospinal fluid biomarkers: A meta-analysis
Journal: J Clin Neurosci
Year: 2022
Epub Date: 20220623

Author: Kang, J., Tian, Z., Wei, J., Mu, Z., Liang, J. and Li, M.

Keywords: Research article
Neurology
Obstructive sleep apnea
Simoa Bead
China

Abstract: INTRODUCTION: Recent studies indicate that Alzheimer's disease- (AD) related biomarkers, including amyloid β (Aβ40 and Aβ42) and tau proteins (P-tau and T-tau), in blood and cerebrospinal fluid (CSF) are associated with obstructive sleep apnea (OSA). However, the results have been inconsistent. Therefore, the primary purpose of this meta-analysis was to determine the relationship between blood and CSF AD-related biomarkers and OSA. METHODS: We searched the Embase, PubMed, Scopus, and Cochrane Library databases for relevant articles till February 2022. RESULTS: Eight articles were finally included after the literature screening, including 446 patients with OSA and 286 controls. Pooled analysis showed that CSF Aβ42 (SMD = -0.220, P = 0.136), T-tau (SMD = 0.012, P = 0.89), and P-tau (SMD = 0.099, P = 0.274) levels were not different between patients with OSA and controls. In patients with moderate to severe OSA, CSF Aβ42 (SMD = -0.482, P = 0.031) were significantly lower than in controls. Blood T-tau (SMD = 0.560, P = 0.026), P-tau (SMD = 0.621, P < 0.001), and Aβ40 (SMD = 0.656, P < 0.001) levels were significantly higher in patients with OSA than in controls. Blood Aβ42 (SMD = 0.241, P = 0.232) were not different between patients with OSA and controls. CONCLUSION: OSA is associated with changes in AD-related markers. Higher OSA severity may be associated with the development of AD. AD-related biomarkers, especially in the blood, are clinically efficient, less invasively assessed and monitored, and may be useful for detecting OSA and related cognitive impairments. Further studies are needed to confirm these results.

Title: Investigating the use of plasma pTau181 in retired contact sports athletes
Journal: J Neurol
Year: 2022
Epub Date: 20220625

Author: Vasilevskaya, A., Taghdiri, F., Multani, N., Ozzoude, M., Tarazi, A., Khodadadi, M., Wennberg, R., Rusjan, P., Houle, S., Green, R., Colella, B., Blennow, K., Zetterberg, H., Karikari, T., Mikulis, D., Hazrati, L. N., Kovacs, G. G., Davis, K. D., Tator, C. and Tartaglia, M. C.

Keywords: Research article
Neurology
TBI
Simoa Bead

plasma pTau181 homebrew
plasma NfL, tau kit
HD-1

Abstract: BACKGROUND: Considering the wide range of outcomes following sport-related concussions, biomarkers are needed to detect underlying pathological changes. The objective was to analyze the use of plasma phosphorylated tau 181 (pTau181) as a non-invasive measure of underlying brain changes in a cohort of retired contact sports athletes at risk of neurodegeneration. METHODS: Fifty-four retired contact sport athletes and 27 healthy controls whose blood plasma was analyzed for pTau181 were included. A portion (N = 21) of retired athletes had a 2-years follow-up visit. All participants had completed a neuropsychological battery and MRI imaging. RESULTS: Plasma pTau181 was significantly higher in retired athletes compared to healthy controls (8.94 ± 5.08 pg/mL vs. 6.00 ± 2.53 pg/mL, respectively; 95% BCa CI 1.38-4.62; p = 0.02); and was significantly associated with fornix fractional anisotropy values only in the athletes group (β = - 0.002; 95% BCa CI - 0.003 to - 0.001; p = 0.002). When the retired athletes cohort was divided into high vs. normal pTau181 groups, the corpus callosum (CC) volume and white-matter integrity was significantly lower in high pTau181 compared to older healthy controls (CC volume: 1.57 ± 0.19 vs. 2.02 ± 0.32, p = 0.002; CC medial diffusivity: 0.96 ± 0.04 × 10(-3) mm(2)/s vs. 0.90 ± 0.03 × 10(-3) mm(2)/s, p = 0.003; CC axial diffusivity: 1.49 ± 0.04 × 10(-3) mm(2)/s vs. 1.41 ± 0.02 × 10(-3) mm(2)/s, p < 0.001, respectively). CONCLUSIONS: Although high plasma pTau181 levels were associated with abnormalities in CC and fornix, baseline pTau181 did not predict longitudinal changes in regional brain volumes or white-matter integrity in the athletes. pTau181 may be useful for identifying those with brain abnormalities related to repeated concussion but not for predicting progression.

Title: Clinical and Blood Biomarker Trajectories after Concussion: New Insights from a Longitudinal Pilot Study of Professional Flat-Track Jockeys
Journal: J Neurotrauma
Year: 2022
Epub Date: 20220722

Author: McDonald, S. J., Piantella, S., O'Brien, W. T., Hale, M. W., O'Halloran, P., Kinsella, G., Horan, B., O'Brien, T. J., Maruff, P., Shultz, S. R. and Wright, B. J.

Keywords: Research article
Neurology
TBI
Simoa Bead
serum N4PB (GFAP, tau, UCH-L1, NfL)
HD-X

Abstract: There is a recognized need for objective tools for detecting and tracking clinical and neuropathological recovery after sports-related concussion (SRC). Although computerized neurocognitive testing has been shown to be sensitive to cognitive deficits after SRC, and some blood biomarkers have shown promise as indicators of axonal and glial damage, the potential utility of these measures in isolation and combination for assisting SRC diagnosis and tracking recovery is not well understood. To provide new insights, we conducted a prospective study of 64 male and female professional flat-track jockeys (49 non-SRC, 15 SRC), with each jockey undergoing symptom evaluation,

cognitive testing using the CogSport battery, and serum biomarker quantification of glial fibrillary acidic protein (GFAP), tau, and neurofilament light (NfL) using a Simoa HD-X Analyzer. Measures were performed at baseline (i.e., pre-injury), and 2 and 7 days and 1 and 12 months after SRC. Symptoms were most pronounced at 2 days and had largely resolved by either 7 days or 1 month. CogSport testing at 2 days revealed cognitive impairments relative to both non-concussed peers and their own pre-injury baselines, with SRC classification utility found at 2 days, and to a slightly lesser extent, at 7 days. Relatively prolonged changes in serum NfL were observed, with elevated levels and classification utility persisting beyond the resolution of SRC symptoms and cognitive deficits. Finally, SRC classification performance throughout the 1st month after SRC was optimized through the combination of cognitive testing and serum biomarkers. Considered together, these findings provide further evidence for a role of computerized cognitive testing and fluid biomarkers of neuropathology as objective measures to assist in the identification of SRC and the monitoring of clinical and neuropathological recovery.

Title: A Method to Combine Neurofilament Light Measurements From Blood Serum and Plasma in Clinical and Population-Based Studies
Journal: Frontiers in Neurology
Year: 2022
Date: 2022-June-14

Author: Rübsamen, Nicole, Willemse, Eline A. J., Leppert, David, Wiendl, Heinz, Nauck, Matthias, Karch, André, Kuhle, Jens and Berger, Klaus

Keywords: Research article
Neurology
Simoa Bead
serum NfL
plasma NfL
kit
HD-X

Abstract: Introduction: Neurofilament light (NfL) can be detected in blood of healthy individuals and at elevated levels in those with different neurological diseases. We investigated if the choice of biological matrix can affect results when using NfL as biomarker in epidemiological studies. Method: We obtained paired serum and EDTA-plasma samples of 299 individuals aged 37–67 years (BiDirect study) and serum samples of 373 individuals aged 65–83 years (MEMO study). In BiDirect, Passing–Bablok analyses were performed to assess proportional and systematic differences between biological matrices. Associations between serum or EDTA-plasma NfL and renal function (serum creatinine, serum cystatin C, glomerular filtration rate, and kidney disease) were investigated using linear or logistic regression, respectively. All regression coefficients were estimated (1) per one ng/L increase and (2) per one standard deviation increase (standardization using z-scores). In MEMO, regression coefficients were estimated (1) per one ng/L increase of serum or calculated EDTA-plasma NfL and (2) per one standard deviation increase providing a comparison to the results from BiDirect. Results: We found proportional and systematic differences between paired NfL measurements in BiDirect, i.e., serum NfL [ng/L] = −0.33 [ng/L] + 1.11 × EDTA-plasma NfL [ng/L]. Linear regression coefficients for the associations between NfL and renal function did not vary between the different NfL measurements. In MEMO, one standard deviation increase in serum NfL was associated with greater changes in the outcomes than in BiDirect. Conclusion: Although there are differences between serum and EDTA-plasma NfL, results can be used

interchangeably if standardized values are used.

Title: Association of Plasma Neurofilament Light Chain With Glycaemic Control and Insulin Resistance in Middle-Aged Adults
Journal: Front Endocrinol (Lausanne)
Year: 2022
Epub Date: 20220620

Author: Thota, R. N., Chatterjee, P., Pedrini, S., Hone, E., Ferguson, J. J. A., Garg, M. L. and Martins, R. N.

Keywords: Research article
Neurology
type 2 Diabetes
Simoa Bead
plasma NfL
kit

Abstract: AIMS: This study aimed to determine the association of plasma neurofilament light (NfL), a marker of neurodegeneration, with diabetes status and glycaemic parameters in people with normal glycaemia (NG), pre-diabetes (PD) and type 2 diabetes (T2D). METHODS: Clinical and descriptive data for the diagnostic groups, NG (n=30), PD (n=48) and T2D (n=29), aged between 40 and 75 years were included in this cross-sectional analysis. Plasma NfL levels were analyzed using the ultra-sensitive single-molecule array (Simoa) platform. RESULTS: A positive correlation was evident between plasma NfL and fasting glucose (r = 0.2824; p = 0.0032). Plasma NfL levels were not correlated with fasting insulin and insulin resistance. Plasma Nfl levels were significantly different across the diabetes groups (T2D >PD >NG, p=0.0046). Post-hoc analysis indicated significantly higher plasma NfL levels in the T2D [12.4 (5.21) pg/mL] group than in the PD [10.2 (4.13) pg/mL] and NG [8.37 (5.65) pg/mL] groups. The relationship between diabetes status and NfL remained significant after adjusting for age, sex, BMI, HOMA-IR and physical activity (adjusted r(2) = 0.271, p = 0.035). CONCLUSIONS: These results show biomarker evidence of neurodegeneration in adults at risk or with T2D. Larger sample size and longitudinal analysis are required to better understand the application of NfL in people with risk and overt T2D.

Title: Linking Plasma Amyloid Beta and Neurofilament Light Chain to Intracortical Myelin Content in Cognitively Normal Older Adults
Journal: Front Aging Neurosci
Year: 2022
Epub Date: 20220617

Author: Fernandez-Alvarez, M., Atienza, M., Zallo, F., Matute, C., Capetillo-Zarate, E. and Cantero, J. L.
Short Title: Linking Plasma Amyloid Beta and Neurofilament Light Chain to Intracortical Myelin Content in Cognitively Normal Older Adults

Keywords: Research article
Neurology
Alzheimer's disease

Simoa Bead
plasma NfL, Abeta42
kit
HD-1

Abstract: Evidence suggests that lightly myelinated cortical regions are vulnerable to aging and Alzheimer's disease (AD). However, it remains unknown whether plasma markers of amyloid and neurodegeneration are related to deficits in intracortical myelin content, and whether this relationship, in turn, is associated with altered patterns of resting-state functional connectivity (rs-FC). To shed light into these questions, plasma levels of amyloid-β fragment 1-42 (Aβ(1-42)) and neurofilament light chain (NfL) were measured using ultra-sensitive single-molecule array (Simoa) assays, and the intracortical myelin content was estimated with the ratio T1-weigthed/T2-weighted (T1w/T2w) in 133 cognitively normal older adults. We assessed: (i) whether plasma Aβ(1-42) and/or NfL levels were associated with intracortical myelin content at different cortical depths and (ii) whether cortical regions showing myelin reductions also exhibited altered rs-FC patterns. Surface-based multiple regression analyses revealed that lower plasma Aβ(1-42) and higher plasma NfL were associated with lower myelin content in temporo-parietal-occipital regions and the insular cortex, respectively. Whereas the association with Aβ(1-42) decreased with depth, the NfL-myelin relationship was most evident in the innermost layer. Older individuals with higher plasma NfL levels also exhibited altered rs-FC between the insula and medial orbitofrontal cortex. Together, these findings establish a link between plasma markers of amyloid/neurodegeneration and intracortical myelin content in cognitively normal older adults, and support the role of plasma NfL in boosting aberrant FC patterns of the insular cortex, a central brain hub highly vulnerable to aging and neurodegeneration.

Title: Serum neurofilament light chain levels in Covid-19 patients without major neurological manifestations
Journal: J Neurol
Year: 2022
Epub Date: 20220704

Author: Verde, F., Milone, I., Bulgarelli, I., Peverelli, S., Colombrita, C., Maranzano, A., Calcagno, N., Ticozzi, N., Perego, G. B., Parati, G., Torresani, E., Ratti, A. and Silani, V.

Keywords: Research article
Infectious disease
Covid-19
Simoa Bead
Serum NfL
kit
SR-X

Abstract: BACKGROUND: Increased serum levels of neurofilament light chain (sNFL), a biomarker of neuroaxonal damage, have been reported in patients with Covid-19. We aimed at investigating whether sNFL is increased in Covid-19 patients without major neurological manifestations, is associated with disease severity, respiratory and routine blood parameters, and changes longitudinally in the short term. METHODS: sNFL levels were measured with single molecule array (Simoa) technology in 57 hospitalized Covid-19 patients without major neurological manifestations and in 30 neurologically healthy controls.

Patients were evaluated for PaO2/FiO2 ratio on arterial blood gas, Brescia Respiratory Covid Severity Scale (BRCSS), white blood cell counts, serum C-reactive protein (CRP), plasma D-dimer, plasma fibrinogen, and serum creatinine at admission. In 20 patients, NFL was also measured on serum samples obtained at a later timepoint during the hospital stay. RESULTS: Covid-19 patients had higher baseline sNFL levels compared to controls, regardless of disease severity. Baseline sNFL correlated with serum CRP and plasma D-dimer in patients with mild disease, but was not associated with measures of respiratory impairment. Longitudinal sNFL levels tended to be higher than baseline ones, albeit not significantly, and correlated with serum CRP and plasma D-dimer. The PaO2/FiO2 ratio was not associated with longitudinal sNFL, whereas BRCSS only correlated with longitudinal sNFL variation. CONCLUSIONS: We provide neurochemical evidence of subclinical axonal damage in Covid-19 also in the absence of major neurological manifestations. This is apparently not fully explained by hypoxic injury; rather, systemic inflammation might promote this damage. However, a direct neurotoxic effect of SARS-CoV-2 cannot be excluded.

Title: Ultrasensitive multiplexed chemiluminescent enzyme-linked immunosorbent assays in 384-well plates
Journal: J Immunol Methods
Year: 2022
Epub Date: 20220701

Author: Chen, T., Ubaidu, A., Douglas, S., Carranza, S., Wong, A., Kan, C. W. and Duffy, D. C.

Keywords: Research article
Technology
planar
SP-X
IL-5, IL-6, IL-10, TNFa

Abstract: We have developed an ultrasensitive multiplexed immunoassay using 384-well microtiter plates capable of detecting proteins at subfemtomolar concentrations that requires as little as 2.5 µL of sample. Arrays of up to 4 capture antibodies were patterned on the bottom of the wells of a 384-well plate either by directly printing the capture antibodies or by printing anti-peptide tag anchor antibodies and incubating these arrays with capture antibodies conjugated to the corresponding peptide tags ("customized" assays). Samples were incubated with the antibody arrays and shaken orbitally at 2000 rpm to achieve the greatest sensitivity. Chemiluminescence (CL) from immunocomplexes labeled with horseradish peroxidase was imaged across the entire plate to quantify the amount of protein bound to each antibody spot of the arrays. The 384-well assay had a throughput 5-fold greater than 96-well plates that was achieved from simultaneous imaging of CL in all 384-wells and the use of automated pipettors to allow parallel processing of 384 assays. We developed 4 assays based on the 384-well CL ELISA: a direct print assay for IL-10 (limit of detection (LOD) = 0.075 fM); a customized assay for IL-6 (0.22 fM); a customized pharmacokinetic (PK) assay for measuring adalimumab (7.3 pg/mL); and a customized 4-plex assay for IL-5 (0.1 fM), IL-6 (0.52 fM), IL-10 (0.2 fM), and TNF-α (3.2 fM). The sensitivity and precision of the cytokine assays were comparable to current ultrasensitive protein detection methods in 96-well formats. The PK assay for adalimumab was 650 times more sensitive than a commercially available 96-well plate ELISA. We used the 384-well CL ELISAs to measure endogenous levels of the cytokines in the serum and plasma of healthy humans: the mean concentrations and precision were comparable to those from 96-well immunoassays. This 384-well format with

subfemtomolar sensitivity will enable ultrasensitive multiplexed immunoassays to be performed with higher throughput and lower sample volumes than currently possible, a particularly important capability for clinical studies in drug development.

Title: P-tau subgroups in AD relate to distinct amyloid production and synaptic integrity profiles
Journal: Alzheimers Res Ther
Year: 2022
Epub Date: 20220715

Author: Wesenhagen, K. E. J., Tijms, B. M., Boonkamp, L., Hoede, P. L., Goossens, J., Dewit, N., Scheltens, P., Vanmechelen, E., Visser, P. J. and Teunissen, C. E.

Keywords: Research article
Neurology
Alzheimer's Disease
Simoa Bead
CSF VAMP-2
Homebrew

Abstract: BACKGROUND: We previously identified four Alzheimer's disease (AD) subgroups with increasingly higher cerebrospinal fluid (CSF) levels of tau phosphorylated at threonine 181 (p-tau). These subgroups included individuals across the cognitive spectrum, suggesting p-tau subgroups could reflect distinct biological changes in AD, rather than disease severity. Therefore, in the current study, we further investigated which potential processes may be related with p-tau subgroups, by comparing individuals on CSF markers for presynaptic structure [vesicle-associated membrane protein 2 (VAMP2)], postsynaptic structure [neurogranin (NRGN)], axonal damage [neurofilament light (NfL)], and amyloid production [beta-secretase 1 (BACE1) and amyloid-beta 1-40 (Aβ40)]. METHODS: We selected 348 amyloid-positive (A+) individuals (53 preclinical, 102 prodromal, 193 AD dementia) and 112 amyloid-negative (A-) cognitively normal (CN) individuals from the Amsterdam Dementia Cohort (ADC). Individuals were labeled according to their p-tau subgroup (subgroup 1: p-tau ≤ 56 pg/ml; subgroup 2: 57-96 pg/ml; subgroup 3: 97-159 pg/ml; subgroup 4: > 159 pg/ml). CSF protein levels were measured with ELISA (NRGN, BACE1, Aβ40, NfL) or single-molecule array (Simoa) (VAMP2). We tested whether protein levels differed between the p-tau subgroups within A+ individuals with linear models corrected for age and sex and whether disease stage influenced these relationships. RESULTS: Among A+ individuals, higher p-tau subgroups showed a higher percentage of AD dementia [subgroup 1: n = 41/94 (44%); subgroup 2: n = 81/147 (55%); subgroup 3: n = 59/89 (66%); subgroup 4: n = 7/11 (64%)]. Relative to controls, subgroup 1 showed reduced CSF levels of BACE1, Aβ40, and VAMP2 and higher levels of NfL. Subgroups 2 to 4 showed gradually increased CSF levels of all measured proteins, either across the first three (NfL and Aβ40) or across all subgroups (VAMP2, NRGN, BACE1). The associations did not depend on the clinical stage (interaction p-values ranging between 0.19 and 0.87). CONCLUSIONS: The results suggest that biological heterogeneity in p-tau levels in AD is related to amyloid metabolism and synaptic integrity independent of clinical stage. Biomarkers reflecting amyloid metabolism and synaptic integrity may be useful outcome measures in clinical trials targeting tau pathology.

Title: Sarm1 knockout modifies biomarkers of neurodegeneration and spinal cord circuitry but not disease progression in the mSOD1(G93A) mouse model of ALS

Journal: Neurobiol Dis
Year: 2022
Epub Date: 20220718

Author: Collins, J. M., Atkinson, R. A. K., Matthews, L. M., Murray, I. C., Perry, S. E. and King, A. E.

Keywords: Research article
Neurology
ALS
Simoa Bead
mouse serum N4PA
kit

Abstract: The mechanisms underlying the loss of motor neuron axon integrity in amyotrophic lateral sclerosis (ALS) are unclear. SARM1 has been identified as a genetic risk variant in sporadic ALS, and the SARM1 protein is a key mediator of axon degeneration. To investigate the role of SARM1 in ALS-associated axon degeneration, we knocked out Sarm1 (Sarm1(KO)) in mSOD1(G93ATg) (mSOD1) mice. Animals were monitored for ALS disease onset and severity, with motor function assessed at pre-symptomatic and late-stage disease and lumbar spinal cord and sciatic nerve harvested for immunohistochemistry at endpoint (20 weeks). Serum was collected monthly to assess protein concentrations of biomarkers linked to axon degeneration (neurofilament light (NFL) and tau), and astrogliosis (glial fibrillary acidic protein (GFAP)), using single molecule array (Simoa®) technology. Overall, loss of Sarm1 in mSOD1 mice did not slow or delay symptom onset, failed to improve functional declines, and failed to protect motor neurons. Serum NFL levels in mSOD1 mice increased between 8 -12 and 16-20 weeks of age, with the later increase significantly reduced by loss of SARM1. Similarly, loss of SARM1 significantly reduced an increase in serum GFAP between 16 and 20 weeks of age in mSOD1 mice, indicating protection of both global axon degeneration and astrogliosis. In the spinal cord, Sarm1 deletion protected against loss of excitatory VGluT2-positive puncta and attenuated astrogliosis in mSOD1 mice. In the sciatic nerve, absence of SARM1 in mSOD1 mice restored the average area of phosphorylated neurofilament reactivity towards WT levels. Together these data suggest that Sarm1(KO) in mSOD1 mice is not sufficient to ameliorate functional decline or motor neuron loss but does alter serum biomarker levels and provide protection to axons and glutamatergic synapses. This indicates that treatments targeting SARM1 could warrant further investigation in ALS, potentially as part of a combination therapy.

Title: Amyloid-beta misfolding and GFAP predict risk of clinical Alzheimer's disease diagnosis within 17 years
Journal: Alzheimers Dement
Year: 2022
Epub Date: 20220719

Author: Beyer, L., Stocker, H., Rujescu, D., Holleczek, B., Stockmann, J., Nabers, A., Brenner, H. and Gerwert, K.

Keywords: Research article
Neurology
Alzheimer's disease

Simoa Bead
plasma N4PE kit
plasma pTau181V2 kit
HD-X

Abstract: INTRODUCTION: Blood-based biomarkers for Alzheimer's disease (AD) are urgently needed. Here, four plasma biomarkers were measured at baseline in a community-based cohort followed over 17 years, and the association with clinical AD risk was determined. METHODS: Amyloid beta (Aβ) misfolding status as a structure-based biomarker as well as phosphorylated tau 181 (P-tau181), glial fibrillary acidic protein (GFAP), and neurofilament light (NfL) concentration levels were determined at baseline in heparin plasma from 68 participants who were diagnosed with AD and 240 controls without dementia diagnosis throughout follow-up. RESULTS: Aβ misfolding exhibited high disease prediction accuracy of AD diagnosis within 17 years. Among the concentration markers, GFAP showed the best performance, followed by NfL and P-tau181. The combination of Aβ misfolding and GFAP increased the accuracy. DISCUSSION: Aβ misfolding and GFAP showed a strong ability to predict clinical AD risk and may be important early AD risk markers. Aβ misfolding illustrated its potential as a prescreening tool for AD risk stratification in older adults.

Title: Hepatic and renal function impact concentrations of plasma biomarkers of neuropathology
Journal: Alzheimers Dement (Amst)
Year: 2022
Epub Date: 20220712

Author: Berry, K., Asken, B. M., Grab, J. D., Chan, B., Lario Lago, A., Wong, R., Seetharaman, S., LaHue, S. C., Possin, K. L., Rojas, J. C., Kramer, J. H., Boxer, A. L., Lai, J. C. and VandeVrede, L.

Keywords: Research article
Neurology
cirrhosis
Simoa Bead
plasma pTau181 V2 kit
plasma N4PA (GFAP, UCHL-1, NfL, UCH-L1) kit
HD-X

Abstract: INTRODUCTION: The impact of hepatorenal function on plasma biomarkers of neuropathology is unknown. Herein, we measured several plasma biomarkers in patients with cirrhosis. METHODS: Plasma phosphorylated tau (p-tau181), neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), total tau (t-tau), and ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) were measured in 135 adults with cirrhosis and 22 healthy controls using Simoa. Within cirrhosis, associations between biomarkers and hepatorenal function were explored using linear regression. RESULTS: p-tau181, NfL, t-tau, and UCHL1 were increased 2- to 4-fold in cirrhosis, whereas GFAP was not increased. Within cirrhosis, creatinine moderately correlated with p-tau181 ($\beta = 0.75$, $P < .01$), NfL ($\beta = 0.32$, $P < .01$), and t-tau ($\beta = 0.31$, $P < .01$), but not GFAP ($\beta = -0.01$, $P = .88$) or UCHL1 ($\beta = -0.05$, $P = .60$), whereas albumin showed weak, inverse correlations: p-tau181 ($\beta = -0.18$, $P < .01$), NfL ($\beta = -0.22$, $P < .01$), GFAP ($\beta = -0.17$, $P < .05$), t-tau ($\beta = -0.20$, $P = .02$), and UCHL1 ($\beta = -0.15$, $P = .09$). CONCLUSIONS: Elevated p-tau181, NfL, and t-tau in cirrhosis were associated with renal impairment and hypoalbuminemia, suggesting that hepatorenal function may be important when interpreting plasma biomarkers of neuropathology.

Title: Sex differences in plasma p-tau181 associations with Alzheimer's disease biomarkers, cognitive decline, and clinical progression
Journal: Mol Psychiatry
Year: 2022
Epub Date: 20220629

Author: Tsiknia, A. A., Edland, S. D., Sundermann, E. E., Reas, E. T., Brewer, J. B., Galasko, D. and Banks, S. J.

Keywords: Research article
Neurology
Alzheimer's disease
Simoa Bead
plasma pTau181 homebrew
HD-X

Abstract: Studies have shown that women on the Alzheimer's disease (AD) continuum have more pathological tau in the brain and cerebrospinal fluid (CSF), than men. Some studies have found that higher levels of tau biomarkers are more strongly associated with clinical AD, cognitive decline and neurodegeneration in women than in men. Despite major developments in the use of plasma tau phosphorylated at threonine 181 (p-tau181) as an AD biomarker, it is unknown whether these sex differences apply to plasma p-tau181. In 1060 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants (47% women, 73.8 ± 7.6 years old), we examined sex differences in plasma p-tau181 levels and their association with other biomarkers, cognitive decline and incident AD. Linear regressions tested for an effect of sex on plasma p-tau181 levels and for plasma p-tau181 × sex interactions on CSF p-tau181, as well as entorhinal cortex tau, cortical amyloid-β (Aβ) deposition, and brain glucose metabolism, quantified using PET imaging. Linear mixed effects models tested for a sex × baseline plasma p-tau181 interaction on change in cognition over time. Finally, Cox models tested for a sex × plasma p-tau181 interaction on the risk of AD dementia in participants who were free of dementia at baseline. Despite similar plasma p-tau181 levels between sexes, women had lower brain glucose metabolism, greater brain Aβ and entorhinal cortex tau deposition, higher CSF p-tau181 and faster cognitive decline in relation to higher baseline plasma p-tau181 levels compared with men. Among Aβ positive, dementia-free participants, women had higher rates of incident AD dementia associated with increasing baseline plasma p-tau181 levels, relative to men. Our results suggest that sex may impact the clinical interpretation of plasma p-tau181 concentrations. If replicated, these findings could have important implications for the use of plasma p-tau181 as an accessible AD biomarker and screening tool for preventive and therapeutic clinical trials.

Title: Titrating the Translational Relevance of a Low-Level Repetitive Head Impact Model
Journal: Front Neurol
Year: 2022
Epub Date: 20220616

Author: Boucher, M. L., Conley, G., Nowlin, J., Qiu, J., Kawata, K., Bazarian, J. J., Meehan, W. P. and Mannix, R.

Keywords: Research article
Neurology
TBI
Simoa Bead
serum & cortical tissue lysate N2PB (GFAP, NfL) kit
serum & cortical tissue lysate mouse IL-1b, mouse IL-6 kit

Abstract: Recently, there has been increased attention in the scientific community to the phenomenon of sub-concussive impacts, those hits to the head that do not cause the signs and symptoms of a concussion. Some authors suggest that sub-concussive impacts may alter behavior and cognition, if sustained repetitively, but the mechanisms underlying these changes are not well-defined. Here, we adapt our well-established weight drop model of repetitive mild traumatic brain injury (rmTBI) to attempt to produce a model of low-level repetitive head impacts (RHI). The model was modified to eliminate differences in latency to right following impact and gross behavioral changes after a single cluster of hits. Further, we varied our model in terms of repetition of impact over a 4-h span to mimic the repeated sub-concussive impacts that may be experienced by an athlete within a single day of play. To understand the effects of a single cluster of RHIs, as well as the effect of an increased impact frequency within the cluster, we evaluated classical behavioral measures, serum biomarkers, cortical protein quantification, and immunohistochemistry both acutely and sub-acutely following the impacts. In the absence of gross behavioral changes, the impact protocol did generate pathology, in a dose-dependent fashion, in the brain. Evaluation of serum biomarkers revealed limited changes in GFAP and NF-L, which suggests that their diagnostic utility may not emerge until the exposure to low-level head impacts reaches a certain threshold. Robust decreases in both IL-1β and IL-6 were observed in the serum and the cortex, indicating downregulation of inflammatory pathways. These experiments yield initial data on pathology and biomarkers in a mouse model of low-level RHIs, with relevance to sports settings, providing a starting point for further exploration of the potential role of anti-inflammatory processes in low-level RHI outcomes, and how these markers may evolve with repeated exposure.

Title: Comparative analytical performance of multiple plasma Aβ42 and Aβ40 assays and their ability to predict positron emission tomography amyloid positivity
Journal: Alzheimers Dement
Year: 2022
Epub Date: 20220712

Author: Zicha, S., Bateman, R. J., Shaw, L. M., Zetterberg, H., Bannon, A. W., Horton, W. A., Baratta, M., Kolb, H. C., Dobler, I., Mordashova, Y., Saad, Z. S., Raunig, D. L., Spanakis, E. M., Li, Y., Schindler, S. E., Ferber, K., Rubel, C. E., Martone, R. L., Weber, C. J., Edelmayer, R. M., Meyers, E. A., Bollinger, J. G., Rosenbaugh, E. G. and Potter, W. Z.

Keywords: Research article
Neurology
Alzheimer's disease
Simoa Bead
plasma N4PE
plasma Abeta40, Abeta42

Abstract: INTRODUCTION: This report details the approach taken to providing a dataset allowing for analyses on the performance of recently developed assays of amyloid beta (Aβ) peptides in plasma and the extent to which they improve the prediction of amyloid positivity. METHODS: Alzheimer's Disease Neuroimaging Initiative plasma samples with corresponding amyloid positron emission tomography (PET) data were run on six plasma Aβ assays. Statistical tests were performed to determine whether the plasma Aβ measures significantly improved the area under the receiver operating characteristic curve for predicting amyloid PET status compared to age and apolipoprotein E (APOE) genotype. RESULTS: The age and APOE genotype model predicted amyloid status with an area under the curve (AUC) of 0.75. Three assays improved AUCs to 0.81, 0.81, and 0.84 ($P < .05$, uncorrected for multiple comparisons). DISCUSSION: Measurement of Aβ in plasma contributes to addressing the amyloid component of the ATN (amyloid/tau/neurodegeneration) framework and could be a first step before or in place of a PET or cerebrospinal fluid screening study. HIGHLIGHTS: The Foundation of the National Institutes of Health Biomarkers Consortium evaluated six plasma amyloid beta (Aβ) assays using Alzheimer's Disease Neuroimaging Initiative samples. Three assays improved prediction of amyloid status over age and apolipoprotein E (APOE) genotype. Plasma Aβ42/40 predicted amyloid positron emission tomography status better than Aβ42 or Aβ40 alone.

Title: Biochemical and clinical biomarkers in adult SMA 3-4 patients treated with nusinersen for 22 months
Journal: Ann Clin Transl Neurol
Year: 2022
Epub Date: 20220714

Author: De Wel, B., De Schaepdryver, M., Poesen, K. and Claeys, K. G.

Keywords: Research article
Neurology
spinal muscular atrophy (SMA)
Simoa Bead
serum, CSF NfL kit

Abstract: OBJECTIVE: To investigate biomarkers of disease progression in cerebrospinal fluid (CSF) and serum in adult patients with spinal muscular atrophy (SMA). Furthermore, we assess the clinical response to nusinersen treatment in adults with SMA over a longer follow-up period than the previously reported 6-14 months. METHODS: We included 16 adults with SMA type 3-4 for nusinersen treatment over 22 months in this prospective study. We evaluated chitotriosidase-1 (CHIT1) and chitinase-3-like protein 1 (YKL-40) as neuroinflammatory biomarkers in CSF, and neurofilament light chain (NfL) and heavy chain (pNfH) as neurodegenerative markers in CSF and serum at baseline, month 6, 14 and 22, together with a wide range of clinical outcome measures. RESULTS: Levels of CHIT1 increased significantly ($p = 0.048$) throughout the 22-month treatment period and pNfH decreased significantly ($p = 0.022$) in CSF, but both did not correlate with clinical outcome measures. YKL-40 correlated strongly with neurofilaments in CSF ($rho = 0.76$) and decreased significantly ($p = 0.037$) in patients with improvements in the revised upper limb module (RULM). Finally, patients showed significant improvements in hand grip strength, hand motor function, medical research council (MRC) sum score, and peak expiratory flow (PEF) after 22 months of treatment. INTERPRETATION: YKL-40 in CSF correlated with clinical improvements during nusinersen treatment. In contrast, CHIT1 and pNfH in CSF changed significantly during treatment but did not correlate with clinical outcomes. Finally, we demonstrated a

sustained clinical effect of nusinersen treatment in adults after 22 months.

Title: Establishment of reference values for plasma neurofilament light based on healthy individuals aged 5-90 years
Journal: Brain Commun
Year: 2022
Epub Date: 20220704

Author: Simrén, J., Andreasson, U., Gobom, J., Suarez Calvet, M., Borroni, B., Gillberg, C., Nyberg, L., Ghidoni, R., Fernell, E., Johnson, M., Depypere, H., Hansson, C., Jonsdottir, I. H., Zetterberg, H. and Blennow, K.

Keywords: Research article
Neurology
healthy reference values
Simoa Bead
plasma, serum NfL
kit
HD-X, HD-1

Abstract: The recent development of assays that accurately quantify neurofilament light, a neuronal cytoskeleton protein, in plasma has generated a vast literature supporting that it is a sensitive, dynamic, and robust biomarker of neuroaxonal damage. As a result, efforts are now made to introduce plasma neurofilament light into clinical routine practice, making it an easily accessible complement to its cerebrospinal fluid counterpart. An increasing literature supports the use of plasma neurofilament light in differentiating neurodegenerative diseases from their non-neurodegenerative mimics and suggests it is a valuable biomarker for the evaluation of the effect of putative disease-modifying treatments (e.g. in multiple sclerosis). More contexts of use will likely emerge over the coming years. However, to assist clinical interpretation of laboratory test values, it is crucial to establish normal reference intervals. In this study, we sought to derive reliable cut-offs by pooling quantified plasma neurofilament light in neurologically healthy participants (5-90 years) from eight cohorts. A strong relationship between age and plasma neurofilament light prompted us to define the following age-partitioned reference limits (upper 95(th) percentile in each age category): 5-17 years = 7 pg/mL; 18-50 years = 10 pg/mL; 51-60 years = 15 pg/mL; 61-70 years = 20 pg/mL; 70 + years = 35 pg/mL. The established reference limits across the lifespan will aid the introduction of plasma neurofilament light into clinical routine, and thereby contribute to diagnostics and disease-monitoring in neurological practice.

Title: Detection of Brain Tau Pathology in Down Syndrome Using Plasma Biomarkers
Journal: JAMA Neurol
Year: 2022
Epub Date: 20220705

Author: Janelidze, S., Christian, B. T., Price, J., Laymon, C., Schupf, N., Klunk, W. E., Lott, I., Silverman, W., Rosas, H. D., Zaman, S., Mapstone, M., Lai, F., Ances, B. M., Handen, B. L. and Hansson, O.

Keywords: Research article
Neurology
Alzheimer's disease
Simoa Bead
plasma GFAP kit
Plasma Abeta42. Abeta40, NfL, tau kit

Abstract: IMPORTANCE: Novel plasma biomarkers, especially phosphorylated tau (p-tau), can detect brain tau aggregates in Alzheimer disease. OBJECTIVE: To determine which plasma biomarker combinations can accurately detect tau pathological brain changes in Down syndrome (DS). DESIGN, SETTING, AND PARTICIPANTS: The cross-sectional, multicenter Alzheimer's Biomarker Consortium-Down Syndrome study included adults with DS and a control group of siblings without DS. All participants with plasma, positron emission tomography (PET), and cognitive measures available by the time of data freeze 1.0 were included. Participants were enrolled between 2016 and 2019, and data were analyzed from August 2021 to April 2022. EXPOSURES: Plasma p-tau217, glial fibrillary acidic protein (GFAP), amyloid β42/40 (Aβ42/Aβ40), neurofilament light (NfL), and total tau (t-tau); tau positron emission tomography (tau-PET) and Aβ-PET. MAIN OUTCOMES AND MEASURES: The primary outcome was tau-PET status. Secondary outcomes included Aβ-PET status and cognitive performance. RESULTS: Among 300 participants with DS and a control group of 37 non-DS siblings, mean (SD) age was 45.0 (10.1) years, and 167 (49.6%) were men. Among participants with DS who all underwent plasma p-tau217 and GFAP analyses, 258 had other plasma biomarker data available and 119, 213, and 288 participants had tau-PET, Aβ-PET, and cognitive assessments, respectively. Plasma p-tau217 and t-tau were significantly increased in Aβ-PET-positive tau-PET-positive (A+T+) DS and A+T- DS compared with A-T- DS while GFAP was only increased in A+T+ DS. Plasma p-tau217 levels were also significantly higher in A+T+ DS than A+T- DS. In participants with DS, plasma p-tau217 and GFAP (but not other plasma biomarkers) were consistently associated with abnormal tau-PET and Aβ-PET status in models covaried for age (odds ratio range, 1.59 [95% CI, 1.05-2.40] to 2.32 [95% CI, 1.36-3.96]; P < .03). A combination of p-tau217 and age performed best when detecting tau-PET abnormality in temporal and neocortical regions (area under the curve [AUC] range, 0.96-0.99). The most parsimonious model for Aβ-PET status included p-tau217, t-tau, and age (AUC range, 0.93-0.95). In multivariable models, higher p-tau217 levels but not other biomarkers were associated with worse performance on DS Mental Status Examination (β, -0.24, 95% CI, -0.36 to -0.12; P < .001) and Cued Recall Test (β, -0.40; 95% CI, -0.53 to -0.26; P < .001). CONCLUSIONS AND RELEVANCE: Plasma p-tau217 is a very accurate blood-based biomarker of both tau and Aβ pathological brain changes in DS that could help guide screening and enrichment strategies for inclusion of individuals with DS in future AD clinical trials, especially when it is combined with age as a covariate.

Title: Plasma Neurofilament Light Chain Is Associated with Cognitive Impairment after Posterior Circulation Stroke
Journal: Evidence-Based Complementary and Alternative Medicine
Year: 2022
Date: 2022/06/28

Author: Jiang, Lianyan, Wang, Zhiqiang, Wang, Rongyu, Li, Mao, Zhang, Yaodan and Yang, Dongdong

Keywords: Research article
Neurology
Stroke

Simoa Bead
plasma NfL
China

Abstract: Background: Neurofilament light chain (NfL) is a biomarker for large-caliber axonal degeneration in the subcortex. The purpose of this research was to examine the relationship between plasma neurofilament light chain (pNfL) and cognitive impairment following a posterior circulation stroke. Methods: Patients over the age of 18 with their first-ever acute ischemic stroke (AIS) of the posterior cerebral circulation within 24h of symptom onset were included from July 1, 2017, to December 31, 2019. Blood samples were collected within 48h after the stroke. The Montreal Cognitive Assessment (MOCA) (MOCA<26) was adopted to define poststroke cognitive impairment (PSCI) 90 days after stroke onset. Results: A total of 264 patients were analyzed in this research 101 (38.30%) patients were clinically diagnosed with PSCI. The PNfL concentration was significantly higher in the PSCI group compared with the non-PSCI group (p<0.001). The pNfL concentration (OR 1.044; p<0.001) remained to be a significant predictor for PSCI after a multivariable logistic regression analysis, even after adjusting for factors including age, sex, education background (OR 1.044; p<0.001), baseline NIHSS, infarct volume, and TOAST classification (OR 1.035; p<0.001). The diagnostic efficacy of pNfL concentration for PSCI was then explored with a ROC analysis. The optimum pNfL concentration threshold was 38.12 pg/ml, with a sensitivity of 78.20%, a specificity of 66.9% and an AUC of 0.782 (p<0.001). Conclusion: This research showed that pNfL concentration, independent of established conventional risk factors, could predict the cognitive impairment in 90 days following posterior circulation stroke.

Title: Promising Blood Biomarkers for Clinical Use in Alzheimer's Disease: A Focused Update
Journal: J Clin Neurol
Year: 2022

Author: Park, S. A., Jang, Y. J., Kim, M. K., Lee, S. M. and Moon, S. Y.

Keywords: Review
Neurology
Alzheimer's disease
Simoa Bead

Abstract: Alzheimer's disease (AD) is the most-common cause of neurodegenerative dementia, and it is characterized by abnormal amyloid and tau accumulation, which indicates neurodegeneration. AD has mostly been diagnosed clinically. However, ligand-specific positron emission tomography (PET) imaging, such as amyloid PET, and cerebrospinal fluid (CSF) biomarkers are needed to accurately diagnose AD, since they supplement the shortcomings of clinical diagnoses. Using biomarkers that represent the pathology of AD is essential (particularly when disease-modifying treatment is available) to identify the corresponding pathology of targeted therapy and for monitoring the treatment response. Although imaging and CSF biomarkers are useful, their widespread use is restricted by their high cost and the discomfort during the lumbar puncture, respectively. Recent advances in AD blood biomarkers shed light on their future use for clinical purposes. The amyloid β (Aβ)42/Aβ40 ratio and the concentrations of phosphorylated tau at threonine 181 and at threonine 217, and of neurofilament light in the blood were found to represent the pathology of Aβ, tau, and neurodegeneration in the brain when using automatic electrochemiluminescence technologies, single-molecule arrays, immunoprecipitation coupled with

mass spectrometry, etc. These blood biomarkers are imminently expected to be incorporated into clinical practice to predict, diagnose, and determine the stage of AD. In this review we focus on advancements in the measurement technologies for blood biomarkers and the promising biomarkers that are approaching clinical application. We also discuss the current limitations, the needed further investigations, and the perspectives on their use.

Title: Potential association of bone mineral density loss with cognitive impairment and central and peripheral amyloid-β changes: a cross-sectional study
Journal: BMC Musculoskelet Disord
Year: 2022
Epub Date: 20220630

Author: Zhang, P., Zhou, Y., Chen, G., Li, J., Wang, B. and Lu, X.

Keywords: Research article
Neurology
Cognitive impairment
Simoa Bead
plasma N3PA (Abeta40, Abeta42, tau)
HD-1
China

Abstract: BACKGROUND: There is some evidence in the literature that older adults with cognitive impairments have a higher risk for falls and osteoporotic hip fractures. Currently, the associations between bone health and cognitive health have not been extensively studied. Thus, the present cross-sectional study aims to investigate the relationship between markers of bone loss and cognitive performance in older adults with and without osteopenia as well as older adults with cognitive impairments (i.e., Alzheimer's disease [AD]). METHODS: Sixty-two non-osteopenia participants and one hundred three osteopenia participants as the cohort 1 and 33 cognitively normal non-AD participants and 39 AD participants as the cohort 2 were recruited. To assess cognitive and bone health, hip bone mineral density (BMD) and cognitive performance (via Minimal Mental State Examination [MMSE] and/or Auditory Verbal Learning Test-delayed recall [AVLT-DR]) were assessed. Furthermore, in cohort 1, plasma amyloid-β (Aβ) levels, and in cohort 2, cerebrospinal fluid (CSF) Aβ levels were determined. RESULTS: We observed that (1) compared with non-osteopenia participants, BMD values ($t = -22.806$; 95%CI: - 1.801, - 1.484; $p < 0.001$), MMSE scores ($t = -5.392$; 95%CI: - 3.260, - 1.698; $p < 0.001$), and AVLT-DR scores ($t = -4.142$; 95%CI: - 2.181, - 0.804; $p < 0.001$), plasma Aβ42 levels ($t = -2.821$; 95%CI: - 1.737, - 0.305; $p = 0.01$), and Aβ42/40 ratio ($t = -2.020$; 95%CI: - 0.009, - 0.001; $p = 0.04$) were significantly lower in osteopenia participants; (2) plasma Aβ42/40 ratio showed a mediate effect for the association between BMD values and the performance of cognitive function in osteopenia participants by mediation analysis, adjusting age, sex, years of education, and body mass index (BMI); (3) BMD values (95%CI: - 1.085, 0.478; $p < 0.001$) were significantly reduced in AD participants as compared with cognitively normal non-AD participants; (4) in AD participants, the interactive effects of BMD and CSF Aβ42/40 ratio on MMSE scores was found by regression analysis, controlling age, sex, years of education, and BMI; (5) BMD can distinguish AD participants from cognitively normal non-AD participants with AUC of 0.816 and distinguish participants with the cognitive impairment from cognitively normal participants with AUC of 0.794. CONCLUSION: Our findings suggest a relationship between bone health and cognitive health. Given the correlations between BMD and important markers of cognitive health (e.g., central

and peripheral pathological change of Aβ), BMD might serve as a promising and easy-accessible biomarker. However, more research is needed to further substantiate our findings.

Title: Epitope alteration by small molecules and applications in drug discovery
Journal: Chemical Science
Year: 2022

Author: Zhu, Biyue, Yang, Jing, Van, Richard, Yang, Fan, Yu, Yue, Yu, Astra, Ran, Kathleen, Yin, Keyi, Liang, Yingxia, Shen, Xunuo, Yin, Wei, Choi, Se Hoon, Lu, Ying, Wang, Changning, Shao, Yihan, Shi, Liang, Tanzi, Rudolph E., Zhang, Can, Cheng, Yan, Zhang, Zhirong and Ran, Chongzhao

Keywords: Research article
Technology
Simoa Bead

Abstract: Small molecules and antibodies are normally considered separately in drug discovery, except in the case of covalent conjugates. We unexpectedly discovered several small molecules that could inhibit or enhance antibody–epitope interactions which opens new possibilities in drug discovery and therapeutic modulation of auto-antibodies. We first discovered a small molecule, CRANAD-17, that enhanced the binding of an antibody to amyloid beta (Aβ), one of the major hallmarks of Alzheimer's disease, by stable triplex formation. Next, we found several small molecules that altered antibody–epitope interactions of tau and PD-L1 proteins, demonstrating the generality of this phenomenon. We report a new screening technology for ligand discovery, screening platform based on epitope alteration for drug discovery (SPEED), which is label-free for both the antibody and small molecule. SPEED, applied to an Aβ antibody, led to the discovery of a small molecule, GNF5837, that inhibits Aβ aggregation and another, obatoclax, that binds Aβ plaques and can serve as a fluorescent reporter in brain slices of AD mice. We also found a small molecule that altered the binding between Aβ and auto-antibodies from AD patient serum. SPEED reveals the sensitivity of antibody–epitope interactions to perturbation by small molecules and will have multiple applications in biotechnology and drug discovery.

Title: A point-prevalence study on community and inpatient Clostridioides difficile infections (CDI): results from Combatting Bacterial Resistance in Europe CDI (COMBACTE-CDI), July to November 2018
Journal: Euro Surveill
Year: 2022

Author: Viprey, V. F., Davis, G. L., Benson, A. D., Ewin, D., Spittal, W., Vernon, J. J., Rupnik, M., Banz, A., Allantaz, F., Cleuziat, P., Wilcox, M. H. and Davies, K. A.

Keywords: Research article
Infectious disease
Clostridioides difficile
Simoa Bead
fecal C. difficile toxin A, Toxin B homebrew

Abstract: Background: There is a paucity of data on community-based Clostridioides difficile infection (CDI) and how these compare with inpatient CDI. Aim: To compare data on the populations with CDI in

hospitals vs the community across 12 European countries. Methods: For this point-prevalence study (July-November 2018), testing sites sent residual diagnostic material on sampling days to a coordinating laboratory for CDI testing and PCR ribotyping (n = 3,163). Information on whether CDI testing was requested at the original site was used to identify undiagnosed CDI. We used medical records to identify differences between healthcare settings in patient demographics and risk factors for detection of C. difficile with or without free toxin. Results: The CDI positivity rate was 4.4% (country range: 0-16.2) in hospital samples, and 1.3% (country range: 0-2.2%) in community samples. The highest prevalence of toxinotype IIIb (027, 181 and 176) was seen in eastern European countries (56%; 43/77), the region with the lowest testing rate (58%; 164/281). Different predisposing risk factors were observed (use of broad-spectrum penicillins in the community (OR: 8.09 (1.9-35.6), p = 0.01); fluoroquinolones/cephalosporins in hospitals (OR: 2.2 (1.2-4.3), p = 0.01; OR: 2.0 (1.1-3.7), p = 0.02)). Half of community CDI cases were undetected because of absence of clinical suspicion, accounting for three times more undiagnosed adults in the community compared with hospitals (ca 111,000 vs 37,000 cases/year in Europe). Conclusion: These findings support recommendations for improving diagnosis in patients presenting with diarrhoea in the community, to guide good practice to limit the spread of CDI.

Title: Phase 3, multicentre, randomised, placebo-controlled study evaluating the efficacy and safety of ustekinumab in patients with systemic lupus erythematosus
Journal: Ann Rheum Dis
Year: 2022
Epub Date: 20220707

Author: van Vollenhoven, R. F., Kalunian, K. C., Dörner, T., Hahn, B. H., Tanaka, Y., Gordon, R. M., Shu, C., Fei, K., Gao, S., Seridi, L., Gallagher, P., Lo, K. H., Berry, P. and Zuraw, Q. C.

Keywords: Research article
Inflammation
systemic lupus erythematosus (SLE)
Simoa Bead
serum IFNa

Abstract: OBJECTIVE: Evaluate the efficacy and safety of ustekinumab, an anti-interleukin-12/23 p40 antibody, in a phase 3, randomised, placebo-controlled study of patients with active systemic lupus erythematosus (SLE) despite receiving standard-of-care. METHODS: Active SLE patients (SLE Disease Activity Index 2000 (SLEDAI-2K) ≥6 during screening and SLEDAI-2K ≥4 for clinical features at week 0) despite receiving oral glucocorticoids, antimalarials, or immunomodulatory drugs were randomised (3:2) to receive ustekinumab (intravenous infusion ~6 mg/kg at week 0, followed by subcutaneous injections of ustekinumab 90 mg at week 8 and every 8 weeks) or placebo through week 48. The primary endpoint was SLE Responder Index (SRI)-4 at week 52, and major secondary endpoints included time to flare through week 52 and SRI-4 at week 24. RESULTS: At baseline, 516 patients were randomised to placebo (n=208) or ustekinumab (n=308). Following the planned interim analysis, the sponsor discontinued the study due to lack of efficacy but no safety concerns. Efficacy analyses included 289 patients (placebo, n=116; ustekinumab, n=173) who completed or would have had a week 52 visit at study discontinuation. At week 52, 44% of ustekinumab patients and 56% of placebo patients had an SRI-4 response; there were no appreciable differences between the treatment groups in the major secondary endpoints. Through week 52, 28% of ustekinumab patients and 32% of placebo patients had a British Isles Lupus Assessment Group flare, with a mean time to first flare of 204.7 and 200.4 days, respectively. Through

week 52, 70% of ustekinumab patients and 74% of placebo patients had ≥1 adverse event. CONCLUSIONS: Ustekinumab did not demonstrate superiority over placebo in this population of adults with active SLE; adverse events were consistent with the known safety profile of ustekinumab. TRIAL REGISTRATION NUMBER: NCT03517722.

Title: Improved prediction of early cognitive impairment in multiple sclerosis combining blood and imaging biomarkers
Journal: Brain Commun
Year: 2022
Epub Date: 20220708

Author: Brummer, T., Muthuraman, M., Steffen, F., Uphaus, T., Minch, L., Person, M., Zipp, F., Groppa, S., Bittner, S. and Fleischer, V.

Keywords: Research article
Neurology
multiple sclerosis
Simoa Bead
serum NfL
kit
HD-1

Abstract: Disability in multiple sclerosis is generally classified by sensory and motor symptoms, yet cognitive impairment has been identified as a frequent manifestation already in the early disease stages. Imaging- and more recently blood-based biomarkers have become increasingly important for understanding cognitive decline associated with multiple sclerosis. Thus, we sought to determine the prognostic utility of serum neurofilament light chain levels alone and in combination with MRI markers by examining their ability to predict cognitive impairment in early multiple sclerosis. A comprehensive and detailed assessment of 152 early multiple sclerosis patients (Expanded Disability Status Scale: 1.3 ± 1.2, mean age: 33.0 ± 10.0 years) was performed, which included serum neurofilament light chain measurement, MRI markers (i.e. T(2)-hyperintense lesion volume and grey matter volume) acquisition and completion of a set of cognitive tests (Symbol Digits Modalities Test, Paced Auditory Serial Addition Test, Verbal Learning and Memory Test) and mood questionnaires (Hospital Anxiety and Depression scale, Fatigue Scale for Motor and Cognitive Functions). Support vector regression, a branch of unsupervised machine learning, was applied to test serum neurofilament light chain and combination models of biomarkers for the prediction of neuropsychological test performance. The support vector regression results were validated in a replication cohort of 101 early multiple sclerosis patients (Expanded Disability Status Scale: 1.1 ± 1.2, mean age: 34.4 ± 10.6 years). Higher serum neurofilament light chain levels were associated with worse Symbol Digits Modalities Test scores after adjusting for age, sex Expanded Disability Status Scale, disease duration and disease-modifying therapy (B = -0.561; SE = 0.192; P = 0.004; 95% CI = -0.940 to -0.182). Besides this association, serum neurofilament light chain levels were not linked to any other cognitive or mood measures (all P-values > 0.05). The tripartite combination of serum neurofilament light chain levels, lesion volume and grey matter volume showed a cross-validated accuracy of 88.7% (90.8% in the replication cohort) in predicting Symbol Digits Modalities Test performance in the support vector regression approach, and outperformed each single biomarker (accuracy range: 68.6-75.6% and 68.9-77.8% in the replication cohort), as well as the dual biomarker combinations (accuracy range: 71.8-82.3% and 72.6-85.6% in the replication cohort). Taken

together, early neuro-axonal loss reflects worse information processing speed, the key deficit underlying cognitive dysfunction in multiple sclerosis. Our findings demonstrate that combining blood and imaging measures improves the accuracy of predicting cognitive impairment, highlighting the clinical utility of cross-modal biomarkers in multiple sclerosis.

Title: Association of Plasma and Electroencephalography Markers With Motor Subtypes of Parkinson's Disease
Journal: Front Aging Neurosci
Year: 2022
Epub Date: 20220712

Author: Yang, X., Li, Z., Bai, L., Shen, X., Wang, F., Han, X., Zhang, R., Li, Z., Zhang, J., Dong, M., Wang, Y., Cao, T., Zhao, S., Chu, C., Liu, C. and Zhu, X.

Keywords: Research article
Neurology
Parkinson’s disease
Simoa Bead
plasma NfL, a-syn, N3PA (Abeta40, Abeta42, tau) kit
China

Abstract: OBJECTIVE: The aim of this study was to investigate the correlations of plasma neurodegenerative proteins and electroencephalography (EEG) dynamic functional network (DFN) parameters with disease progression in early Parkinson's disease (PD) with different motor subtypes, including tremor-dominant (TD) and postural instability and gait disorder (PIGD). METHODS: In our study, 33 patients with PD (21 TD and 12 PIGD) and 33 healthy controls (HCs) were enrolled. Plasma neurofilament light chain (NfL), α-synuclein (α-syn), total-tau (t-tau), β-amyloid 42 (Aβ42), and β-amyloid 40 (Aβ40) levels were measured using an ultrasensitive single-molecule array (Simoa) immunoassay. All the patients with PD underwent EEG quantified by DFN analysis. The motor and non-motor performances were evaluated by a series of clinical assessments. Subsequently, a correlation analysis of plasma biomarkers and EEG measures with clinical scales was conducted. RESULTS: In the TD group, plasma NfL exhibited a significant association with MDS-UPDRS III and Montreal Cognitive Assessment (MoCA). A higher Aβ42/40 level was significantly related to a decrease in Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) in the PIGD group. In terms of the correlation between EEG characteristic parameters and clinical outcomes, trapping time (TT) delta was positively correlated with MDS-UPDRS III and MoCA scores in the TD group, especially in the prefrontal and frontal regions. For other non-motor symptoms, there were significant direct associations of k (PLI) theta with HAMD and HAMA, especially in the prefrontal region, and k (PLI) gamma was particularly correlated with Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire (RBDSQ) scores in the prefrontal, frontal, and parietal regions in the TD group. Furthermore, there was a significant positive correlation between plasma t-tau and k (PLI) , and pairwise correlations were found among plasma NfL, theta TT, and MoCA scores in the TD group. CONCLUSION: These results provide evidence that plasma neurodegenerative proteins and EEG measures have great potential in predicting the disease progression of PD subtypes, especially for the TD subtype. A combination of these two kinds of markers may have a superposition effect on monitoring and estimating the prognosis of PD subtypes and deserves further research in larger, follow-up PD cohorts.

Title: Serum glial fibrillary acidic protein (GFAP) predicts outcome after intracerebral and subarachnoid hemorrhage
Journal: Neurol Sci
Year: 2022
Epub Date: 20220727

Author: Gyldenholm, T., Hvas, C. L., Hvas, A. M. and Hviid, C. V. B.

Keywords: Research article
Neurology
subarachnoid hemorrhage
Simoa Bead
GFAP

Abstract: BACKGROUND AND PURPOSE: Intracerebral and subarachnoid hemorrhage are critical conditions with a high mortality, and the outcome for the individual patient is notoriously difficult to predict. Biomarkers that reflect disease severity and predict outcome are therefore warranted. METHODS: Blood samples from 40 patients with intracerebral, 46 patients with subarachnoid hemorrhage, and 70 healthy individuals were collected. Levels of glial fibrillary acidic protein (GFAP) and neuroglobin were measured by ultra-sensitive single molecule array and enzyme-linked immunosorbent assay, respectively. Clinical information including mortality and functional outcome was recorded. RESULTS: Blood levels of GFAP and neuroglobin in intracerebral and subarachnoid hemorrhage patients were significantly elevated when compared to healthy individuals (all $p < 0.0001$). GFAP levels were significantly higher in patients dying or with poor functional outcome than in healthy individuals (all $p \leq 0.01$). GFAP levels separated survivors from non-survivors with an area under receiver operating characteristics (AUROC) = 0.78 (confidence interval (CI) 0.59-0.98) for intracerebral hemorrhage and 0.82 (CI 0.69-0.94) for subarachnoid hemorrhage patients. The Akaike and Bayesian information criteria (AIC/BIC) for mortality/poor outcome prediction improved when combining GFAP levels with hematoma volume ($p = 0.04/p < 0.01$), National Institutes of Health Stroke Scale (NIHSS) ($p = 0.09/p < 0.01$), Hunt-Hess ($p < 0.05/p = 0.21$), or Fischer score ($p < 0.05/p = 0.02$). CONCLUSIONS: Elevated GFAP levels at admission to hospital predicted mortality and poor outcome in our cohort of intracerebral and subarachnoid hemorrhage patients. Neuroglobin levels did not provide additional information. Combining GFAP measurements with clinical disease severity scores increased outcome prediction precision. This may suggest that GFAP measurement could improve prognostication in patients with intracerebral or subarachnoid hemorrhage. REGISTRATION: This sub-trial was not registered.

Title: Serum assessment of traumatic axonal injury: the correlation of GFAP, t-Tau, UCH-L1, and NfL levels with diffusion tensor imaging metrics and its prognosis utility
Journal: J Neurosurg
Year: 2022
Epub Date: 20220715

Author: Castaño-Leon, A. M., Sánchez Carabias, C., Hilario, A., Ramos, A., Navarro-Main, B., Paredes, I., Munarriz, P. M., Panero, I., Eiriz Fernández, C., García-Pérez, D., Moreno-Gomez, L. M., Esteban-Sinovas, O., Garcia Posadas, G., Gomez, P. A. and Lagares, A.

Keywords: Research article
Neurology
TBI
Simoa Bead
serum N4PA
HD-1

Abstract: OBJECTIVE: Diagnosis of traumatic axonal injury (TAI) is challenging because of its underestimation by conventional MRI and the technical requirements associated with the processing of diffusion tensor imaging (DTI). Serum biomarkers seem to be able to identify patients with abnormal CT scanning findings, but their potential role to assess TAI has seldomly been explored. METHODS: Patients with all severities of traumatic brain injury (TBI) were prospectively included in this study between 2016 and 2021. They underwent blood extraction within 24 hours after injury and imaging assessment, including DTI. Serum concentrations of glial fibrillary acidic protein, total microtubule-associated protein (t-Tau), ubiquitin C-terminal hydrolase L1 (UCH-L1), and neurofilament light chain (NfL) were measured using an ultrasensitive Simoa multiplex assay panel, a digital form of enzyme-linked immunosorbent assay. The Glasgow Outcome Scale-Extended score was determined at 6 months after TBI. The relationships between biomarker concentrations, volumetric analysis of corpus callosum (CC) lesions, and fractional anisotropy (FA) were analyzed by nonparametric tests. The prognostic utility of the biomarker was determined by calculating the C-statistic and an ordinal regression analysis. RESULTS: A total of 87 patients were included. Concentrations of all biomarkers were significantly higher for patients compared with controls. Although the concentration of the biomarkers was affected by the presence of mass lesions, FA of the CC was an independent factor influencing levels of UCH-L1 and NfL, which positioned these two biomarkers as better surrogates of TAI. Biomarkers also performed well in determining patients who would have had unfavorable outcome. NfL and the FA of the CC are independent complementary factors related to outcome. CONCLUSIONS: UCH-L1 and NfL seem to be the biomarkers more specific to detect TAI. The concentration of NfL combined with the FA of the CC might help predict long-term outcome.

Title: Lifestyle factors in multiple sclerosis disability progression and silent brain damage: A cross-sectional study
Journal: Multiple Sclerosis and Related Disorders
Year: 2022
Date: 2022/09/01/

Author: Van Hijfte, Liesbeth, Loret, Griet, Bachmann, Helen, Reynders, Tatjana, Breuls, Marleen, Deschepper, Ellen, Kuhle, Jens, Willekens, Barbara and Laureys, Guy

Keywords: Research article
Neurology
Multiple sclerosis
Simoa Bead
serum NfL

Abstract: Objective To determine the association between lifestyle risk factors with 1/ the Multiple Sclerosis Severity Score (MSSS) and 2/ ongoing subclinical brain damage in non-active MS patients on high-efficacy treatment. Methods Cross-sectional study in persons with Multiple Sclerosis (PwMS)

investigating lifestyle factors including cognitive reserve (CR), physical activity (PA), smoking status, alcohol use, dietary habits, body mass index (BMI), blood pressure (BP) and cholesterol ratio. Data were collected through validated questionnaires, clinical and laboratory examination. Serum Neurofilament light chain (sNfL) levels were used as a proxy for ongoing brain damage in a subgroup of persons with non-active MS on high-efficacy treatment. Multiple regression analysis (MRA) models explored the relationship between lifestyle factors with the MSSS score and sNfL. Results 351 PwMS were included (43.04 ± 11.77 years, 69.8% female). Higher CR and PA were associated with a lower MSSS; overweight or obesity and higher systolic BP with a higher MSSS. The MRA model explained 22.2% of the variance for MSSS (R^2.255, adjusted R^2.222). Higher BMI and BP were related to lower sNfL. Twenty-3% (R^2.279, adjusted R^2.230) of the variance was explained in the MRA model for sNfL. Conclusion Our study suggests an association between a 'brain healthy lifestyle' with disability progression in MS. A cognitive and physical active lifestyle alongside a normal body weight and blood pressure may help to prevent future disability in MS. Longitudinal and interventional research is necessary to gain insight in the causal pathway of these risk factors in preventing disability progression in MS.

Title: Stool Toxin Concentration Does Not Distinguish Clostridioides difficile Infection from Colonization in Children Less Than 3 Years of Age
Journal: Journal of the Pediatric Infectious Diseases Society
Year: 2022

Author: Sandora, Thomas J, Williams, David N, Daugherty, Kaitlyn, Geer, Christine, Cuddemi, Christine, Kociolek, Larry K, Chen, Xinhua, Xu, Hua, Savage, Timothy J, Banz, Alice, Garey, Kevin W, Gonzales-Luna, Anne J, Kelly, Ciarán P and Pollock, Nira R

Keywords: Research article
Infectious disease
C. difficile
Simoa Bead
fecal C. difficile toxin A, Toxin B homebrew

Abstract: In a prospective cohort study, stools from children <3 years with and without diarrhea who were Clostridioides difficile nucleic acid amplification test-positive underwent ultrasensitive and quantitative toxin measurement. Among 37 cases and 46 controls, toxin concentration distributions overlapped substantially. Toxin concentration alone does not distinguish C. difficile infection from colonization in young children.

Title: Blood-based Aβ42 increases in the earliest pre-pathological stage before decreasing with progressive amyloid pathology in preclinical models and human subjects: opening new avenues for prevention
Journal: Acta Neuropathologica
Year: 2022
Date: 2022/07/07

Author: Botella Lucena, Pablo, Vanherle, Sarah, Lodder, Chritica, Gutiérrez de Ravé, Manuel, Stancu, Ilie-Cosmin, Lambrichts, Ivo, Vangheluwe, Riet, Bruffaerts, Rose and Dewachter, Ilse

Keywords: Research article
Neurology
Alzheimer's disease
Simoa Bead
plasma N3PA (Abeta40, Abeta42, tau)
SR-X

Abstract: Blood-based (BB) biomarkers for Aβ and tau can indicate pathological processes in the brain, in the early pathological, even pre-symptomatic stages in Alzheimer's disease. However, the relation between BB biomarkers and AD-related processes in the brain in the earliest pre-pathology stage before amyloid pathology develops, and their relation with total brain concentrations of Aβ and tau, is poorly understood. This stage presents a critical window for the earliest prevention of AD. Preclinical models with well-defined temporal progression to robust amyloid and tau pathology provide a unique opportunity to study this relation and were used here to study the link between BB biomarkers with AD-related processes in pre- and pathological stages. We performed a cross-sectional study at different ages assessing the link between BB concentrations and AD-related processes in the brain. This was complemented with a longitudinal analysis and with analysis of age-related changes in a small cohort of human subjects. We found that BB-tau concentrations increased in serum, correlating with progressive development of tau pathology and with increasing tau aggregates and p-tau concentrations in brain in TauP301S mice (PS19) developing tauopathy. BB-Aβ42 concentrations in serum decreased between 4.5 and 9 months of age, correlating with the progressive development of robust amyloid pathology in APP/PS1 (5xFAD) mice, in line with previous findings. Most importantly, BB-Aβ42 concentrations significantly increased between 1.5 and 4.5 months, i.e., in the earliest pre-pathological stage, before robust amyloid pathology develops in the brain, indicating biphasic BB-Aβ42 dynamics. Furthermore, increasing BB-Aβ42 in the pre-pathological phase, strongly correlated with increasing Aβ42 concentrations in brain. Our subsequent longitudinal analysis of BB-Aβ42 in 5xFAD mice, confirmed biphasic BB-Aβ42, with an initial increase, before decreasing with progressive robust pathology. Furthermore, in human samples, BB-Aβ42 concentrations were significantly higher in old (> 60 years) compared to young (< 50 years) subjects, as well as to age-matched AD patients, further supporting age-dependent increase of Aβ42 concentrations in the earliest pre-pathological phase, before amyloid pathology. Also BB-Aβ40 concentrations were found to increase in the earliest pre-pathological phase both in preclinical models and human subjects, while subsequent significantly decreasing concentrations in the pathological phase were characteristic for BB-Aβ42. Together our data indicate that BB biomarkers reflect pathological processes in brain of preclinical models with amyloid and tau pathology, both in the pathological and pre-pathological phase. Our data indicate a biphasic pattern of BB-Aβ42 in preclinical models and a human cohort. And most importantly, we here show that BB-Aβ increased and correlated with increasing concentrations of Aβ in the brain, in the earliest pre-pathological stage in a preclinical model. Our data thereby identify a novel critical window for prevention, using BB-Aβ as marker for accumulating Aβ in the brain, in the earliest pre-pathological stage, opening new avenues for personalized early preventive strategies against AD, even before amyloid pathology develops.

Title: Inflammatory biomarkers, multi-morbidity, and biologic aging
Journal: Journal of International Medical Research
Year: 2022

Author: St. Sauver, Jennifer, Rocca, Walter, LeBrasseur, Nathan, Chamberlain, Alanna, Olson, Janet, Jacobson, Debra, McGree, Michaela and Mielke, Michelle

Keywords: Research article
Inflammation
aging
Simoa Bead
plasma IL-6, IL-10, TNFa
HD-1

Abstract: Objectives: To study the association between multi-morbidity percentiles, which is a measure of clinical aging, and interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α. Methods: Participants 50 to 95 years of age from the Mayo Clinic Study of Aging were assigned age- and sex-specific multi-morbidity percentiles using look-up tables that were reported previously (n = 1646). Percentiles were divided into quintiles for analysis. Plasma IL-6, IL-10, and TNF-α levels were measured in 1595 participants. Median inflammatory marker levels were compared across multi-morbidity quintiles using nonparametric tests. Results: People with higher multi-morbidity percentiles had significantly higher IL-6 and TNF-α levels compared with those with lower multi-morbidity percentiles. Tests for trend across five multi-morbidity quintiles were significant among women for IL-6 and among participants 70 years of age or older for IL-6 and TNF-α. IL-10 was not associated with multi-morbidity percentiles. Conclusions: Multi-morbidity percentiles may be a useful clinical index of biological age for future studies, particularly in women and people 70 years of age and older.

Title: Abnormal prion protein, infectivity and neurofilament light-chain in blood of macaques with experimental variant Creutzfeldt-Jakob disease
Journal: Journal of General Virology
Year: 2022

Author: Yakovleva, Oksana, Bett, Cyrus, Pilant, Teresa, Asher, David M. and Gregori, Luisa

Keywords: Research article
Neurology
Creutzfeldt-Jakob disease
Simoa Bead
macaque plasma N4PA (NfL, tau, GFAP, UCH-L1)

Abstract: Transmissible spongiform encephalopathies (TSEs) are fatal neurodegenerative infections. Variant Creutzfeldt-Jakob disease (vCJD) and sporadic CJD (sCJD) are human TSEs that, in rare cases, have been transmitted by human-derived therapeutic products. There is a need for a blood test to detect infected donors, identify infected individuals in families with TSEs and monitor progression of disease in patients, especially during clinical trials. We prepared panels of blood from cynomolgus and rhesus macaques experimentally infected with vCJD, as a surrogate for human blood, to support assay development. We detected abnormal prion protein (PrPTSE) in those blood samples using the protein misfolding cyclic amplification (PMCA) assay. PrPTSE first appeared in the blood of pre-symptomatic cynomolgus macaques as early as 2 months post-inoculation (mpi). In contrast, PMCA detected PrPTSE much later in the blood of two pre-symptomatic rhesus macaques, starting at 19 and 20 mpi, and in one rhesus macaque only when symptomatic, at 38 mpi. Once blood of either species of macaque became PMCA-positive, PrPTSE persisted through terminal illness at relatively constant concentrations. Infectivity in buffy coat samples from terminally ill cynomolgus macaques as well as a sample collected

9 months before clinical onset of disease in one of the macaques was assayed in vCJD-susceptible transgenic mice. The infectivity titres varied from 2.7 to 4.3 infectious doses ml–1. We also screened macaque blood using a four-member panel of biomarkers for neurodegenerative diseases to identify potential non-PrPTSE pre-symptomatic diagnostic markers. Neurofilament light-chain protein (NfL) increased in blood before the onset of clinical vCJD. Cumulatively, these data confirmed that, while PrPTSE is the first marker to appear in blood of vCJD-infected cynomolgus and rhesus macaques, NfL might offer a useful, though less specific, marker for forthcoming neurodegeneration. These studies support the use of macaque blood panels to investigate PrPTSE and other biomarkers to predict onset of CJD in humans.

Title: Association of plasma neurofilament light chain with disease activity in chronic inflammatory demyelinating polyradiculoneuropathy
Journal: European Journal of Neurology
Year: 2022

Author: Kapoor, Mahima, Carr, Aisling, Foiani, Martha, Heslegrave, Amanda, Zetterberg, Henrik, Malaspina, Andrea, Compton, Laura, Hutton, Elspeth, Rossor, Alexander, Reilly, Mary M. and Lunn, Michael P.

Keywords: Research article
Neurology
chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
Simoa Bead
plasma NfL
kit
HD-1

Abstract: Abstract: Background and purpose: This study was undertaken to explore associations between plasma neurofilament light chain (pNfL) concentration (pg/ml) and disease activity in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and examine the usefulness of pNfL concentrations in determining disease remission. Methods: We examined pNfL concentrations in treatment-naïve CIDP patients (n = 10) before and after intravenous immunoglobulin (IVIg) induction treatment, in pNfL concentrations in patients on maintenance IVIg treatment who had stable (n = 15) versus unstable disease (n = 9), and in clinically stable IVIg-treated patients (n = 10) in whom we suspended IVIg to determine disease activity and ongoing need for maintenance IVIg. pNfL concentrations in an age-matched healthy control group were measured for comparison. Results: Among treatment-naïve patients, pNfL concentration was higher in patients before IVIg treatment than healthy controls and subsequently reduced to be comparable to control group values after IVIg induction. Among CIDP patients on IVIg treatment, pNfL concentration was significantly higher in unstable patients than stable patients. A pNFL concentration > 16.6 pg/ml distinguished unstable treated CIDP from stable treated CIDP (sensitivity = 86.7%, specificity = 66.7%, area under receiver operating characteristic curve = 0.73). Among the treatment withdrawal group, there was a statistically significant correlation between pNfL concentration at time of IVIg withdrawal and the likelihood of relapse ($r = 0.72$, $p < 0.05$), suggesting an association of higher pNfL concentration with active disease. Conclusions: pNfL concentrations may be a sensitive, clinically useful biomarker in assessing subclinical disease activity.

Title: Systematic Review on Saliva Biomarkers in Patients Diagnosed with Morbus Alzheimer and Morbus Parkinson
Journal: Biomedicines
Year: 2022
Epub Date: 20220714

Author: Wolgin, M., Zobernig, M., Dvornyk, V., Braun, R. J. and Kielbassa, A. M.

Keywords: Review
Neurology
Alzheimer's disease
Parkinson's disease
Simoa Bead

Abstract: Extracellular plaques composed of the hydrophobic peptide amyloid-β and intraneuronal accumulation of the hyperphosphorylated protein tau (p-tau) are pathological hallmarks found in the brains of most people affected by Alzheimer's disease (AD). In Parkinson's disease (PD), Lewy bodies, i.e., intraneuronal protein deposits comprising the protein α-synuclein, are a typical disease feature. As these hallmarks located in the brain are hardly traceable, reliable biomarkers from easily accessible body fluids are key for accurate diagnosis. The aim of the present work was to review the available literature regarding potential biomarkers of AD and PD in the saliva. The databases PubMed, Google Scholar, LILACS, LIVIVO, VHL regional portal, Cochrane Library, eLIBRARY, and IOS Press were consulted for the literature search. Screening of titles and abstracts followed the PRISMA guidelines, while data extraction and the assessment of full texts were carried out in accordance with the Newcastle-Ottawa Scale assessment. The review shows significant increases in levels of the amyloid-β Aβ1-42 and elevated p-tau to total tau (t-tau) ratios in salivary samples of AD patients, in comparison with healthy controls. In PD patients, levels of α-synuclein in salivary samples significantly decreased compared to healthy controls, whereas oligomeric α-synuclein and the ratio of oligomeric α-synuclein to total α-synuclein markedly increased. Salivary biomarkers represent a promising diagnostic tool for neurodegenerative diseases. Further high-quality case-control studies are needed to substantiate their accuracy.

Title: A review on comparative studies addressing exosome isolation methods from body fluids
Journal: Analytical and Bioanalytical Chemistry
Date: 2022/07/15
Year: 2022

Author: Martins, Tânia Soares, Vaz, Margarida and Henriques, Ana Gabriela
Short Title: A review on comparative studies addressing exosome isolation methods from body fluids

Keywords: Review
Technology
Exosomes
Simoa Bead

Abstract: Exosomes emerged as valuable sources of disease biomarkers and new therapeutic tools. However, extracellular vesicles isolation with exosome-like characteristics from certain biofluids is still

challenging which can limit their potential use in clinical settings. While ultracentrifugation-based procedures are the gold standard for exosome isolation from cell cultures, no unique and standardized method for exosome isolation from distinct body fluids exists. The complexity, specific composition, and physical properties of each biofluid constitute a technical barrier to obtain reproducible and pure exosome preparations, demanding a detailed characterization of both exosome isolation and characterization methods. Moreover, some isolation procedures can affect downstream proteomic or RNA profiling analysis. This review compiles and discussed a set of comparative studies addressing distinct exosome isolation methods from human biofluids, including cerebrospinal fluid, plasma, serum, saliva, and urine, also focusing on body fluid specific challenges, physical properties, and other potential variation sources. This summarized information will facilitate the choice of exosome isolation methods, based on the type of biological samples available, and hopefully encourage the use of exosomes in translational and clinical research.

Title: FutureMS cohort profile: a Scottish multicentre inception cohort study of relapsing-remitting multiple sclerosis
Journal: BMJ Open
Year: 2022
Epub Date: 20220629

Author: Kearns, P. K. A., Martin, S. J., Chang, J., Meijboom, R., York, E. N., Chen, Y., Weaver, C., Stenson, A., Hafezi, K., Thomson, S., Freyer, E., Murphy, L., Harroud, A., Foley, P., Hunt, D., McLeod, M., O'Riordan, J., Carod-Artal, F. J., MacDougall, N. J. J., Baranzini, S. E., Waldman, A. D., Connick, P. and Chandran, S.

Keywords: Research article
Neurology
multiple sclerosis
Simoa Bead

Abstract: PURPOSE: Multiple sclerosis (MS) is an immune-mediated, neuroinflammatory disease of the central nervous system and in industrialised countries is the most common cause of progressive neurological disability in working age persons. While treatable, there is substantial interindividual heterogeneity in disease activity and response to treatment. Currently, the ability to predict at diagnosis who will have a benign, intermediate or aggressive disease course is very limited. There is, therefore, a need for integrated predictive tools to inform individualised treatment decision making. PARTICIPANTS: Established with the aim of addressing this need for individualised predictive tools, FutureMS is a nationally representative, prospective observational cohort study of 440 adults with a new diagnosis of relapsing-remitting MS living in Scotland at the time of diagnosis between May 2016 and March 2019. FINDINGS TO DATE: The study aims to explore the pathobiology and determinants of disease heterogeneity in MS and combines detailed clinical phenotyping with imaging, genetic and biomarker metrics of disease activity and progression. Recruitment, baseline assessment and follow-up at year 1 is complete. Here, we describe the cohort design and present a profile of the participants at baseline and 1 year of follow-up. FUTURE PLANS: A third follow-up wave for the cohort has recently begun at 5 years after first visit and a further wave of follow-up is funded for year 10. Longer-term follow-up is anticipated thereafter.

Title: Plasma biomarkers for prognosis of cognitive decline in patients with mild cognitive impairment

Journal: Brain Commun
Year: 2022
Epub Date: 20220614

Author: Kivisäkk, P., Magdamo, C., Trombetta, B. A., Noori, A., Kuo, Y. K. E., Chibnik, L. B., Carlyle, B. C., Serrano-Pozo, A., Scherzer, C. R., Hyman, B. T., Das, S. and Arnold, S. E.

Keywords: Research article
Neurology
Alzheimer's disease
Simoa Bead
plasma pTau181 V2 kit
HD-X

Abstract: Plasma-based biomarkers present a promising approach in the research and clinical practice of Alzheimer's disease as they are inexpensive, accessible and minimally invasive. In particular, prognostic biomarkers of cognitive decline may aid in planning and management of clinical care. Although recent studies have demonstrated the prognostic utility of plasma biomarkers of Alzheimer pathology or neurodegeneration, such as pTau-181 and NF-L, whether other plasma biomarkers can further improve prediction of cognitive decline is undetermined. We conducted an observational cohort study to determine the prognostic utility of plasma biomarkers in predicting progression to dementia for individuals presenting with mild cognitive impairment due to probable Alzheimer's disease. We used the Olink™ Proximity Extension Assay technology to measure the level of 460 circulating proteins in banked plasma samples of all participants. We used a discovery data set comprised 60 individuals with mild cognitive impairment (30 progressors and 30 stable) and a validation data set consisting of 21 stable and 21 progressors. We developed a machine learning model to distinguish progressors from stable and used 44 proteins with significantly different plasma levels in progressors versus stable along with age, sex, education and baseline cognition as candidate features. A model with age, education, APOE genotype, baseline cognition, plasma pTau-181 and 12 plasma Olink protein biomarker levels was able to distinguish progressors from stable with 86.7% accuracy (mean area under the curve = 0.88). In the validation data set, the model accuracy was 78.6%. The Olink proteins selected by the model included those associated with vascular injury and neuroinflammation (e.g. IL-8, IL-17A, TIMP-4, MMP7). In addition, to compare these prognostic biomarkers to those that are altered in Alzheimer's disease or other types of dementia relative to controls, we analyzed samples from 20 individuals with Alzheimer, 30 with non-Alzheimer dementias and 34 with normal cognition. The proteins NF-L and PTP-1B were significantly higher in both Alzheimer and non-Alzheimer dementias compared with cognitively normal individuals. Interestingly, the prognostic markers of decline at the mild cognitive impairment stage did not overlap with those that differed between dementia and control cases. In summary, our findings suggest that plasma biomarkers of inflammation and vascular injury are associated with cognitive decline. Developing a plasma biomarker profile could aid in prognostic deliberations and identify individuals at higher risk of dementia in clinical practice.

Title: Phenotypic Heterogeneity of Fulminant COVID-19--Related Myocarditis in Adults
Journal: J Am Coll Cardiol
Date: Jul 26

Author: Barhoum, P., Pineton de Chambrun, M., Dorgham, K., Kerneis, M., Burrel, S., Quentric, P.,

Parizot, C., Chommeloux, J., Bréchot, N., Moyon, Q., Lebreton, G., Boussouar, S., Schmidt, M., Yssel, H., Lefevre, L., Miyara, M., Charuel, J. L., Marot, S., Marcelin, A. G., Luyt, C. E., Leprince, P., Amoura, Z., Montalescot, G., Redheuil, A., Combes, A., Gorochov, G. and Hékimian, G.

Keywords: Research article
Infectious disease
Covid-19
multisystem inflammatory syndrome
Simoa Bead
planar
serum IL-17A and IFNa (bead)
Serum CorPlex (IL-1b, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-22, IFNg, TNFa)
HD-1
SP-X

Abstract: BACKGROUND: Adults who have been infected with SARS-CoV-2 can develop a multisystem inflammatory syndrome (MIS-A), including fulminant myocarditis. Yet, several patients fail to meet MIS-A criteria, suggesting the existence of distinct phenotypes in fulminant COVID-19-related myocarditis. OBJECTIVES: This study sought to compare the characteristics and clinical outcome between patients with fulminant COVID-19-related myocarditis fulfilling MIS-A criteria (MIS-A(+)) or not (MIS-A(-)). METHODS: A monocentric retrospective analysis of consecutive fulminant COVID-19-related myocarditis in a 26-bed intensive care unit (ICU). RESULTS: Between March 2020 and June 2021, 38 patients required ICU admission (male 66%; mean age 32 ± 15 years) for suspected fulminant COVID-19-related myocarditis. In-ICU treatment for organ failure included dobutamine 79%, norepinephrine 60%, mechanical ventilation 50%, venoarterial extracorporeal membrane oxygenation 42%, and renal replacement therapy 29%. In-hospital mortality was 13%. Twenty-five patients (66%) met the MIS-A criteria. MIS-A(-) patients compared with MIS-A(+) patients were characterized by a shorter delay between COVID-19 symptoms onset and myocarditis, a lower left ventricular ejection fraction, and a higher rate of in-ICU organ failure, and were more likely to require mechanical circulatory support with venoarterial extracorporeal membrane oxygenation (92% vs 16%; $P < 0.0001$). In-hospital mortality was higher in MIS-A(-) patients (31% vs 4%). MIS-A(+) had higher circulating levels of interleukin (IL)-22, IL-17, and tumor necrosis factor-α (TNF-α), whereas MIS-A(-) had higher interferon-α2 (IFN-α2) and IL-8 levels. RNA polymerase III autoantibodies were present in 7 of 13 MIS-A(-) patients (54%) but in none of the MIS-A(+) patients. CONCLUSION: MIS-A(+) and MIS-A(-) fulminant COVID-19-related myocarditis patients have 2 distinct phenotypes with different clinical presentations, prognosis, and immunological profiles. Differentiating these 2 phenotypes is relevant for patients' management and further understanding of their pathophysiology.

Title: The relationship between plasma biomarkers and amyloid PET in dementia with Lewy bodies
Journal: Parkinsonism Relat Disord
Year: 2022
Epub Date: 20220719

Author: Donaghy, P. C., Firbank, M., Petrides, G., Lloyd, J., Barnett, N., Olsen, K., Heslegrave, A., Zetterberg, H., Thomas, A. J. and O'Brien, J. T.

Keywords: Research article

Neurology
Dementia with Lewy bodies
Simoa Bead
plasma N4PE, pTau181 (kit)
HD-1

Abstract: INTRODUCTION: Amyloid-β (Aβ) deposition is common in dementia with Lewy bodies (DLB) and has been associated with more rapid disease progression. An effective biomarker that identified the presence of significant brain Aβ in people with DLB may be useful to identify and stratify participants for research studies and to inform prognosis in clinical practice. Plasma biomarkers are emerging as candidates to fulfil this role. METHODS: Thirty-two participants with DLB had brain amyloid (18F-florbetapir) PET, of whom 27 also had an MRI to enable the calculation of 18F-florbetapir SUVR. Plasma Aβ42/40, phosphorylated tau (p-tau181), glial fibrillary acidic protein (GFAP) and neurofilament light (NfL) were measured using single molecule array (Simoa). The plasma biomarkers were investigated for correlation with 18F-florbetapir SUVR, discriminant ability to identify Aβ-positive cases based on a predefined SUVR threshold of 1.10 and correlation with subsequent cognitive decline over one year. RESULTS: All four plasma markers significantly correlated with 18F-florbetapir SUVR (|β| = 0.40-0.49; $p < .05$). NfL had the greatest area under the receiver operating characteristic curve to identify Aβ-positive cases (AUROC 0.84 (95% CI 0.66, 1); β = 0.46, p = .001), whereas Aβ42/40 had the smallest (AUROC 0.73 (95% CI 0.52, 0.95); β = -0.47, p = .01). Accuracy was highest when combining all four biomarkers (AUROC 0.92 (95% CI 0.80, 1)). Lower plasma Aβ42/40 was significantly associated with more rapid decline in cognition (β = 0.53, $p < .01$). CONCLUSIONS: Plasma biomarkers have the potential to identify Aβ deposition in DLB. Further work in other cohorts is required to determine and validate optimal cut-offs for these biomarkers.

Title: Reactive astrogliosis is associated with higher cerebral glucose consumption in the early Alzheimer's continuum
Journal: Eur J Nucl Med Mol Imaging
Year: 2022
Epub Date: 20220718

Author: Salvadó, G., Milà-Alomà, M., Shekari, M., Ashton, N. J., Operto, G., Falcon, C., Cacciaglia, R., Minguillon, C., Fauria, K., Niñerola-Baizán, A., Perissinotti, A., Benedet, A. L., Kollmorgen, G., Suridjan, I., Wild, N., Molinuevo, J. L., Zetterberg, H., Blennow, K., Suárez-Calvet, M. and Gispert, J. D.

Keywords: Research article
Neurology
Alzheimer's disease
Simoa Bead
plasma, CSF GFAP (kit)
HD-X

Abstract: PURPOSE: Glial activation is one of the earliest mechanisms to be altered in Alzheimer's disease (AD). Glial fibrillary acidic protein (GFAP) relates to reactive astrogliosis and can be measured in both cerebrospinal fluid (CSF) and blood. Plasma GFAP has been suggested to become altered earlier in AD than its CSF counterpart. Although astrocytes consume approximately half of the glucose-derived energy in the brain, the relationship between reactive astrogliosis and cerebral glucose metabolism is

poorly understood. Here, we aimed to investigate the association between fluorodeoxyglucose ([(18)F]FDG) uptake and reactive astrogliosis, by means of GFAP quantified in both plasma and CSF for the same participants. METHODS: We included 314 cognitively unimpaired participants from the ALFA + cohort, 112 of whom were amyloid-β (Aβ) positive. Associations between GFAP markers and [(18)F]FDG uptake were studied. We also investigated whether these associations were modified by Aβ and tau status (AT stages). RESULTS: Plasma GFAP was positively associated with glucose consumption in the whole brain, while CSF GFAP associations with [(18)F]FDG uptake were only observed in specific smaller areas like temporal pole and superior temporal lobe. These associations persisted when accounting for biomarkers of Aβ pathology but became negative in Aβ-positive and tau-positive participants (A + T +) in similar areas of AD-related hypometabolism. CONCLUSIONS: Higher astrocytic reactivity, probably in response to early AD pathological changes, is related to higher glucose consumption. With the onset of tau pathology, the observed uncoupling between astrocytic biomarkers and glucose consumption might be indicative of a failure to sustain the higher energetic demands required by reactive astrocytes.

Title: A randomized controlled pilot trial of anakinra for hemodialysis inflammation
Journal: Kidney Int
Year: 2022
Epub Date: 20220719

Author: Dember, L. M., Hung, A., Mehrotra, R., Hsu, J. Y., Raj, D. S., Charytan, D. M., Mc Causland, F. R., Regunathan-Shenk, R., Landis, J. R., Kimmel, P. L., Kliger, A. S., Himmelfarb, J. and Ikizler, T. A.

Keywords: Research article
Inflammation
hemodialysis patients
Simoa Bead
plasma IL-6, IL-10, IL-1b, TNFa

Abstract: Chronic inflammation is highly prevalent among patients receiving maintenance hemodialysis and is associated with morbidity and mortality. Inhibiting inflammation with anti-cytokine therapy has been proposed but not well studied in this population. Therefore, we conducted the ACTION trial, a pilot, multicenter, randomized, placebo-controlled trial of an IL-1 receptor antagonist, anakinra, to evaluate safety, tolerability, and feasibility, and explore efficacy. Eighty hemodialysis patients with plasma concentrations of high sensitivity C-reactive protein (hsCRP) 2 mg/L and above were randomized 1:1 to placebo or anakinra 100 mg, three times per week via the hemodialysis circuit for 24 weeks, with an additional 24 weeks of post-treatment safety monitoring. Efficacy outcomes included change in hsCRP (primary), cytokines, and patient-reported outcomes. Rates of serious adverse events and deaths were similar with anakinra and placebo (serious adverse events: 2.71 vs 2.74 events/patient-year; deaths: 0.12 vs 0.22 events/patient-year). The rate of adverse events of interest (including infections and cytopenias) was significantly lower with anakinra than placebo (0.48 vs 1.40 events/patient-year). Feasibility was demonstrated by attaining the enrollment target, a retention rate of 80%, and administration of 72% of doses. The median decrease in hsCRP from baseline to Week 24 was 41% in the anakinra group and 6% in the placebo group, a between-group difference that was not statistically significant. For IL-6, the median decreases were significant; 25% and 0% in the anakinra and placebo groups, respectively. An effect of anakinra on patient-reported outcomes was not evident. Thus, anakinra was well tolerated and did not increase infections or cytopenias. The promising safety data and

potential efficacy on CRP and IL-6 provide support for conducting definitive trials of IL-1 inhibition to improve outcomes in hemodialysis patients.

Title: Findings of (18) F-PI-2620 tau PET imaging in patients with Alzheimer's disease and healthy controls in relation to the plasma P-tau181 levels in a Japanese sample
Journal: Neuropsychopharmacol Rep
Year: 2022
Epub Date: 20220717

Author: Bun, S., Moriguchi, S., Tezuka, T., Sato, Y., Takahata, K., Seki, M., Nakajima, S., Yamamoto, Y., Sano, Y., Suzuki, N., Morimoto, A., Ueda, R., Tabuchi, H., Ito, D. and Mimura, M.

Keywords: Research article
Neurology
Alzheimer’s disease
Simoa Bead
plasma pTau181, NfL
kit
HD-1, SR-X

Abstract: BACKGROUND: Alzheimer's disease (AD) is the most common cause of dementia worldwide. In AD, abnormal tau accumulates within neurons of the brain, facilitated by extracellular β-amyloid deposition, leading to neurodegeneration, and eventually, cognitive impairment. As this process is thought to be irreversible, early identification of abnormal tau in the brain is crucial for the development of new therapeutic interventions. AIMS: (18) F-PI-2620 is one of the second-generation tau PET tracers with presumably less off-target binding than its predecessors. Although a few clinical studies have recently reported the use of (18) F-PI-2620 tau PET in patients with AD, its applicability to AD is yet to be thoroughly examined. METHODS: In the present pilot study, we performed (18) F-PI-2620 tau PET in seven cases of probable AD (AD group) and seven healthy controls (HC group). Standardized uptake value ratios (SUVR) in regions of interest (ROIs) in the medial temporal region and neocortex were compared between the AD and HC groups. Furthermore, correlations between regional SUVR and plasma p-tau181 as well as cognitive test scores were also analyzed. RESULTS: The uptake of (18) F-PI-2620 was distinctly increased in the AD group across all the ROIs. SUVR in all the target ROIs were significantly correlated with plasma p-tau181 levels, as well as with MMSE and ADAS-cog scores. DISCUSSION & CONCLUSION: Our results add to accumulating evidence suggesting that (18) F-PI-2620 is a promising tau PET tracer that allows patients with AD to be distinguished from healthy controls, although a study with a larger sample size is warranted.

Title: The TAS Test project: a prospective longitudinal validation of new online motor-cognitive tests to detect preclinical Alzheimer's disease and estimate 5-year risks of cognitive decline and dementia
Journal: BMC Neurol
Year: 2022
Epub Date: 20220718

Author: Alty, J., Bai, Q., Li, R., Lawler, K., St George, R. J., Hill, E., Bindoff, A., Garg, S., Wang, X., Huang, G., Zhang, K., Rudd, K. D., Bartlett, L., Goldberg, L. R., Collins, J. M., Hinder, M. R., Naismith, S. L., Hogg, D. C.,

King, A. E. and Vickers, J. C.

Keywords: Research article
Neurology
Alzheimer Disease
Simoa Bead

Abstract: BACKGROUND: The worldwide prevalence of dementia is rapidly rising. Alzheimer's disease (AD), accounts for 70% of cases and has a 10-20-year preclinical period, when brain pathology covertly progresses before cognitive symptoms appear. The 2020 Lancet Commission estimates that 40% of dementia cases could be prevented by modifying lifestyle/medical risk factors. To optimise dementia prevention effectiveness, there is urgent need to identify individuals with preclinical AD for targeted risk reduction. Current preclinical AD tests are too invasive, specialist or costly for population-level assessments. We have developed a new online test, TAS Test, that assesses a range of motor-cognitive functions and has capacity to be delivered at significant scale. TAS Test combines two innovations: using hand movement analysis to detect preclinical AD, and computer-human interface technologies to enable robust 'self-testing' data collection. The aims are to validate TAS Test to [1] identify preclinical AD, and [2] predict risk of cognitive decline and AD dementia. METHODS: Aim 1 will be addressed through a cross-sectional study of 500 cognitively healthy older adults, who will complete TAS Test items comprising measures of motor control, processing speed, attention, visuospatial ability, memory and language. TAS Test measures will be compared to a blood-based AD biomarker, phosphorylated tau 181 (p-tau181). Aim 2 will be addressed through a 5-year prospective cohort study of 10,000 older adults. Participants will complete TAS Test annually and subtests of the Cambridge Neuropsychological Test Battery (CANTAB) biennially. 300 participants will undergo in-person clinical assessments. We will use machine learning of motor-cognitive performance on TAS Test to develop an algorithm that classifies preclinical AD risk (p-tau181-defined) and determine the precision to prospectively estimate 5-year risks of cognitive decline and AD. DISCUSSION: This study will establish the precision of TAS Test to identify preclinical AD and estimate risk of cognitive decline and AD. If accurate, TAS Test will provide a low-cost, accessible enrichment strategy to pre-screen individuals for their likelihood of AD pathology prior to more expensive tests such as blood or imaging biomarkers. This would have wide applications in public health initiatives and clinical trials. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT05194787 , 18 January 2022. Retrospectively registered.

Title: Minocycline treatment in clinically isolated syndrome and serum NfL, GFAP, and metalloproteinase levels
Journal: Mult Scler
Year: 2022
Epub Date: 20220718

Author: Camara-Lemarroy, C., Metz, L., Kuhle, J., Leppert, D., Willemse, E., Li, D. K., Traboulsee, A., Greenfield, J., Cerchiaro, G., Silva, C. and Yong, V. W.

Keywords: Research article
Neurology
Multiple sclerosis
Clinically Isolated Syndrome
Simoa Bead

serum, plasma GFAP, NfL (kit)
HD-X

Abstract: BACKGROUND: In the trial of Minocycline in Clinically Isolated Syndrome (MinoCIS), minocycline significantly reduced the risk of conversion to clinically definite multiple sclerosis (CDMS). Neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) are emerging biomarkers in MS, and minocycline modulates matrix metalloproteinases (MMPs). OBJECTIVE: To assess the value of blood NfL and GFAP as a biomarker of baseline and future disease activity and its utility to monitor treatment response in minocycline-treated patients with clinically isolated syndrome (CIS). METHODS: We measured NfL, GFAP, and MMPs in blood samples from 96 patients with CIS from the MinoCIS study and compared biomarkers with clinical and radiologic characteristics and outcome. RESULTS: At baseline, NfL levels correlated with T(2) lesion load and number of gadolinium-enhancing lesions. Baseline NfL levels predicted conversion into CDMS at month 6. GFAP levels at baseline were correlated with T(2) lesion volume. Minocycline treatment significantly increased NfL levels at 3 months but not at 6 months, and decreased GFAP levels at month 6. Minocycline decreased MMP-7 concentrations at month 1. DISCUSSION: Blood NfL levels are associated with measures of disease activity in CIS and have prognostic value. Minocycline increased NfL levels at month 3, but reduced GFAP and MMP-7 levels.

Title: Plasma Aβ42/40 ratio, p-tau181, GFAP, and NfL across the Alzheimer's disease continuum: A cross-sectional and longitudinal study in the AIBL cohort
Journal: Alzheimer's & Dementia
Year: 2022

Author: Chatterjee, Pratishtha, Pedrini, Steve, Doecke, James D., Thota, Rohith, Villemagne, Victor L., Doré, Vincent, Singh, Abhay K., Wang, Penghao, Rainey-Smith, Stephanie, Fowler, Christopher, Taddei, Kevin, Sohrabi, Hamid R., Molloy, Mark P., Ames, David, Maruff, Paul, Rowe, Christopher C., Masters, Colin L., Martins, Ralph N. and Group, the AIBL Research

Keywords: Research article
Neurology
Alzheimer's disease
Simoa Bead
plasma N4PE (Ab42, Ab40, GFAP, NfL) kit
plasma pTau181 V2 kit

Abstract: Abstract: Introduction: Plasma amyloid beta (Aβ)1-42/Aβ1-40 ratio, phosphorylated-tau181 (p-tau181), glial fibrillary acidic protein (GFAP), and neurofilament light (NfL) are putative blood biomarkers for Alzheimer's disease (AD). However, head-to-head cross-sectional and longitudinal comparisons of the aforementioned biomarkers across the AD continuum are lacking. Methods: Plasma Aβ1-42, Aβ1-40, p-tau181, GFAP, and NfL were measured utilizing the Single Molecule Array (Simoa) platform and compared cross-sectionally across the AD continuum, wherein Aβ-PET (positron emission tomography)–negative cognitively unimpaired (CU Aβ−, n = 81) and mild cognitive impairment (MCI Aβ−, n = 26) participants were compared with Aβ-PET–positive participants across the AD continuum (CU Aβ+, n = 39; MCI Aβ+, n = 33; AD Aβ+, n = 46) from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) cohort. Longitudinal plasma biomarker changes were also assessed in MCI (n = 27) and AD (n = 29) participants compared with CU (n = 120) participants. In addition, associations between baseline plasma biomarker levels and prospective cognitive decline and Aβ-PET load were assessed over

a 7 to 10-year duration. Results: Lower plasma Aβ1-42/Aβ1-40 ratio and elevated p-tau181 and GFAP were observed in CU Aβ+, MCI Aβ+, and AD Aβ+, whereas elevated plasma NfL was observed in MCI Aβ+ and AD Aβ+, compared with CU Aβ− and MCI Aβ−. Among the aforementioned plasma biomarkers, for models with and without AD risk factors (age, sex, and apolipoprotein E (APOE) ε4 carrier status), p-tau181 performed equivalent to or better than other biomarkers in predicting a brain Aβ−/+ status across the AD continuum. However, for models with and without the AD risk factors, a biomarker panel of Aβ1-42/Aβ1-40, p-tau181, and GFAP performed equivalent to or better than any of the biomarkers alone in predicting brain Aβ−/+ status across the AD continuum. Longitudinally, plasma Aβ1-42/Aβ1-40, p-tau181, and GFAP were altered in MCI compared with CU, and plasma GFAP and NfL were altered in AD compared with CU. In addition, lower plasma Aβ1-42/Aβ1-40 and higher p-tau181, GFAP, and NfL were associated with prospective cognitive decline and lower plasma Aβ1-42/Aβ1-40, and higher p-tau181 and GFAP were associated with increased Aβ-PET load prospectively. Discussion: These findings suggest that plasma biomarkers are altered cross-sectionally and longitudinally, along the AD continuum, and are prospectively associated with cognitive decline and brain Aβ-PET load. In addition, although p-tau181 performed equivalent to or better than other biomarkers in predicting an Aβ−/+ status across the AD continuum, a panel of biomarkers may have superior Aβ−/+ status predictive capability across the AD continuum. HIGHLIGHTS: Area under the curve (AUC) of p-tau181 ≥ AUC of Aβ42/40, GFAP, NfL in predicting PET Aβ−/+ status (Aβ−/+). AUC of Aβ42/40+p-tau181+GFAP panel ≥ AUC of Aβ42/40/p-tau181/GFAP/NfL for Aβ−/+. Longitudinally, Aβ42/40, p-tau181, and GFAP were altered in MCI versus CU. Longitudinally, GFAP and NfL were altered in AD versus CU. Aβ42/40, p-tau181, GFAP, and NfL are associated with prospective cognitive decline. Aβ42/40, p-tau181, and GFAP are associated with increased PET Aβ load prospectively.

Title: Evaluation of in vivo staging of amyloid deposition in cognitively unimpaired elderly aged 78-94
Journal: Mol Psychiatry
Year: 2022
Epub Date: 20220720

Author: Michalowska, M. M., Herholz, K., Hinz, R., Amadi, C., McInnes, L., Anton-Rodriguez, J. M., Karikari, T. K., Blennow, K., Zetterberg, H., Ashton, N. J., Pendleton, N. and Carter, S. F.

Keywords: Research article
Neurology
cognitively unimpaired
Simoa Bead
plasma pTau181 homebrew
HD-X

Abstract: Amyloid-beta (Aβ) deposition is common in cognitively unimpaired (CU) elderly >85 years. This study investigated amyloid distribution and evaluated three published in vivo amyloid-PET staging schemes from a cognitively unimpaired (CU) cohort aged 84.9 ± 4.3 years (n = 75). SUV-based principal component analysis (PCA) was applied to (18)F-flutemetamol PET data to determine an unbiased regional covariance pattern of tracer uptake across grey matter regions. PET staging schemes were applied to the data and compared to the PCA output. Concentration of p-tau181 was measured in blood plasma. The PCA revealed three distinct components accounting for 91.2% of total SUV variance. PC1 driven by the large common variance of uptake in neocortical and striatal regions was significantly positively correlated with global SUVRs, APOE4 status and p-tau181 concentration. PC2 represented

mainly non-specific uptake in typical amyloid-PET reference regions, and PC3 the occipital lobe. Application of the staging schemes demonstrated that the majority of the CU cohort (up to 93%) were classified as having pathological amount and distribution of Aβ. Good correspondence existed between binary (+/-) classification and later amyloid stages, however, substantial differences existed between schemes for low stages with 8-17% of individuals being unstageable, i.e., not following the sequential progression of Aβ deposition. In spite of the difference in staging outcomes there was broad spatial overlap between earlier stages and PC1, most prominently in default mode network regions. This study critically evaluated the utility of in vivo amyloid staging from a single PET scan in CU elderly and found that early amyloid stages could not be consistently classified. The majority of the cohort had pathological Aβ, thus, it remains an open topic what constitutes abnormal brain Aβ in the oldest-old and what is the best method to determine that.

Title: Biomarkers of Neurodegenerative Diseases: Biology, Taxonomy, Clinical Relevance, and Current Research Status
Journal: Biomedicines
Year: 2022
Epub Date: 20220721

Author: Koníčková, D., Menšíková, K., Tučková, L., Hényková, E., Strnad, M., Friedecký, D., Stejskal, D., Matěj, R. and Kaňovský, P.

Keywords: Review
neurodegenerative diseases
Simoa Bead

Abstract: The understanding of neurodegenerative diseases, traditionally considered to be well-defined entities with distinguishable clinical phenotypes, has undergone a major shift over the last 20 years. The diagnosis of neurodegenerative diseases primarily requires functional brain imaging techniques or invasive tests such as lumbar puncture to assess cerebrospinal fluid. A new biological approach and research efforts, especially in vivo, have focused on biomarkers indicating underlying proteinopathy in cerebrospinal fluid and blood serum. However, due to the complexity and heterogeneity of neurodegenerative processes within the central nervous system and the large number of overlapping clinical diagnoses, identifying individual proteinopathies is relatively difficult and often not entirely accurate. For this reason, there is an urgent need to develop laboratory methods for identifying specific biomarkers, understand the molecular basis of neurodegenerative disorders and classify the quantifiable and readily available tools that can accelerate efforts to translate the knowledge into disease-modifying therapies that can improve and simplify the areas of differential diagnosis, as well as monitor the disease course with the aim of estimating the prognosis or evaluating the effects of treatment. The aim of this review is to summarize the current knowledge about clinically relevant biomarkers in different neurodegenerative diseases.

Title: No increase of serum neurofilament light in relapsing-remitting multiple sclerosis patients switching from standard to extended-interval dosing of natalizumab
Journal: Multiple Sclerosis Journal
Year: 2022

Author: Johnsson, Magnus, Farman, Helen H, Blennow, Kaj, Zetterberg, Henrik, Malmeström, Clas, Axelsson, Markus and Lycke, Jan

Keywords: Research article
Neurology
Multiple sclerosis
Simoa Bead
serum NfL
kit
HD-X

Abstract: Background: Accumulating evidence supports the efficacy of administering natalizumab (NZ) with extended-interval dosing (EID) in patients with relapsing-remitting multiple sclerosis (RRMS). Objectives: We switched NZ dosing from 4-week to 6-week intervals in patients with RRMS, and investigated the effect on serum neurofilament light chain (sNfL) concentrations. Methods: We included two cohorts of patients with RRMS treated with NZ: one received the standard-interval dosing (4 weeks) at baseline, and were switched to 6-week intervals (EID4–6, N = 45). The other cohort received EID (5- or 6-week intervals) both at baseline and during follow-up (EID5/6, N = 25). Serum samples were collected in the EID4–6 cohort at every NZ infusion, for 12 months. The primary outcome was the change in sNfL concentrations after switching to EID. Results: The baseline mean sNfL concentration in the EID4–6 cohort was 10.5 ng/L (standard deviation (SD) = 6.1), and it remained unchanged at 12 months. Moreover, individual sNfL concentrations did not change significantly after extending the NZ dosing intervals. In addition, the EID4–6 and EID5/6 cohorts had similar baseline sNfL concentrations. Conclusion: We concluded that extending the NZ dosing interval did not increase axonal damage, as determined with sNfL, in patients with RRMS.

Title: Dendrimer nanotherapy for severe COVID-19 attenuates inflammation and neurological injury markers and improves outcomes in a phase2a clinical trial
Journal: Sci Transl Med
Year: 2022
Epub Date: 20220720

Author: Gusdon, A. M., Faraday, N., Aita, J. S., Kumar, S., Mehta, I., Choi, H. A., Cleland, J. L., Robinson, K., McCullough, L. D., Ng, D. K., Kannan, R. M. and Kannan, S.

Keywords: Research article
Infectious disease
COVID-19
Simoa Bead
serum N4PA (NfL, GFAP, Tau, UCH-L1)

Abstract: Hyperinflammation triggered by SARS-CoV-2 is a major cause of disease severity, with activated macrophages implicated in this response. OP-101, a hydroxyl-polyamidoamine dendrimer-N-acetylcysteine conjugate that specifically targets activated macrophages, improves outcomes in preclinical models of systemic inflammation and neuroinflammation. In this multicenter, randomized, double-blind, placebo-controlled, adaptive phase 2a trial, we evaluated safety and preliminary efficacy of OP-101 in patients with severe COVID-19. Twenty-four patients classified as

having severe COVID-19 with a baseline World Health Organization seven-point ordinal scale of ≥5 were randomized to receive a single intravenous dose of placebo (n = 7 patients) or OP-101 at 2 (n = 6), 4 (n = 6), or 8 mg/kg (n = 5 patients). All study participants received standard of care, including corticosteroids. OP-101 at 4 mg/kg was better than placebo at decreasing inflammatory markers; OP-101 at 4 and 8 mg/kg was better than placebo at reducing neurological injury markers, (neurofilament light chain and glial fibrillary acidic protein). Risk for the composite outcome of mechanical ventilation or death at 30 and 60 days after treatment was 71% (95% CI: 29%, 96%) for placebo and 18% (95% CI: 4%, 43%; P = 0.021) for the pooled OP-101 treatment arms. At 60 days, 3 of 7 patients given placebo and 14 of 17 OP-101-treated patients were surviving. No drug-related adverse events were reported. These data show that OP-101 was well tolerated and may have potential to treat systemic inflammation and neuronal injury, reducing morbidity and mortality in hospitalized patients with severe COVID-19.

Title: Neurofilament light increases over time in severe COVID-19 and is associated with delirium
Journal: Brain Communications
Year: 2022

Author: Smeele, Patrick J, Vermunt, Lisa, Blok, Siebe, Duitman, Jan Willem, Biobank, AmsterdamUMC COVID-19, Nossent, Esther J, van Agtmael, Michiel A, Heunks, Leo M A, Horn, Janneke, Bogaard, Harm Jan and Teunissen, Charlotte E

Keywords: Research article
Neurology
COVID-19
Simoa Bead
plasma NfL
kit

Abstract: Neurological monitoring in sedated Intensive Care Unit patients is constrained by the lack of reliable blood-based biomarkers. Neurofilament light is a cross-disease biomarker for neuronal damage with potential clinical applicability for monitoring Intensive Care Unit patients. We studied the trajectory of neurofilament light over a month in Intensive Care Unit patients diagnosed with severe COVID-19 and explored its relation to clinical outcomes and pathophysiological predictors. Data were collected over a month in 31 Intensive Care Unit patients (166 plasma samples) diagnosed with severe COVID-19 at Amsterdam University Medical Centre, and in the first week after emergency department admission in 297 patients with COVID-19 (635 plasma samples) admitted to Massachusetts General hospital. We observed that Neurofilament light increased in a non-linear fashion in the first month of Intensive Care Unit admission and increases faster in the first week of Intensive Care Unit admission when compared with mild-moderate COVID-19 cases. We observed that baseline Neurofilament light did not predict mortality when corrected for age and renal function. Peak neurofilament light levels were associated with a longer duration of delirium after extubation in Intensive Care Unit patients. Disease severity, as measured by the sequential organ failure score, was associated to higher neurofilament light values, and tumour necrosis factor alpha levels at baseline were associated with higher levels of neurofilament light at baseline and a faster increase during admission. These data illustrate the dynamics of Neurofilament light in a critical care setting and show associations to delirium, disease severity and markers for inflammation. Our study contributes to determine the clinical utility and interpretation of neurofilament light levels in Intensive Care Unit patients.

Title: Association of Cerebrospinal Fluid Neurofilament Heavy Protein Levels With Clinical Progression in Patients With Parkinson Disease
Journal: JAMA Netw Open
Year: 2022
Epub Date: 20220701

Author: Wang, L., Zhang, W., Liu, F., Mao, C., Liu, C. F., Cheng, W. and Feng, J.

Keywords: Research article
Neurology
Parkinson Disease
Simoa Bead
serum NfL
kit
China

Abstract: IMPORTANCE: Neurofilament light in biofluids has been associated with progression of Parkinson disease (PD), but the association between neurofilament heavy (NfH) and progression of PD has not been investigated. OBJECTIVE: To evaluate the associations of cerebrospinal fluid (CSF) NfH (cNfH) levels and motor and cognitive progression in PD. DESIGN, SETTING, AND PARTICIPANTS: This cohort study used data from the Parkinson Progression Marker Initiative ranging from June 2010 to November 2018. Participants were recruited from 24 participating sites worldwide (United States, Europe, and Australia). Data were analyzed from October 20 to December 18, 2021. EXPOSURES: Concentrations of NfH in CSF. MAIN OUTCOMES AND MEASURES: The primary outcomes were Movement Disorder Society-sponsored revisions of the Unified Parkinson Disease Rating Scale (MDS-UPDRS) Part III; scores range from 0 to 132, with higher scores indicating worse motor function, and Montreal Cognitive Assessment (MoCA); scores range from 0 to 30, with higher scores indicating better cognitive function. The associations of cNfH levels and longitudinal change in MDS-UPDRS-Part-III and MoCA were examined using linear mixed-effects models with PD duration as the time scale. Partial correlation analysis was conducted to examine the associations of cNfH levels and α-synuclein, amyloid-β 1-42 (Aβ42), phosphorylated tau at threonine 181 position (P-tau), and total tau (T-tau) levels in CSF. RESULTS: A total of 404 patients with PD (mean [SD] age, 61.7 [9.7] years; 263 were men [65.1%]; within 2 years of diagnosis; Hoehn and Yahr <3) were included. Higher baseline cNfH levels were associated with greater increases in MDS-UPDRS Part-III (β = 0.39; 95% CI, 0.12-0.66; P = .003) and faster decreases in MoCA (β = -0.18; CI, -0.24 to -0.11; P < .001). Levels of cNfH were correlated with CSF levels of α-synuclein (Spearman r = 0.25; 95% CI, 0.15-0.34; P < .001), Aβ42 (Spearman r = 0.18; 95% CI, 0.08-0.27; P < .001), P-tau (Spearman r = 0.25; 95% CI, 0.15-0.35; P < .001), and T-tau (Spearman r = 0.31; 95% CI, 0.21-0.40; P < .001) at baseline. CONCLUSIONS AND RELEVANCE: Higher baseline cNfH levels were associated with faster motor and cognitive progression. This finding suggests that cNfH may be of some value for stratifying patients with PD who have different progression rates.

Title: Portable Vertical Graphene@Au-Based Electrochemical Aptasensing Platform for Point-of-Care Testing of Tau Protein in the Blood
Journal: Biosensors (Basel)
Year: 2022
Epub Date: 20220725

Author: Liu, Y., Liu, X., Li, M., Liu, Q. and Xu, T.

Keywords: Research article
Technology
Alzheimer's disease
Simoa Bead
tau
China

Abstract: Alzheimer's disease (AD) is a long-term neurodegenerative disease that poses a serious threat to human life and health. It is very important to develop a portable quantitative device for AD diagnosis and personal healthcare. Herein, we develop a portable electrochemical sensing platform for the point-of-care detection of AD biomarkers in the blood. Such a portable platform integrates nanoAu-modified vertical graphene (VG@Au) into a working electrode, which can significantly improve sensitivity and reduce detection limit due to the large specific surface, excellent electrical conductivity, high stability, and good biocompatibility. The tau protein, as an important factor in the course of AD, is selected as a key AD biomarker. The results show that the linear range of this sensing platform is 0.1 pg/mL to 1 ng/mL, with a detection limit of 0.034 pg/mL (S/N = 3), indicating that this portable sensing platform meets the demand for the detection of the tau protein in the blood. This work offers great potential for AD diagnosis and personal healthcare.

Title: Serum neurofilament light reflects cognitive dysfunctions in children with obstructive sleep apnea
Journal: BMC Pediatr
Year: 2022
Epub Date: 20220726

Author: Shi, Y., Feng, Y., Chen, X., Ma, L., Cao, Z., Shang, L., Zhao, B., She, N., Zhang, Y., Si, C., Liu, H., Zhao, J. and Ren, X.

Keywords: Research article
Neurology
obstructive sleep apnea
Simoa Bead
serum NfL, tau
China

Abstract: BACKGROUND: In children, obstructive sleep apnea (OSA) can cause cognitive dysfunctions. Amyloid-beta and tau are elevated in OSA. Neurofilament light (NfL) is a marker of neuro-axonal damage, but there are no reports of NfL for OSA. The objective was to investigate the serum levels of NfL and tau in children with or without OSA and explore their relationship with cognitive dysfunctions caused by OSA. METHODS: This retrospective case-control study included children diagnosed with adenoid tonsil hypertrophy from July 2017 to September 2019 at the Second Affiliated Hospital of Xi'an Jiaotong University. Correlations between cognitive scores and tau and NfL were examined. RESULTS: Fifty-six OSA and 49 non-OSA children were included. The serum NfL levels were higher in the OSA group (31.68 (27.29-36.07) pg/ml) than in the non-OSA group (19.13 (17.32-20.95) pg/ml) ($P < 0.001$). Moreover, NfL was correlated with the course of the disease, apnea-hypopnea index (AHI), obstructive

apnea index (OAI), obstructive apnea-hypopnea index (OAHI), average oxygen saturation (SaO(2)), respiratory arousal index (RAI), and cognitive dysfunctions evaluated by the Chinese Wechsler Intelligence Scale for Children (C-WISC) (all $P < 0.05$). The area under the receiver operating characteristics curve (AUC) of NfL was 0.816 (95%CI: 0.736-0.897). Multiple regression analysis revealed that NfL was significantly associated with verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ) and full-scale intelligence quotient (FIQ) ($P < 0.001$, respectively). CONCLUSIONS: Serum NfL levels are associated with the severity of cognitive dysfunctions in children diagnosed with adenoid tonsil hypertrophy and might be a candidate noninvasive, objective marker to identify cognitive dysfunctions in children with OSA.

Title: Functional validation of novel variants in B4GALNT1 associated with early-onset complex hereditary spastic paraplegia with impaired ganglioside synthesis
Journal: Am J Med Genet A
Year: 2022
Epub Date: 20220701

Author: Alecu, J. E., Ohmi, Y., Bhuiyan, R. H., Inamori, K. I., Nitta, T., Saffari, A., Jumo, H., Ziegler, M., de Gusmao, C. M., Sharma, N., Ohno, S., Manabe, N., Yamaguchi, Y., Kambe, M., Furukawa, K., Sahin, M., Inokuchi, J. I., Furakawa, K. and Ebrahimi-Fakhari, D.

Keywords: Research article
Neurology
hereditary spastic paraplegia
Simoa Bead
plasma NfL
kit
HD-X

Abstract: Childhood-onset forms of hereditary spastic paraplegia are ultra-rare diseases and often present with complex features. Next-generation-sequencing allows for an accurate diagnosis in many cases but the interpretation of novel variants remains challenging, particularly for missense mutations. Where sufficient knowledge of the protein function and/or downstream pathways exists, functional studies in patient-derived cells can aid the interpretation of molecular findings. We here illustrate the case of a 13-year-old female who presented with global developmental delay and later mild intellectual disability, progressive spastic diplegia, spastic-ataxic gait, dysarthria, urinary urgency, and loss of deep tendon reflexes of the lower extremities. Exome sequencing showed a novel splice-site variant in trans with a novel missense variant in B4GALNT1 [NM_001478.5: c.532-1G>C/c.1556G>C (p.Arg519Pro)]. Functional studies in patient-derived fibroblasts and cell models of GM2 synthase deficiency confirmed a loss of B4GALNT1 function with no synthesis of GM2 and other downstream gangliosides. Collectively these results established the diagnosis of B4GALNT1-associated HSP (SPG26). Our approach illustrates the importance of careful phenotyping and functional characterization of novel gene variants, particularly in the setting of ultra-rare diseases, and expands the clinical and molecular spectrum of SPG26, a disorder of complex ganglioside biosynthesis.

Title: Pathophysiology of neurodegenerative diseases: An interplay among axonal transport failure, oxidative stress, and inflammation?

Journal: Semin Immunol
Year: 2022
Epub Date: 20220629

Author: Tesco, G. and Lomoio, S.

Keywords: Review
Neurology
Simoa Bead

Abstract: Neurodegenerative diseases (NDs) are heterogeneous neurological disorders characterized by a progressive loss of selected neuronal populations. A significant risk factor for most NDs is aging. Considering the constant increase in life expectancy, NDs represent a global public health burden. Axonal transport (AT) is a central cellular process underlying the generation and maintenance of neuronal architecture and connectivity. Deficits in AT appear to be a common thread for most, if not all, NDs. Neuroinflammation has been notoriously difficult to define in relation to NDs. Inflammation is a complex multifactorial process in the CNS, which varies depending on the disease stage. Several lines of evidence suggest that AT defect, axonopathy and neuroinflammation are tightly interlaced. However, whether these impairments play a causative role in NDs or are merely a downstream effect of neuronal degeneration remains unsettled. We still lack reliable information on the temporal relationship between these pathogenic mechanisms, although several findings suggest that they may occur early during ND pathophysiology. This article will review the latest evidence emerging on whether the interplay between AT perturbations and some aspects of CNS inflammation can participate in ND etiology, analyze their potential as therapeutic targets, and the urge to identify early surrogate biomarkers.

Title: Extracellular vesicle biomarkers for cognitive impairment in Parkinson's disease
Journal: Brain
Year: 2022
Epub Date: 20220714

Author: Blommer, J., Pitcher, T., Mustapic, M., Eren, E., Yao, P. J., Vreones, M. P., Pucha, K. A., Dalrymple-Alford, J., Shoorangiz, R., Meissner, W. G., Anderson, T. and Kapogiannis, D.

Keywords: Research article
Neurology
Parkinson’s disease
Simoa Bead
exosomes
CD9, CD63, CD81

Abstract: Besides motor symptoms, many individuals with Parkinson's disease develop cognitive impairment perhaps due to co-existing α-synuclein and Alzheimer's disease pathologies and impaired brain insulin signaling. Discovering biomarkers for cognitive impairment in Parkinson's disease could help clarify the underlying pathogenic processes and improve Parkinson's disease diagnosis and prognosis. This study used plasma samples from 271 participants: 103 Parkinson's disease individuals with normal cognition, 121 Parkinson's disease individuals with cognitive impairment (81 with mild cognitive impairment, 40 with dementia), and 49 age and sex-matched Controls. Plasma extracellular

vesicles enriched for neuronal origin were immunocaptured by targeting L1 cell adhesion molecule, then biomarkers were quantified using immunoassays. α-synuclein was lower in Parkinson's disease compared to Control individuals ($p = 0.004$) and in cognitively impaired Parkinson's disease individuals compared to Parkinson's disease with normal cognition ($p < 0.001$) and Control ($p < 0.001$) individuals. Amyloid-beta42 did not differ between groups. Phosphorylated Tau (T181) was higher in Parkinson's disease than Control individuals ($p = 0.003$), and in cognitively impaired compared to cognitively normal Parkinson's disease individuals ($p < 0.001$) and Controls ($p < 0.001$). Total tau was not different between groups. Tyrosine-phosphorylated insulin receptor substrate-1 was lower in Parkinson's disease compared to Control individuals ($p = 0.03$), and in cognitively impaired compared to cognitively normal Parkinson's disease individuals ($p = 0.02$) and Controls ($p = 0.01$), and also decreased with increasing motor symptom severity ($p = 0.005$); Serine312-phosphorylated insulin receptor substrate-1 was not different between groups. Mechanistic target of rapamycin was not different between groups, whereas phosphorylated mechanistic target of rapamycin trended lower in cognitively impaired compared to cognitively normal Parkinson's disease individuals ($p = 0.05$). The ratio of α-synuclein to phosphorylated Tau181 was lower in Parkinson's disease compared to Controls ($p = 0.001$), in cognitively impaired compared to cognitively normal Parkinson's disease individuals ($p < 0.001$), and decreased with increasing motor symptom severity ($p < 0.001$). The ratio of insulin receptor substrate-1 phosphorylated Serine312 to insulin receptor substrate-1 phosphorylated Tyrosine was higher in Parkinson's disease compared to Control individuals ($p = 0.01$), in cognitively impaired compared to cognitively normal Parkinson's disease individuals ($p = 0.02$) and increased with increasing motor symptom severity ($p = 0.003$). α-synuclein, phosphorylated Tau181, and insulin receptor substrate-1 phosphorylated Tyrosine contributed in diagnostic classification between groups. These findings suggest that both α-synuclein and Tau pathologies and impaired insulin signaling underlie Parkinson's disease with cognitive impairment. Plasma neuronal extracellular vesicles biomarkers may inform cognitive prognosis in Parkinson's disease.

Title: Alzheimer's disease: a scoping review of biomarker research and development for effective disease diagnosis
Journal: Expert Rev Mol Diagn
Year: 2022
Epub Date: 20220728

Author: Faldu, K. G. and Shah, J. S.

Keywords: Review
Neurology
Alzheimer’s disease
Simoa Bead

Abstract: INTRODUCTION: Alzheimer's disease (AD) is regarded as the foremost reason for neurodegeneration that prominently affects the geriatric population. Characterized by extracellular accumulation of amyloid-beta (Aβ), intracellular aggregation of hyperphosphorylated tau (p-tau), and neuronal degeneration that causes impairment of memory and cognition.
Amyloid/tau/neurodegeneration (ATN) classification is utilized for research purposes and involves amyloid, tau, and neuronal injury staging through MRI, PET scanning, and CSF protein concentration estimations. CSF sampling is invasive, and MRI and PET scanning requires sophisticated radiological facilities which limit its widespread diagnostic use. ATN classification lacks effectiveness in preclinical AD.

AREAS COVERED: This publication intends to collate and review the existing biomarker profile and the current research and development of a new arsenal of biomarkers for AD pathology from different biological samples, microRNA (miRNA), proteomics, metabolomics, artificial intelligence, and machine learning for AD screening, diagnosis, prognosis, and monitoring of AD treatments. EXPERT OPINION: It is an accepted observation that AD-related pathological changes occur over a long period of time before the first symptoms are observed providing ample opportunity for detection of biological alterations in various biological samples that can aid in early diagnosis and modify treatment outcomes.

Title: Association of Plasma Biomarkers of Amyloid and Neurodegeneration with Cerebrovascular Disease and Alzheimer's Disease
Journal: Neurobiology of Aging
Year: 2022
Date: 2022/07/24/

Author: Graff-Radford, Jonathan, Mielke, Michelle M., Hofrenning, Ekaterina I., Kouri, Naomi, Lesnick, Timothy G., Moloney, Christina M., Rabinstein, Alejandro, Cabrera-Rodriguez, Janisse N., Rothberg, Darren M., Przybelski, Scott A., Petersen, Ronald C., Knopman, David S., Dickson, Dennis W., Jack, Clifford R., Algeciras-Schimnich, Alicia, Nguyen, Aivi T., Murray, Melissa E. and Vemuri, Prashanthi

Keywords: Research article
Neurology
Alzheimer's disease
Simoa Bead
plasma N3PA (Ab40, Ab42, tau) kit
plasma NfL homebrew
HD-1

Abstract: Background The objective of this study was to determine the differential mapping of plasma biomarkers to postmortem neuropathology measures. Methods We identified 64 participants in a population-based study with antemortem plasma markers (amyloid-β [Aβ] x-42, Aβx-40, neurofilament light [NfL], and total tau [T-tau]) who also had neuropathologic assessments of Alzheimer's and cerebrovascular pathology. We conducted weighted linear-regression models to evaluate relationships between plasma measures and neuropathology. Results Higher plasma NfL and Aβ42/40 ratio were associated with cerebrovascular neuropathologic scales ($p<0.05$) but not with Braak stage, neuritic plaque score, or Thal phase. Plasma Aβ42/40 and NfL explained up to 18% of the variability in cerebrovascular neuropathologic scales. Discussion In participants predominantly with modest levels of Alzheimer's pathologic change, biomarkers of amyloid and neurodegeneration were associated with cerebrovascular neuropathology. NfL is a non-specific marker of brain injury, therefore its association with cerebrovascular neuropathology was expected. The association between elevated Aβ42/40 and cerebrovascular disease pathology needs further investigation but could be due to the use of less specific amyloid-β assays (x-40, x-42).

Title: Imaging of White Matter Injury Correlates with Plasma and Tissue Biomarkers in Pediatric Porcine Model of Traumatic Brain Injury
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Abstract: Traumatic brain injury (TBI) causes significant white matter injury which have been characterized by various rodent and human clinical studies. However, the exact time course of imaging changes in a pediatric brain after TBI, and its relation to biomarkers of injury and cellular function is unknown. To study the changes in major white matter structures using a valid model of TBI that is comparable to a human pediatric brain in terms of size and anatomical features, we utilized a pediatric porcine model of injury with controlled cortical impact (CCI). Using diffusion tensor imaging (DTI) differential tractography, we show progressive anisotropy changes at major white matter tracts such as the corona radiata and inferior fronto-occipital fasciculus between day 1 and day 30 after injury. Moreover, correlational tractography shows a large part of bilateral corona radiata having positive correlation with the markers of cellular respiration. In contrast, bilateral corona radiata has a negative correlation with the biomarkers of injury such as neurofilament light (NFL) or glial fibrillary acidic protein (GFAP). These are expected correlational findings given that higher integrity of white matter would be expected to correlate with lower injury biomarkers. We then studied the magnetic resonance spectroscopy (MRS) findings and report decrease in N-acetylaspartate/creatinine (NAA/Cr) ratio at the peri-contusional cortex, subcortical white matter, corona radiata, thalamus, genu and splenium of corpus callosum at 30 days indicating injury. There was also an increase in choline/creatinine (Cho/Cr) ratio in these regions indicating rapid membrane turnover. Given the need for a pediatric TBI model that is comparable to human pediatric TBI, these data support the use of pediatric pig model with CCI in future investigations of therapeutic agents. This model will allow future TBI researchers to rapidly translate our preclinical study findings into clinical trials for pediatric TBI.

Title: Lower White Matter Volume and Worse Executive Functioning Reflected in Higher Levels of Plasma GFAP among Older Adults with and Without Cognitive Impairment
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Abstract: OBJECTIVE: There are minimal data directly comparing plasma neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) in aging and neurodegenerative disease research. We evaluated associations of plasma NfL and plasma GFAP with brain volume and cognition in two independent cohorts of older adults diagnosed as clinically normal (CN), mild cognitive impairment (MCI), or Alzheimer's dementia. METHODS: We studied 121 total participants (Cohort 1: n = 50, age 71.6 ± 6.9 years, 78% CN, 22% MCI; Cohort 2: n = 71, age 72.2 ± 9.2 years, 45% CN, 25% MCI, 30% dementia). Gray and white matter volumes were obtained for total brain and broad subregions of interest (ROIs). Neuropsychological testing evaluated memory, executive functioning, language, and visuospatial abilities. Plasma samples were analyzed in duplicate for NfL and GFAP using single molecule array assays (Quanterix Simoa). Linear regression models with structural MRI and cognitive outcomes included plasma NfL and GFAP simultaneously along with relevant covariates. RESULTS: Higher plasma GFAP was associated with lower white matter volume in both cohorts for temporal (Cohort 1: β = -0.33, p = .002; Cohort 2: β = -0.36, p = .03) and parietal ROIs (Cohort 1: β = -0.31, p = .01; Cohort 2: β = -0.35, p = .04). No consistent findings emerged for gray matter volumes. Higher plasma GFAP was associated with lower executive function scores (Cohort 1: β = -0.38, p = .01; Cohort 2: β = -0.36, p = .007). Plasma NfL was not associated with gray or white matter volumes, or cognition after adjusting for plasma GFAP. CONCLUSIONS: Plasma GFAP may be more sensitive to white matter and cognitive changes than plasma NfL. Biomarkers reflecting astroglial pathophysiology may capture complex dynamics of aging and neurodegenerative disease.