HIGHLIGHTS

ECTRIMS 2024

A Sanofi event

Copenhaguen | September 19th

MAT-ES-2402844-1.0 – 10/2024

2024 HIGHLIGHTS ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Novedades en biomarcadores

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Hospital Reina Sofía, Córdoba

MAT-ES-2402844-1.0 – 10/2024

Introducción

Las terapias modificadoras de la enfermedad altamente efectivas han mejorado significativamente la atención de la EM.

Sin embargo, existe la necesidad de biomarcadores sensibles y específicos para:

- Diagnóstico
- Pronóstico
- Seguimiento del tratamiento
- Desarrollo de nuevas intervenciones, particularmente para la EM progresiva.

Biomarcadores clínicamente establecidos en la actualidad

- **Imágenes por resonancia magnética**
  - Las **características** clave incluyen:
    - Ubicación de la lesión (periventricular, yuxtacortical, infratentorial, médula espinal)
    - Morfología (ovoide)
    - Número
    - Realce (indica inflamación activa y alteración de la barrera hematoencefálica)
  - **Realce con gadolinio**:
    - Demuestra una alteración activa de la barrera hematoencefálica.
    - Asociado con la infiltración de células inmunitarias periféricas.
  - **Limitaciones**:
    - Las lesiones pueden no ser específicas.
    - La correlación con la discapacidad clínica es imperfecta.
- **Análisis del líquido cefalorraquídeo**
  - **Bandas oligoclonales**:
    - Presente en el LCR de la mayoría de los pacientes con EM.
    - Indican producción intratecal de inmunoglobulinas.
  - **Limitaciones**:
    - Procedimiento invasivo.
    - No específico de la EM.

Paul A, Comabella M, Gandhi R. Biomarkers in Multiple Sclerosis. Cold Spring Harb Perspect Med. 2019 Mar 1;9(3):a029058. doi: 10.1101/cshperspect.a029058. PMID: 29500303; PMCID: PMC6396336.

Biomarcadores de imagen emergentes

Signo de la vena central

- Señal hipointensa dentro de las lesiones en imágenes ponderadas por susceptibilidad.
- Representa un marcador más específico de la patología de la EM.
- Puede ayudar a diferenciar la EM de otras enfermedades inflamatorias desmielinizantes.

Lesiones con borde paramagnético

- Borde hipointenso que rodea las lesiones en SWI.
- Asociado con la deposición de hierro y la activación microglial.
- Puede reflejar inflamación crónica y neurodegeneración.

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ECTRIMS 2024 | Copenhagen, Denmark
Annual Congress | 18-20 September 2024
Pre-Day | 17 September 2024
Patient Community Day | 20 September 2024
40TH ANNIVERSARY

Clarifying Diagnosis in individuals with White Matter Lesions on cranial MRI: The utility of the Central Vein Sign

Celia Oreja-Guevara1, Lorena Garcia Vasco1, Elda María Alba Suarez1, Irene Gómez Estévez1, Salgado Camara Paula1, Johnny Quezada Sanchez1, Alvarez-Linera Juan2

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Conclusion

In our study, only one case meeting the CVS criteria did not result in a multiple sclerosis diagnosis. The CVS is a significant marker for ruling out MS in patients with WML and uncertain diagnoses in clinical practice promising to improve the precision of differential diagnoses in cases presenting with WML on T2-weighted MRI scans

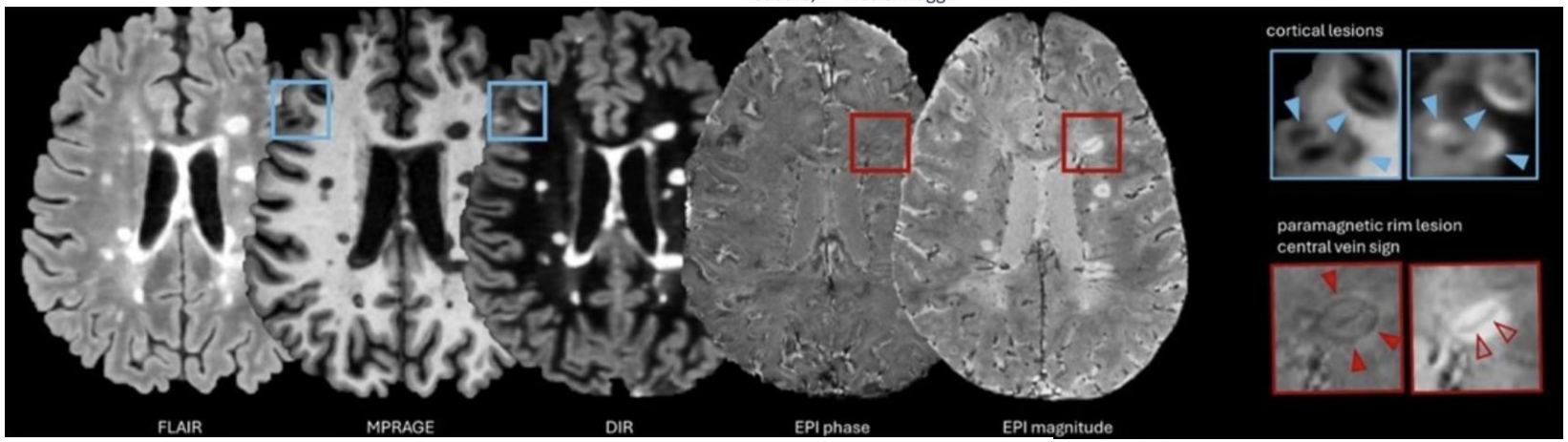
Towards Integration of the Central Vein Sign, Cortical Lesions and Paramagnetic Rim Lesions into Multiple Sclerosis Diagnosis: Insights from Explainable Machine Learning

P718

UCLouvain IoNS INSTITUTE OF NEUROSCIENCE

Maxence Wynen,[1,2*] Colin Vanden Bulcke,[1,2,3*] Serena Borrelli,[2,4] Pedro M. Gordaliza,[5,6] Anna Stölting,[2] François Guisset,[2] Clément Cordier,[1] Maria Sofia Martire,[7] Agnese Tamanti,[8] Benoit Macq,[1] Renaud Du Pasquier,[9] Massimo Filippi,[7,10] Massimiliano Calabrese,[8] Martina Absinta,[11,12] Daniel S. Reich,[13] Meritxell Bach Cuadra,[5,6*] Pietro Maggi[2,3*]

icteam
Imaging and Non-imaging Biomarkers: MRI & PET



Conclusions

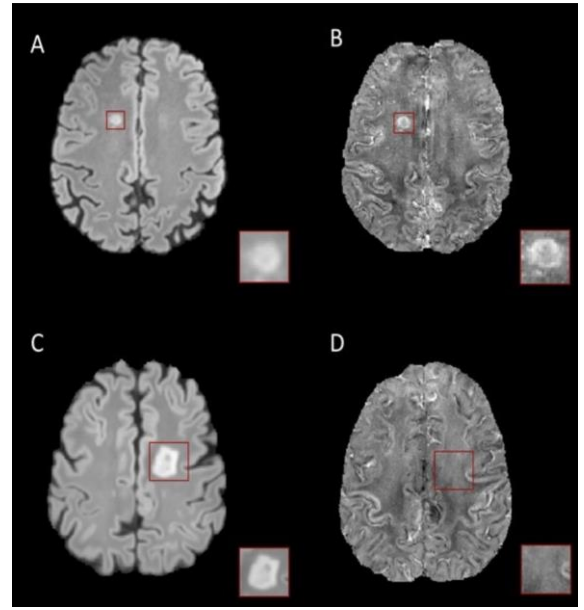
- **CVS** emerges as the **most diagnostically powerful** biomarker
- ML models **combining CVS, CL, and PRL** show the **highest MS diagnostic performance** and clearly outperform the current MS DIS diagnostic criteria.
- **Simplified assessments** are **competitive** against full-count assessments, considerably reducing the time burden associated with image analysis.

Paramagnetic Rim Lesions Predict Cognitive Worsening in Relapse-Free MS Patients Undergoing High-Efficacy Therapies

Boccia VD[1], Leveraro E2, Cipriano E1, Lapucci C1,2, Sirito S1, Cellerino M1, Rebella G3, Nasone L2, Boffa G1, Inglese M1,2

CONCLUSION

Cognitive deterioration is possible even in stable RRMS patients undergoing high-efficacy therapies (HETs). The presence of paramagnetic rim lesions (PRLs), a marker of chronic compartmentalized inflammation, was an independent predictor of SDMT decline. PRLs likely indicate highly disrupted white matter lesions that may worsen cognitive performance over time. Although HETs effectively control inflammatory activity, their impact on PRLs is limited, suggesting that patients with existing PRLs might continue to experience cognitive decline despite optimal treatment.



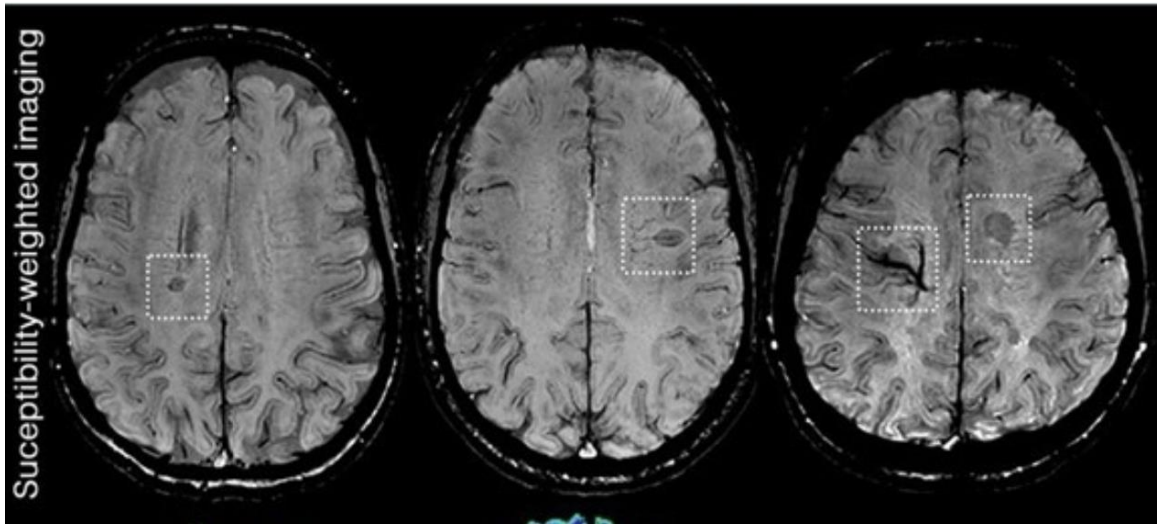
Paramagnetic rim lesions in multiple sclerosis are associated with brain atrophy, whole-brain demyelination, and disability

Elisabeth Sandberg[1, 2], Tobias Granberg[1, 2], Francesca Trogu[1, 3], Nima Chamyani[1], Fredrik Piehl[1, 3], Russell Ouellette[1, 2]

[1] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, [2] Department of Neuroradiology, Karolinska University Hospital, Stockholm, Sweden, [3] Department of Neurology, Karolinska University Hospital, Stockholm, Sweden

Conclusion

- **PRLs** are associated with **brain atrophy**, **whole-brain demyelination**, and **cognitive** and **physical disability**.
- **PRLs** are a **promising marker** for **clinical trials** focusing on progressive aspects of **MS** and potential **remyelinating therapies**.



Biomarcadores de imagen emergentes

- **Tomografía de coherencia óptica (OCT)**
  - Técnica de imagen no invasiva para medir el grosor de la capa de fibras nerviosas de la retina.
  - El adelgazamiento de la RNFL se correlaciona con la progresión de la discapacidad en la EM.
  - Puede ser útil para monitorizar la actividad de la enfermedad y la respuesta al tratamiento

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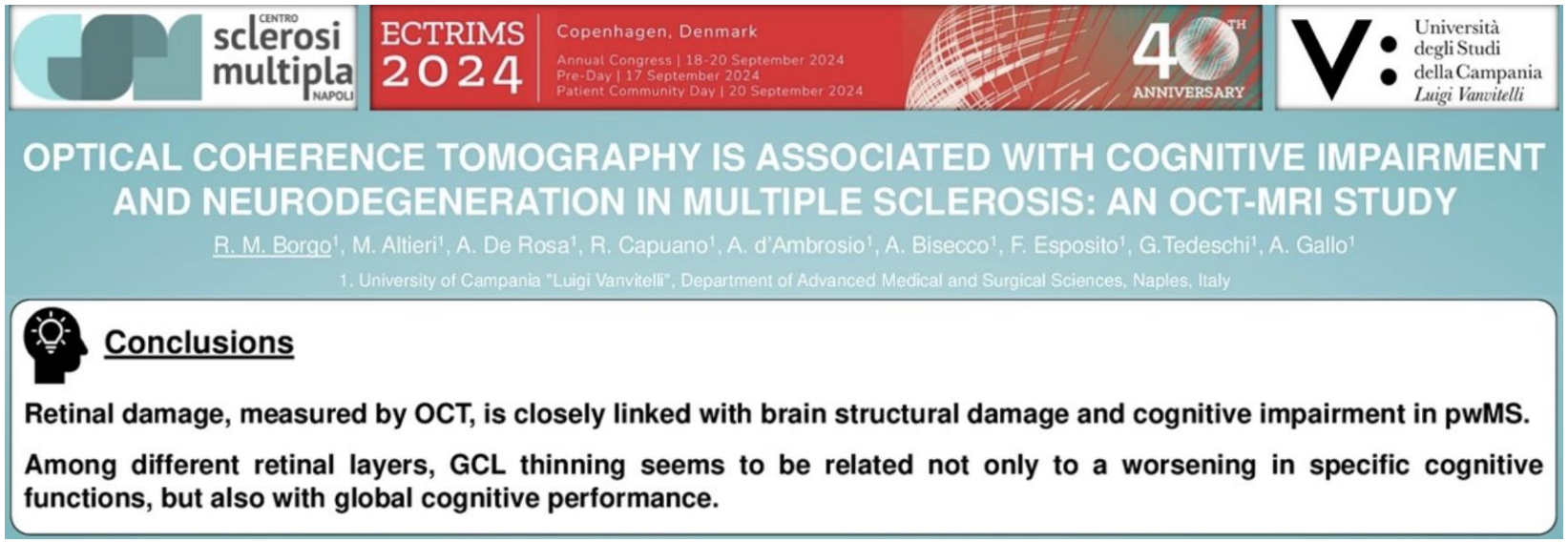
Presentation ID O046

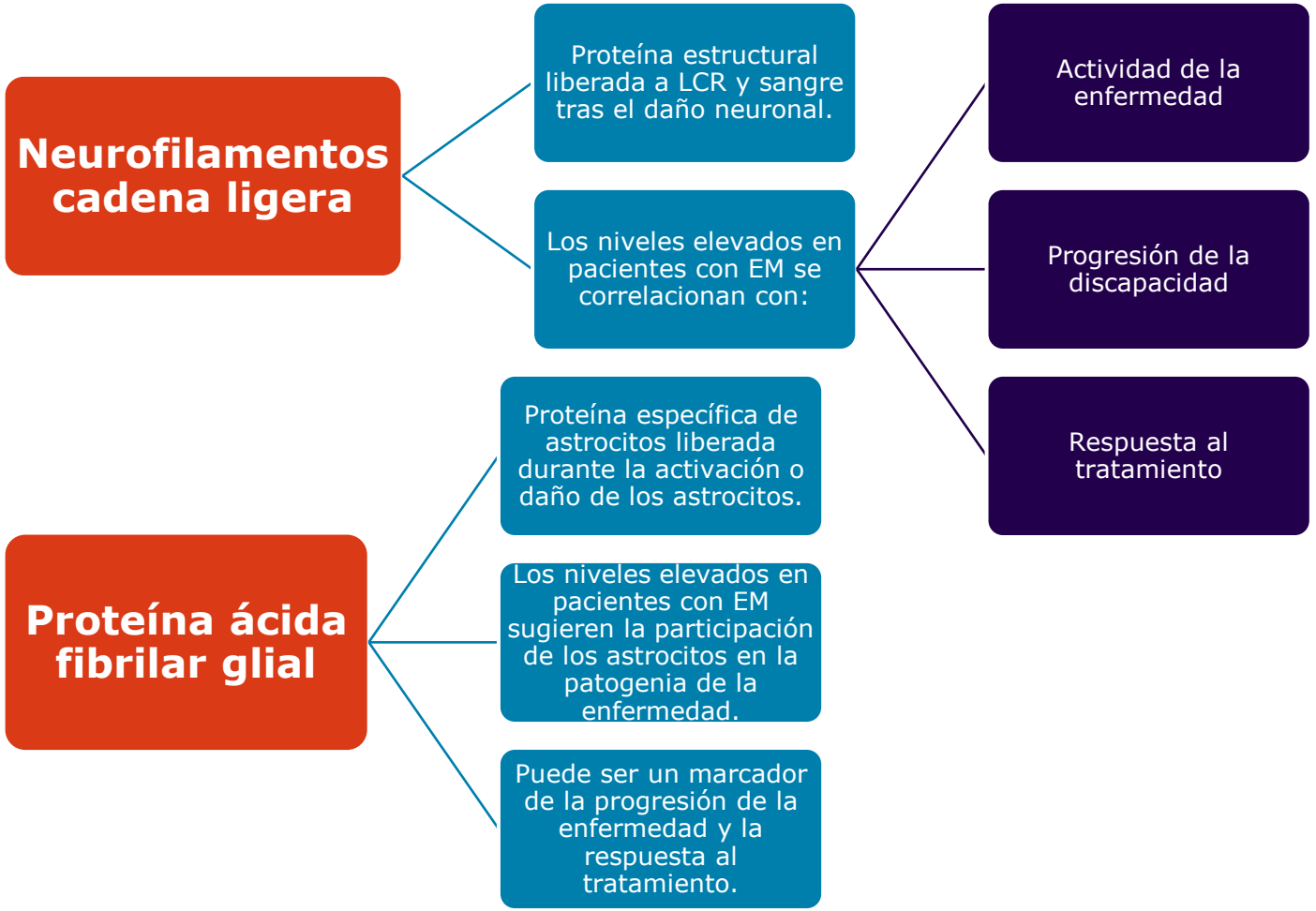
OCT improves risk stratification for PIRA at diagnosis of relapsing multiple sclerosis

Room	**A3**
Date	Thursday, 19 September 2024, 10:30 - 10:40 CEST
Part of session	**> Free Communications 4: Imaging**

- ✓ Assessment of retinal layer thickness at RMS diagnosis improves prediction of PIRA.
- ✓ 313 RMS patients (mean age 30.5 years [SD 7.9], 74.1% female) over a median observation period of 70 months.
- ✓ Retinal layer thickness assessed by OCT improved stratification for risk of PIRA at RMS diagnosis, likely identifying patients with already pronounced subclinical neuroaxonal damage and potentially informing treatment strategy.



Biomarcadores líquidos emergentes



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Clinical utility of the Lumipulse™ immunoassay for plasma neurofilament light chain in multiple sclerosis

V.Nicolella[1], M. Fiorenza[2], I. Monteiro[3,4,5], F. Novarella[1], R.[2], M. D'Angelo[2], G. Carbone[2], E. La Civita[2], A. Esposito[1], V. Criscuolo[3], A. Carotenuto[1,5], M. Petracca[6], R. Lanzillo[1,5], G. Castaldo[3,7], V. Brescia Morra[1,5], D. Terracciano[2], M. Moccia[3,5]

1 - Department of Neuroscience, Reproductive Science and Odontostomatology, Federico II University of Naples, Naples, Italy, 2 - Department of Translational Medical Sciences, Federico II University of Naples, Naples, Italy, 3 - Department of Molecular Medicine and Medical Biotechnology, Federico II University of Naples, Italy, 4 - Neurology Department, Coimbra University Hospital Center, Coimbra, Portugal, 5 - Multiple Sclerosis Unit, Policlinico Federico II University Hospital, Naples, Italy, 6- Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy., 7 - Centre for Advanced Biotechnology (CEINGE), Naples, Italy

CONCLUSIONS

This is the first study showing clinical utility of NfL measured using Lumipulse™ immunoassay in MS. We confirmed that higher values of blood NfL are associated with inflammatory activity and disability, as from neuro-axonal loss.
Lumipulse™ is a novel methodology to analyse blood NfL levels, whose utilization in clinical practice will require integration with individual characteristics, including age and presence of cardiovascular comorbidities.

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Local implementation of an immunoassay for measurement of serum neurofilament light chain on a clinically available platform

Elias Sotirchos[1], Kathryn Fitzgerald[1], Matthew Smith[1], Yasmin Resto[1], Phaedre Mohr[2], Ellen Mowry[1], William Clarke[2], Peter Calabresi[1]

1. Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
2. Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Conclusions

- Serum NfL measurements obtained from the Siemens Atellica acridinium-ester immunoassay, as implemented at our site, exhibited excellent agreement with those from the reference laboratory, with excellent repeatability.
- Local measurement of serum NfL holds promise for improving access to NfL testing and allowing for rapid result reporting that can inform clinical decision-making in real-time.

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CAN SERUM NEUROFILAMENT LIGHT CHAIN TESTING BE USEFUL FOR THERAPEUTIC DECISIONS IN RELAPSING-REMITTING MULTIPLE SCLEROSIS WITH COGNITIVE IMPAIRMENT?

José M García-Domínguez[1], Rocío Gómez-Ballesteros[2], Luis Querol[3], José E Meca-Lallana[4], Lamberto Landete[5], Virginia Meca-Lallana[6], Luisa M Villar[7], Sergio Martínez-Yélamos[8], Elena García-Arcelay[2], Eduardo Agüera[9], Jorge Maurino[2], Ana B Caminero[10], Nicolas Medrano[2], Enric Monreal[11], Gustavo Saposnik[12,13]

CONCLUSIONS

- Suboptimal decision-making is a common phenomenon affecting nearly 5 out of 10 neurologists in a simulated case involving a patient who remained clinically and radiologically stable but experienced cognitive decline and high levels of sNfL.
- Higher prevalence of suboptimal decision-making was associated with the lack of full dedication to MS and a limited perception of sNfL benefits.
- Efforts led by scientific societies may be essential for developing evidence-based guidelines and educational initiatives that enhance neurologists' understanding of sNfL testing and treatment decisions relevant to managing MS patients with cognitive impairment.

P1675 Light chain serum neurofilaments to predict long term evolution in NEDA3 patients

Virginia Meca*1, 1, Clara Aguirre1, Marta Domínguez Gallego1, Beatriz DEL Rio Muñoz1, Luisa Maria Villar Guimerans2
1University Hospital Princesa. Institute of Research Princesa. , Neurology Department. MS Centre, Madrid, 2University Hospital Ramón y Cajal, Immunology, Madrid

CONCLUSIONS

- The majority of patients keep NEDA3 status 3 years later
- NfLs levels predicted activity in the next year
- We consider that the determination of NfLs must be periodically in order to improve the ability to predict activity.

Prognostic Value of Baseline Serum Neurofilament Light Chain Levels in People With Relapsing Multiple Sclerosis by Prior Treatment Status and DMT Type

Stefan Bittner[1], Anne H. Cross[2], Gabriel Pardo[3], Scott S. Zamvil[4], Alit Bhatt[5], Wenjia Wei[6], Ibolya Boer[6], Eric Thouvenot[7,8], Tjalf Ziemssen[9]

CONCLUSIONS

- Baseline sNfL levels were **prognostic for neT2 lesions across previously treated and treatment-naive participants**
  - Among previously treated participants, baseline sNfL levels were prognostic for future lesion formation across most previous DMT types
- The results support the **use of sNfL as a prognostic biomarker in pwRMS who are treatment naive as well as those previously treated with DMTs.** Additional work has been performed to identify and clinically validate a prognostic NfL threshold in pwRMS (see ePoster P1850 for further information)

Serum Glial Fibrillary Acidic Protein (sGFAP) and serum Neurofilament Light Chain (sNfL) as potential biomarkers for cognition and neuropsychiatric symptoms in multiple sclerosis?

Tristan Kölsche[1], Alina Renner[2], Orhan Aktas[1], Sharon Bätge[2], Melanie Filser[2,3], Philipp Albrecht[1,4], Falk Steffen[5], Stefan Bittner[5], Sven G. Meuth[1], Marc Pawlitzki[1], Iris-Katharina Penner[2,6]

CONCLUSIONS & OUTLOOK

- The study findings demonstrate several correlations between serum biomarkers (GFAP and NfL) and various clinical measures in patients with MS:
  - Both sGFAP and sNfL levels increased with age and disease duration.
  - Higher EDSS scores were associated with elevated levels of both biomarkers, indicating a relationship between biomarker concentrations and disability progression.
  - Cognitive performance, especially concerning information processing speed measured by the SDMT, showed a negative correlation with both sGFAP and sNfL levels, suggesting that higher biomarker levels may be associated with cognitive decline. However, association was stronger with sNfL when compared to sGFAP.
  - Fittingly, visuospatial memory, but also fatigue scores were correlated with sNfL but not with sGFAP.
- These findings suggest that serum sGFAP and sNfL may serve as valuable biomarkers for assessing disease progression, some cognitive domains, and fatigue in MS patients. sNfL may have advantages in monitoring neurocognitive status when compared to sGFAP, as previously postulated[1]. However, both show promising associations with classic clinical measures such as the EDSS.

Predictive value of early sGFAP z-scores for disability progression in patients with NEDA3 status in the first year after diagnosis

F. Steffen*, M. Protopapa*, J. Quartey*, M. Schraad, T. Uphaus, K. Pape, V. Fleischer, F. Lüssi, F. Zipp*, S. Bittner*

Results

We used the NIND cohort to calculate sGFAP z-scores adjusted for BMI (negatively associated with sGFAP; **Fig. 1A**), sex (no significant difference; **Fig. 1B**) and age (see **Fig. 1C** for the resulting percentile curves) in our MS cohort. The proportion of females differed between cohorts (MS: 64.4%, Control: 79%, $p < 0.001$) while age was similar. In line with previous publications, females in the MS cohort had higher absolute baseline sGFAP levels ($p = 0.012$; **Fig. 2A**). GAMLSS-derived sGFAP z-scores significantly correlated with sNFL z-scores (spearman rho = 0.206, $p = 0.002$; **Fig. 2B**). MS cohort stratification by sGFAP z-scores (GFAP-low: z-score <1.5; GFAP-high: z-score ≥1.5) showed significant differences in age, symptom duration, and disease-modifying therapy (**Table 1**). Disability progression was faster in the GFAP-high group (LMM, $\beta = 0.10$, 95% confidence interval 0.06 to 0.14, $p < 0.001$; **Fig. 3A; Table 2**).

Biomarcadores líquidos emergentes

Citocinas y quimiocinas

- Moléculas de señalización implicadas en la regulación inmunitaria y la inflamación.
- Niveles alterados en LCR y sangre de pacientes con EM.
- Biomarcadores potenciales para:
  - Actividad de la enfermedad
  - Respuesta al tratamiento
  - Subtipos de EM

Disfunción glial:

- **Proteína ácida fibrilar glial** (como se mencionó anteriormente)
- **Proteína S100B** (asociada con daño a los astrocitos)
- **Quitinasa 3 similar a 1 (CHI3L1)** (implicada en la activación microglial)

Paul A, Comabella M, Gandhi R. Biomarkers in Multiple Sclerosis. Cold Spring Harb Perspect Med. 2019 Mar 1;9(3):a029058. doi: 10.1101/cshperspect.a029058. PMID: 29500303; PMCID: PMC6396336.

Prognostic potential of plasma Interleukin-6 levels as biomarker for long-term cognitive performance

Clàudia Coll-Martínez[1, 2, 3], Joana Maria Huertas Pons[1,3], Albert Miguela Benavides[1], Gary Ciceron Álvarez Bravo[1, 2, 4], Ariadna Gifreu-Fraixinó[1, 2], Judit Salavedra-Pont[1,2], Jordi Gich Fulla[1, 2, 4], Lluís Ramió-Torrentà[1, 2, 3, 4, 5], Ana Quiroga-Varela[1, 3]

Conclusion: Our findings reveal a significant link between higher plasma IL-6 levels and impaired cognitive performance, observed through poorer scores of attention, information processing speed and working memory at baseline and over a 10-year follow-up in pwMS. This highlights plasma IL-6's potential as a predictive biomarker for identifying CI and guiding long-term prognostic assessments in this population.

Interleukin-8 plasma levels as a potential biomarker for predicting middle-term cognitive outcomes

Huertas-Pons J.M. [1,2] , **Miguela-Benavides A.** [1] , **Coll-Martínez C .**[1,2,3], **Gifreu-Fraixinó A.** [1,3] , **Salavedra-Pont J.** [1,3] **Álvarez-Bravo G .**[1,3], **Gich-Fulla J.** [1,3], **Ramió-Torrentà L.** [1,2,4, 5] , **Quiroga-Varela A.** [1,2]

Table 2. Linear regression results (age and education adjusted)

	IL-8		
	β	95 % CI	P value
SDMT Diagnosis	*β*=-0.109	-2.938 to 1.611	p= 0.555
SDMT Follow-up	*β*=-0.375	-5.472 to -0.226	**p= 0.034***

SDMT: symbol Digit Modalities Test

CONCLUSIONS

Baseline IL-8 levels in MS patients are predictive of significant cognitive decline over a 5-year period, positioning IL-8 as a potential biomarker for predicting middle term cognitive progression in MS. This finding underscores the need for further research into IL-8's role in cognitive impairment.

Evaluation of CHI3L1 Levels in Cerebrospinal Fluid as a Potential Biomarker for Disease Progression in Multiple Sclerosis Patients: A Study from the Multiple Sclerosis Unit at Virgen Macarena University Hospital in Seville

Eichau S[1], Garcia-Sanchez MI[2], Lopez-Ruiz, R[1].
1. MS Unit UEMAC. Virgen Macarena Hospital, Sevilla. Spain. 2. Biobanco del Sistema Sanitario Publico de Andalucia/Spanish

CONCLUSIONS:

Despite the absence of statistical significance, graphical trends suggest potential associations between CHI3L1 levels and disease progression.

Notably, patients reaching an EDSS of 3.0 or higher displayed higher CHI3L1 levels and also patients with PIRA had higher CHI3L1 levels at diagnosis .

This pilot study provides insights into the relationship between CHI3L1 and disability progression, supporting its potential as a prognostic biomarker.

In conclusion, this study lays the groundwork for exploring CHI3L1 as a potential biomarker in MS progression. Further research with expanded cohorts is essential for comprehensive validation and clinical implementation.

Emerging CSF biomarkers of Paramagnetic RIM lesions in RRMS showing progression independent of relapse

Anna Signoretto[1], Agnese Tamanti[1], Giulia Zanetti[1], Daniela Anni[1], Arianna Cavagna[1], Federica Virla[1], Ermanna Turano[1], Chiara Eccher[1], Valentina Camera[1], Damiano Marastoni[1], Francesca Benedetta Pizzini[2], Massimiliano Calabrese[1].

CSF

Upregolation of TNF (p=0.039) in PRL+ subjects as compared to PRL- was shown in a preliminary analysis of proteomic CSF profile in MS_PIRA-.

Additionally, **MS_PIRA+** CSF preliminary analyses showed an **upregulation** of **CXCL12** (p=0.018), **TNF** (p=0.041), **CCL25** (p=0.026) in **MS_PIRA+_PRLs+** compared to MS_PIRA+_PRLs-. (Table III)

Table III. MS_PIRA+_PRLs+ vs MS_PIRA+_PRLs- CSF analyses

	Fold Change	p-value*
CXCL12	2.47	0.018
TNF	3.96	0.041
CCL25	4,17	0.026

*Wilcox test

Biomarcadores líquidos emergentes

MicroARN (miARN)

- Pequeños ARN no codificantes que regulan la expresión génica.
- Desregulado en pacientes con EM.
- Biomarcadores potenciales para:
  - Diagnóstico
  - Pronóstico
  - Respuesta al tratamiento

Vesículas extracelulares y exosomas

- Pequeñas vesículas unidas a la membrana liberadas por las células.
- Contienen proteínas, lípidos y ácidos nucleicos que reflejan la célula de origen.
- Biomarcadores potenciales para:
  - Actividad de la enfermedad
  - Respuesta al tratamiento

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Emergentes y futuros según la patogenia

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Daño axonal y neuronal:

- **Cadena ligera de neurofilamentos** (como se mencionó anteriormente)
- **Proteína 14-3-3**
- **Enolasa específica de neuronas**

Disfunción glial:

- **Proteína ácida fibrilar glial** (como se mencionó anteriormente)
- **Proteína S100B** (asociada con daño a los astrocitos)
- **Quitinasa 3 similar a 1 (CHI3L1)** (implicada en la activación microglial)

Desmielinización:

- **Proteína básica de la mielina**
- **Glicoproteína de oligodendrocitos de mielina**

Inflamación:

- Varias **citoquinas**, incluyendo:
  - **Factor de necrosis tumoral alfa**
  - **Interleucina-17**
  - **Interferón gamma**

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Muchas *gracias!*

Tiempo de debate

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