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Proteomic Biomarker Panel for Gauging Multiple Sclerosis Disease Activity: A Case Series from Real-World Use

T. Gonyou[1], J. Eubanks[2], P. Izbicki[2], F. Qureshi[2], W. Boudouris[1], M. Belkin[1], S. Rossman[1]
[1]*Michigan Institute for Neurological Disorders (MIND), Farmington Hills, MI*
[2] *Octave Bioscience, Menlo Park, CA*

OCTAVE

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BACKGROUND

- A multi-protein Multiple Sclerosis Disease Activity (MSDA) test utilizes an algorithm consisting of 18 biomarkers to produce 4 disease pathway scores (i.e. immunomodulation, neuroinflammation, myelin biology, neuroaxonal integrity) (Figure 1 and 2) and an overall disease activity (DA) score.
- The MSDA test has been analytically and clinically validated[1,2]. The MSDA test score is scaled from 1.0 - 10.0 with 0.5 intervals.
- The categories are defined as low, moderate, and high with ranges of 1.0 - 4.0, 4.5 - 7.0, and 7.5 - 10.0, respectively.
- The validated MSDA test was initially piloted in select MS Centers of Excellence, Centers for Comprehensive MS Care, and private MS clinics. It is now broadly available for routine clinical use.

OBJECTIVES

- To describe real-world clinical experience using the MSDA test. We were particularly interested in two exploratory questions:
  - How do the MSDA results reconcile with clinical presentation, radiographic evidence, and patient history?
  - How do these insights into the underlying biology of MS support clinical decisions?

CASE METHODS

- Five persons with MS (pwMS) with various ages, disease durations, disease modifying therapy (DMT) use, and radiographic presentations from MIND are presented in this case series report (Table 1).

	Age	Sex	Ethnicity & Race	Disease Duration (Years)	Current DMT	Test Reason
PwMS 1	35	Female	Caucasian	6	Natalizumab	Relapse
PwMS 2	55	Female	Caucasian	15	Ocrelizumab	Other
PwMS 3	50	Female	Caucasian	6	Ofatumumab	Routine
PwMS 4	29	Female	Other	21	Dimethyl Fumarate	Routine
PwMS 5	46	Female	Caucasian	0.8	None	Baseline

Table 1. Case Series Demographics Overview

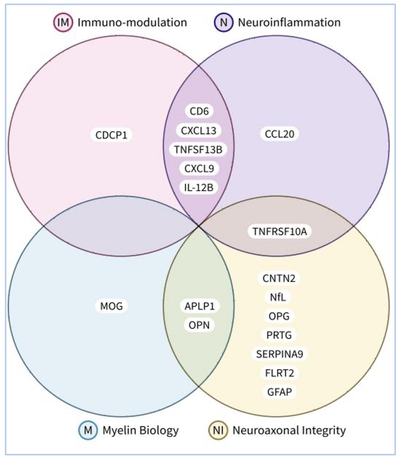

Figure 1. MSDA Pathway Categories and Biomarkers

Biomarker	Pathways	Concentration	MS Range*	Percentile[1]
NfL Neurofilament light	NI	8.36 pg/mL	3.5 - 42 pg/mL	44th
GFAP Glial Fibrillary Acidic Protein	NI	91.78 pg/mL	24 - 220 pg/mL	62nd
SERPINA9 Serpin Family A Member 9	NI	32.71 pg/mL	12 - 160 pg/mL	34th
FLRT2 Leucine-rich repeat transmembrane protein	NI	100.27 pg/mL	63 - 180 pg/mL	44th
CNTN2 Contactin 2	NI	2.54 ng/mL	0.65 - 3.3 ng/mL	93rd
PRTG Protogenin	NI	144.05 pg/mL	71 - 180 pg/mL	84th
OPN Osteopontin	NI M	15.13 ng/mL	9.5 - 39 ng/mL	27th
MOG Myelin Oligodendrocyte Glycoprotein	M	31.45 pg/mL	12 - 47 pg/mL	81st
CXCL9 Monokine Induced by Gamma Interferon	IM N	20.28 pg/mL	17 - 250 pg/mL	7th
CXCL13 C-X-C Motif Chemokine Ligand 13	IM N	56.33 pg/mL	22 - 190 pg/mL	61st
CD6 Cluster of Differentiation 6	IM N	119.99 pg/mL	46 - 250 pg/mL	62nd
CCL20 MIP 3-alpha	N	27.54 pg/mL	2.1 - 52 pg/mL	95th
Inversely Correlated with Disease Activity				
APLP1[2] Amyloid Beta Precursor Like Protein 1	NI M	18.24 ng/mL	5.5 - 22 ng/mL	92nd
OPG[2] Osteoprotegerin	NI	0.58 ng/mL	0.41 - 1.4 ng/mL	27th
TNFRSF10A[2] TRAIL-R1	NI N	3.80 pg/mL	2.8 - 9.7 pg/mL	17th
TNFSF13B[2] BAFF	IM N	3.95 ng/mL	2.3 - 10 ng/mL	36th
IL-12B[2] Interleukin 12B	IM N	69.71 pg/mL	28 - 280 pg/mL	30th
CDCP1[2] CUB domain-containing protein 1	IM	71.10 pg/mL	28 - 230 pg/mL	50th

Figure 2. MSDA Individual Biomarkers Example

PwMS 1

- This is a 35 year old (YO) caucasian female with a disease duration of 6 years that relapsed on natalizumab. She initially presented with optic neuritis in 2016. She subsequently underwent MRIs and lumbar puncture which revealed demyelination and positive oligoclonal bands consistent with a diagnosis of multiple sclerosis. She initially went on glatiramer acetate however she discontinued therapy.
- In June 2021, she developed left hand weakness and full body numbness. MRI of the brain revealed an enhancing lesion and development of new white matter lesions in the bilateral cerebral hemispheres compared to 2018. MRI of the cervical spine revealed a new enhancing lesion. She was then started on natalizumab in October 2021. She had breakthrough disease on a subsequent brain MRI in August 2022 which revealed several new, non-enhancing lesions. Further testing revealed neutralizing antibodies. Her **MSDA score was 8 (high)**, suggesting high disease activity. Natalizumab was discontinued. She was subsequently started on ocrelizumab. We will plan to longitudinally follow this patient.

Disease Activity Score **8.0** High — Patient has a High Disease Activity (DA) Score. A DA Score in this category indicates the probability of significant radiographic disease activity is present and suggests a suboptimal response to current interventions.

PwMS 2

- This is a 55 YO caucasian female with a disease duration of 15 years. She has evidence of demyelination in the brain and cervical spine. She missed 1 dose of ocrelizumab due to infection. An brain MRI subsequently revealed incidental acute infarcts and a new non-enhancing, demyelinating lesion. She was found to have a patent foramen ovale and underwent closure. She resumed ocrelizumab.
- She has since complained of worsening symptoms including cognitive complaints. However, she also felt this to be a residual deficit of her stroke. Recent brain MRI stable. MSDA score ordered to verify this stability. Her **MSDA score was 2 (low)**, suggesting low disease activity.

Disease Activity Score **2.0** Low — Patient has a Low Disease Activity (DA) Score. Generally, this indicates disease activity is well controlled as evidenced by a high probability of minimal or no radiographic worsening.

PwMS 3

- This is a 50 YO caucasian female with a disease duration of 6 years. She was transitioned from diroximel fumarate to ofatumumab in June 2021 after breakthrough disease activity on brain and cervical spine MRI.
- Her subsequent **MSDA score was 1 (low)**, suggesting low disease activity.

Disease Activity Score **1.0** Low — Patient has a Low Disease Activity (DA) Score. Generally, this indicates disease activity is well controlled as evidenced by a high probability of minimal or no radiographic worsening.

PwMS 4

- This is a 29 YO (ethnicity/race other) female with a disease duration of 21 years. Patient was on dimethyl fumarate but was poorly compliant. She stopped DMT for pregnancy. However, in June 2021, she had breakthrough disease on brain MRI during the second trimester of pregnancy. Dimethyl fumarate was subsequently resumed.
- Her **MSDA score was 5 (moderate)**, suggesting moderate disease activity. She has since decided to transition therapy to ocrelizumab. We will plan to longitudinally follow this patient.

Disease Activity Score **5.0** Moderate — Patient has a Moderate Disease Activity (DA) Score. A DA Score in this category indicates the probability of radiographic worsening is greater than in the Low DA category, but less than that observed with High DA scores.

PwMS 5

- This is a 46 YO caucasian female with a disease duration of 8 months and not yet on disease modifying therapy. She presented with paresthesias. Brain MRI revealed demyelination. No demyelination seen in the cervical or thoracic spinal cord. Lumbar puncture with positive oligoclonal bands.
- Her **MSDA score was 6 (moderate)**, suggesting moderate disease activity. She decided to start high efficacy therapy with natalizumab and is stable.

Disease Activity Score **6.0** Moderate — Patient has a Moderate Disease Activity (DA) Score. A DA Score in this category indicates the probability of radiographic worsening is greater than in the Low DA category, but less than that observed with High DA scores.

DISCUSSION AND CONCLUSIONS

- Our case series demonstrate that disease activity scores appear to correlate with clinical relapses, radiographic brain and/or spinal disease, and efficacy of therapy.
- The MSDA test may be used to verify stability and may support the clinical decision to alter therapy. The case studies reported here provide snapshot MSDA scores that may change with both clinical and subclinical disease activity.
- Therefore, the ability to follow patients longitudinally will provide additional insights into patient disease activity and may impact clinical decision-making.
- Future directions include longitudinal following of patients from baseline (specifically PwMS 1, 3, and 5), MSDA scores through disease activity cycle (pre and post relapse), and DMT response signatures and predictors.

REFERENCES AND DISCLOSURES

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CORRESPONDENCE

Taylor Gonyou, DO
Michigan Institute for Neurologic Disorders
Email: tgonyou@mindonline.com
Website:mindonline.com

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