CSF FETUIN-A IS A BIOMARKER OF SUBCLINICAL DISEASE ACTIVITY IN PROGRESSIVE MULTIPLE SCLEROSIS

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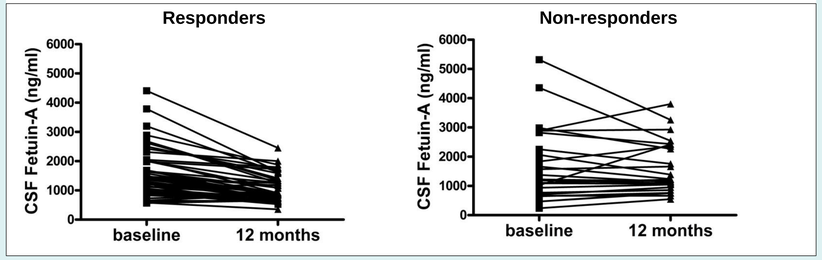
INTRODUCTION

- There is an unmet need for accurate and predictable biomarkers for the effective stratification of treatment for individual MS patients.
- Because disease worsening is difficult to quantify using standard imaging metrics, biomarkers measuring disease activity in progressive MS are of particular interest.
- We recently identified Fetuin-A as a cerebrospinal fluid (CSF) biomarker for disease activity in the relapsing-remitting subtype of MS (RRMS). RRMS patients with active disease show elevated levels, while a therapeutic response to natalizumab correlates with decreased levels (Fig 1).
- Further studies have shown that expression of Fetuin-A is markedly upregulated in demyelinated areas and in the gray matter of human MS and mouse EAE brain samples, and that the protein contributes to disease severity in the animal model.

Figure 1. CSF fetuin-A correlates with a therapeutic response to natalizumab. CSF fetuin-A levels were significantly reduced after 12 months in RRMS patients responding to natalizumab treatment compared to baseline, while non-responders exhibited no significant differences.[1]



OBJECTIVE

To determine if CSF fetuin-A levels correlate with disease progression and/or activity in progressive MS patients

DESIGN & METHODS

- Patients with clinically definite primary and secondary progressive MS (see Table 1) were classified as having disease activity on the basis of patient self-reporting, change in EDSS, and/or change in MRI over a period of 24 months.
- CSF fetuin-A levels were measured by ELISA in all patients. Cutoff values for elevated fetuin-A levels were set at 1000 ng/ml.
- All samples and clinical information were obtained with IRB approval and informed consent
- Statistical significance determined by one-way ANOVA and student's t test.

RESULTS

Table 1. Patient demographics

MS Subtype	N	Gender M:F	Average Age (Range)	Average EDSS (Range)	Average Disease Duration (Range)
RRMS	70	1:3.4	41 (21 - 62)	2.4 (0 – 6.5)	12 (2 – 34)
SPMS	75	1:2.9	53 (30 – 74)	5.6 (2.0 – 9.0)	21 (1 – 40)
PPMS	40	1:1.9	54 (30 – 76)	5.0 (1.5 – 8.5)	14 (1 – 46)

Figure 2. CSF fetuin-A levels by disease subtype. CSF fetuin-A levels are significantly elevated in patients with secondary progressive MS (SPMS) (*p < 0.05)* and primary progressive MS (PPMS) (*p < 0.01)* compared to RRMS patients. Values represent mean ± standard error.

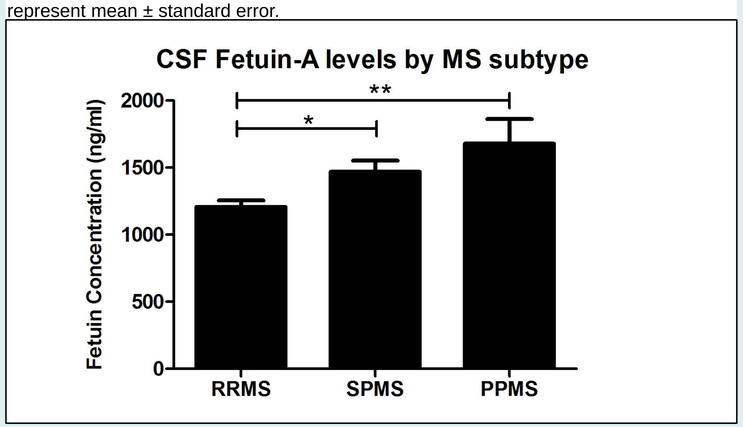


Table 2. MRI activity and fetuin-A levels in clinically active vs. inactive MS. No correlation exists between clinical disease activity and MRI activity. Patients with clinically active MS have significantly elevated CSF fetuin-A levels over patients with inactive disease (see Figure 3). Fetuin-A values represent mean ± standard deviation .

*Clinically **Active** MS*

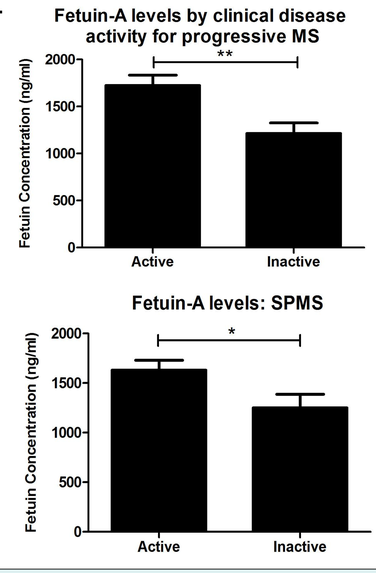
MS Subtype	% Active MRI	% High Fetuin-A (>1000 ng/ml)	CSF Fetuin-A (ng/ml)
Progressive	3%	84%	1724 ± 944
SPMS	2%	86%	1655 ± 656
PPMS	3%	81%	1854 ± 1240

*Clinically **Inactive** MS*

MS Subtype	% Active MRI	% High Fetuin-A (>1000 ng/ml)	CSF Fetuin-A (ng/ml)
Progressive	0%	51%	1213 ± 718
SPMS	0%	53%	1251 ± 770
PPMS	0%	44%	1079 ± 502

RESULTS

Figure 3. Fetuin-A levels in progressive MS. Patients with clinically active, progressive MS have higher levels of CSF fetuin-A than those with inactive disease (**a**, *p < 0.01)*). This difference is more pronounced among the PPMS population (**b**, *p < 0.01)* than in SPMS patients (**c**, *p < 0.05).*



CONCLUSIONS

- **Standard MRI measurements are a poor determinant of disease activity in patients with progressive disease.**
- **CSF fetuin-A levels may provide a quantifiable biomarker of disease activity and appear to correlate with clinical findings, suggesting the possibility of objective determination of therapeutic efficacy in patients with progressive disease.**

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[1]Harris, V. K. *et al*. Cerebrospinal fluid fetuin-A is a biomarker of active multiple sclerosis. *Mult Scler* **19**, 1462-72 (2013)