Pattern of Cognitive Dysfunction Associated with Neuromyelitis Optica (NMO) and Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD)

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Background

- Neuromyelitis optica (NMO) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) present with optic neuritis, transverse myelitis and brain syndromes[1,2].
- Cognitive dysfunction (CD) in NMO and MOGAD is not well recognized and understood[3].
- Our recent work showed ~ 30% of NMO patients experience mild to moderate CD. We also observed pain, neurologic disability, immune therapy, level of education, and race/ethnicity directly influenced cognitive function, whereas gender, relapse rate, lesion location, serological status did not[4].
- The pattern and mechanism of CD in NMO and MOGAD in relation to other neuro degenerative disorders have not been investigated.

Objective

1. To investigate the pattern of CD in NMO and MOGAD patients using neuropsychological testing.
2. To investigate the molecular pathways involved in CD in NMO and MOGAD.

Methods

Neuropsychological analysis. We performed a single center, cross-sectional, retrospective analysis using ICD9/10 codes to search Stanford Research Repository (STARR) database to identify NMO and MOGAD patient who completed neuropsychological testing from 2017-2022.

Plasma biomarker studies. Archived blood samples of NMO, MOGAD, and secondary progressive MS (SPMS) patients (disease control) enrolled in Project BIG (Stanford Brain, Immune and Gut Initiative) from 2019-2022 were studied. We used a high-throughput and fully-automated Lumipulse assay (Fujirebio Diagnostics, US, Malvern, PA) to quantify plasma phosphorylated Tau peptide 181 (pTau181), amyloid beta peptide 42 (Aβ42), and amyloid beta peptide 40 (Aβ40). Plasma samples were thawed, blocked using heterophilic agent, and analyzed (6 replicates/sample) using LUMIPULSE G1200 instrument[5].

Statistical analysis. Plasma peptide concentrations between clinical groups were analyzed by $\log_{10}$- transformed levels using one-way ANOVA, chi-square test, Receiver Operating Characteristic (ROC) curve analysis, Tukey corrected post hoc pairwise comparisons, Mann-Whitney *U* test followed by Dunn's corrected post hoc comparisons.*p<0.05, **<0.01.

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Results

Pattern of cognitive dysfunction

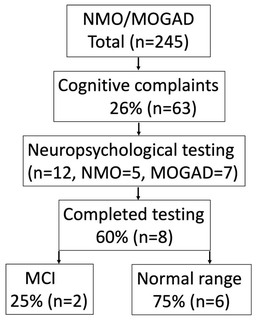

Table 1. Flow chart of cognitive evaluation
MCI, minimal cognitive impairment.

Cognitive functions
- Language
- Confrontation/ set shifting
- Verbal memory
- Sustained attention
- Auditory attention
- Concentration
- Novel problem solving
- Speed of processing
- Delayed recall

Table 2. Defective cognitive domains

Investigation of molecular pathways involved in CD

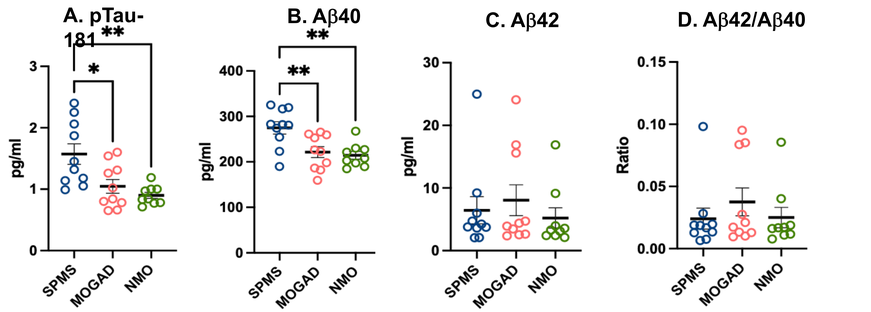

Figure 1. Plasma levels of pTau-181 (**A**), Aβ40 (**B**), Aβ42 (**C**), and Aβ42/ Aβ40 ratio (**D**) in SPMS, MOGAD and NMO patients.

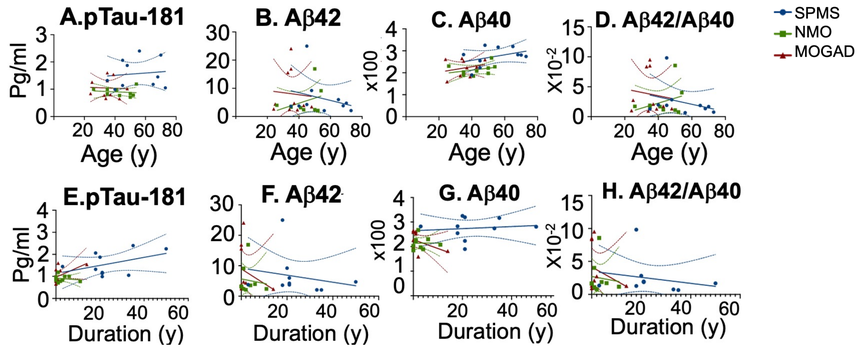

Figure 2. Plasma levels of pTau-181, Aβ40, Aβ42, and Aβ42/ Aβ40 ratio in association with age (**A-D**) and disease duration (**E-H**).

Summary

- Twenty five percent of NMO and MOGAD patients experienced CD, however, <1% is diagnosed with MCI by formal testing.
- Multiple cognitive functions including language, memory and executive function were impacted in NMO and MOGAD patients.
- pTau-181 and Aβ40 expression were significantly lower in the plasma of NMO and MOGAD patients compared to that of SPMS patients.
- Aβ42 and Aβ42/ Aβ40 expression were low in the plasma of NMO, MOGAD and SPMS patients.
- pTau-181, Aβ40, and Aβ42 expression did not change with age or disease duration in NMO and MOGAD unlike in SPMS.

Conclusion and Future Directions

- A quarter of NMO and MOGAD patients experience cognitive symptoms. Multiple domains are impacted on cognitive testing, however, only a small subset meet the diagnosis of cognitive impairment.
- CD in NMO and MOGAD does not appear to have a strong association with Tau and Amyloid pathology based on blood biomarkers.
- Long-term follow up and correlative clinical, imaging and biomarker studies in combination with immunological assays will shed light on the disease pathogenesis and targets for therapy.

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Disclosure

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