Discovery of Blood-Brain Barrier Disruption Regional Variability and Neuronal and Glial Uptake of Fibrinogen in Multiple System Atrophy Using a Novel Color Deconvolution Algorithm

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Background/Hypothesis: Multiple system atrophy (MSA) is a fatal neurodegenerative disorder with unknown mechanisms and no curative treatment. The rationale for this work came from a clinical study that used magnetic resonance imaging to show blood-brain barrier (BBB) disruption in MSA patients; however, it is necessary to validate this finding using autopsy-confirmed MSA brains because clinical diagnosis of MSA has a 62% accuracy rate. It was hypothesized that BBB disruption is significant in MSA and worsens existing alpha-synuclein pathology, a pathological hallmark of MSA, through gliosis. To address the hypothesis, BBB disruption was assessed quantitatively using motor cortex, pontine base, and putamen tissue from human autopsied brains. Methods: This study utilized MSA and age/sex-matched healthy case groups (n=12) for comparisons. Immunohistochemistry (IHC) for fibrinogen, CD68, GFAP, and NACP were used to assess BBB leakage, microgliosis, astrogliosis, and alpha-synuclein pathology respectively. A color deconvolution algorithm was applied for quantitative assessment of IHC results. Results: The results demonstrated a significant difference ($p<0.05$) in BBB disruption between MSA and healthy cases in the pontine base and putamen only, supporting significant BBB leakage in MSA. Additionally, qualitative assessment led of fibrinogen IHC led to the discovery of neuronal and glial uptake of fibrinogen, offering a new perspective in analyzing the neurodegeneration and gliosis in MSA. Spearman correlation testing revealed positive but insignificant correlations between BBB disruption and MSA pathology, suggesting that BBB dysfunction may play only a minor role in exacerbating MSA pathology and disease progression in the motor cortex, pontine base, and putamen.

Awards Won:

Third Award of $1,000