Biomarkers at the Interface of Delirium and Dementia

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Time	Section

01:46	**Overview**
	• This webinar will explore mechanisms that might be common to both delirium and dementia
	• An overview of shared biomarkers
	  o AD biomarkers
	  o Neural injury biomarkers
	  o Neuroinflammatory biomarkers
	  o Neuroimaging biomarkers
	• Future directions

02:17	**Relationship between Delirium and Dementia** • Figure indicating the interrelationship between delirium and dementia
02:57	**Delirium and Dementia: Neuropathological Biomarkers** • Delirium is a risk factor for dementia • Delirium not mediated by classic neuropathology • Higher levels of pathological burden with delirium had steeper slopes for decline in cognitive function
06:00	**Delirium and Dementia: Fluid Biomarkers** • Fluid biomarkers of AD: amyloid, tau, neuroinflammation, neuronal damage, other reactional, and cytokines-chemokines • Amyloid Tau Neurodegeneration (ATN) framework • AD biomarkers change over time (graph) • Plasma p-tau greater in patients with delirium and correlated with delirium severity • Only tau predicted recovery from delirium • All biomarkers increased postoperatively • Biomarker negative and no delirium had lowest delirium severity scores • Biomarker negative and delirium & biomarker positive and no delirium had intermediate delirium severity scores • Biomarker positive and delirium had highest delirium severity scores
15:12	**Neuroinflammation and microglial activation** • Left figure shows normal functioning • Right figure shows pathological conditions • Delirium associated with higher level of CSF sTREM2 only among those without pre-existing dementias
18:35	**Neural Injury** • NFL (left figure) & GFAP (right figure) • Delirious patients had significantly higher difference in NFL levels than non-delirious patients • Delirium associated with exaggerated increases in NFL and neurotoxicity can contribute to the delirium itself, but is independent from inflammation • More involvement with GFAP in patients who develop postoperative delirium • Emergence delirium may be more associated with more significant axonal injury •

28:07	**Summary of Fluid Biomarker Evidence**
	• Neuroinflammation
	  o Associated with both dementia and delirium, separately
	  o The influence of neuroinflammation on delirium in the presence of dementia pathology seems to be variable
	• AD

	○ Most but not all studies support an association between the presence of AD biomarkers and delirium incidence ○ Gene-protein interactions may modify other processes (i.e. neuroinflammation) to promote delirium • Neural injury markers ○ Neuronal, astrocytic and glial biomarkers are mixed ▪ Delirium itself might promote additional injury and further release of injury markers ▪ Multiple injury pathways (via AD, neuroinflammation, etc. may be involved in the relationship between delirium and dementia
29:32	**Delirium and Dementia: Neuroimaging Biomarkers** • Neuroanatomic basis for delirium symptoms ○ Right parahippocampal region and right parietal lobe are associated with acute delirium symptoms • Brain Volume and Cerebral Atrophy ○ Variable findings in association of brain volume and cerebral atrophy and delirium include natural individual variations in brain volumes and differences in measurement techniques • Reduced Grey Matter Volume is a Risk for Delirium ○ Grey matter volume (as a fraction of total volume) can predict delirium ○ In the surgery group, delirium associated with greater decrease in grey matter volume • White Matter Hyperintensities ○ The findings from other studies of white matter hyperintensities and delirium are mixed, possibly due to differences in methodology. Most studies are in post-surgical populations, and the findings may not be generalizable • Diffusion Tensor Imaging ○ Alterations in the microstructure of the white matter may increase risk for delirium • Delirium Duration is Associated with White Matter Disruption ○ Compromised white matter integrity in areas of the brain involved in interhemispheric connectivity are associated with delirium • Diffusion Tensor Imaging Identifies Neural Substrates of Vulnerability to Delirium ○ Structural dysconnectivity and microstructural tissue changes can predispose to delirium under the stress of surgery • MRI Brain Phenotypes Might Predict Delirium • Changes in Cerebral Perfusion ○ Measurements from TCD support reduced blood flow to be associated with delirium ○ No association between global and voxel-wise CBF and POD incidence or severity • Cerebral Hypometabolism ○ Supports hypothesis that delirium results from cerebral metabolic insufficiency • Regional Hypometabolism in Delirium is Independent of Illness and Dementia ○ Regional hypometabolism correlated with increased delirium severity and decreased performance on neuropsychological testing • Association of Postoperative Delirium with Markers of Neurodegeneration and Brain Amyloidosis ○ Brain amyloidosis is unlikely to be a major cause of poor brain resiliency increasing the risk of POD after nonelective surgery ○ Recall that delirium pathophysiology might be independent of Alzheimer's disease
50:09	**Summary of Neuroimaging Findings** • Pre-existing brain damage (cerebral atrophy, ischemic lesions, and white matter lesions) is a strong predictor of delirium • Changes in perfusion and metabolic activity may reflect microscopic tissue damage and glial activity
50:45	**Research Challenges**

	• As delirium results from the interaction between predisposing vulnerabilities and precipitating insults, patient selection may influence imaging outcomes
52:15	**Research Priorities** • Better matching of patient demographics could help strengthen findings • Studies examining changes over time may demonstrate stronger relationships than cross-sectional studies • Longitudinal studies may help define transient effects of delirium from pre-existing vulnerabilities (i.e. dementia), and enables investigation of long-term brain changes associated with delirium • Larger sample sizes would help confirm findings • Studies involving vulnerable patients such as those with acute illness and dementia would be more representative of the clinical population most affected by delirium
53:34	**Questions and Answers**