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Delirium and Alzheimer's Disease: A Proposed Model for Shared Pathophysiology

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1. Introduction

Delirium and Alzheimer's disease (AD) are frequent causes of cognitive impairment among older adults and share a complex relationship in that delirium and AD can occur independently, concurrently, and interactively – for example, delirium can alter the course of an underlying AD. Whether delirium is a marker of vulnerability to AD, unmasks unrecognized AD, accelerates preclinical AD, or *itself* can cause permanent neuronal damage and lead to AD is poorly understood, and addressing these issues is a high-priority focus in aging research¹. In this paper, we propose a novel conceptual model (Figure 1) illustrating how biomarker studies might advance our understanding of the interrelationship of delirium and AD due to neuronal injury. We cite examples of potential neuronal injury biomarkers, their temporal trends, and how they fit within the framework of our model.

2. Delirium, Alzheimer's disease, and their Inter-relationship:

Delirium, an acute decline in cognition and attention, is a common complication of illness, acute trauma, and surgery in older adults, and it has been associated with multiple adverse outcomes including increased morbidity and mortality, falls, decline in cognitive and physical function, and loss of independence. Accordingly, delirium results in longer hospital stays and higher costs to patients, family caregivers, and the healthcare system. Some

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patients develop long-term cognitive decline after delirium, and delirium significantly increases the risk of incident dementia. Delirium is often unrecognized or mistaken for AD.

In contrast, AD is an insidious neurodegenerative condition characterized by chronic and progressive cognitive decline. The prevalence of delirium among patients with dementia is estimated to range from 22% to 89% of hospitalized and community populations aged 65 and older². When patients with AD do develop delirium, they are more likely to experience adverse outcomes including death or placement in a nursing facility and accelerated cognitive decline³.

A number of mechanisms for how delirium may contribute to dementia have been proposed, including inflammation, oxidative stress, neuronal dysfunction and acceleration of dementia pathology⁴. Some insults, such as hypoxia, metabolic derangements or particular drugs (e.g., anticholinergics), may directly cause neuronal dysfunction via alterations in neurotransmitters (e.g., acetylcholine deficiency⁵ while others, such as inflammation, lead to activation of microglia and astrocytes, then in turn to the production of free radicals, complement factors, glutamate, and nitric oxide⁶, and ultimately neuronal injury. Building on prior work examining neuroinflammation and these other potential mechanisms, biomarkers of neuronal injury provide a novel link between delirium and AD⁴ which has not been fully explored.

3. Biomarkers of delirium and AD:

Although not yet used routinely for clinical diagnosis, biomarkers in AD have been employed in large research trials for estimating risk, establishing a diagnosis of preclinical AD or mild cognitive impairment (MCI) due to AD pathology, measuring the progression of AD, and ultimately, for better understanding of the underlying pathophysiology⁷. In delirium, inflammatory, neurodegenerative, metabolic, and neurotransmitter-based biomarkers³ have been investigated as potential research tools for risk stratification, diagnosis, monitoring, and prognosis, though none have yet been validated for clinical applications, such as diagnosis or monitoring of delirium.

Whereas AD is typically slowly progressive, delirium is a relatively rapid and dynamic syndrome in which biomarker levels may change abruptly in response to an acute stressor or stressors (surgery, infection, etc.). For this reason, a useful model of biomarkers in delirium would include how biomarkers change over time, in order to consider those present before onset of disease (risk biomarker), those altered by disease (disease biomarker), and those reflecting the end product of a disease (outcome biomarker)⁸. Due to the complex nature of delirium, with its myriad etiologies and protean manifestation, a model of shared delirium and dementia biomarkers would need to accommodate biomarkers that are common among multiple conditions.

Another important consideration for biomarkers of delirium and AD is the biofluid in which the biomarkers are measured. Cerebrospinal fluid (CSF) is thought to accurately represent brain changes but there are challenges to collecting CSF, particularly in delirious patients, over multiple time points, and in large-scale studies. Despite these challenges, there is

growing interest in using CSF biomarkers to better understand delirium pathophysiology. Blood-based biomarkers, which are more accessible during acute illness, may also be useful in delirium. With the development of ultra-sensitive immunoassays, protein biomarkers of neurodegeneration (tau) and axonal injury (neurofilament light, NfL) can now be measured in blood, although it remains to be determined whether these correlate with levels in the CSF, particularly in the setting of acute illness when most delirium occurs.

Much effort has been focused on protein biomarkers, which while important, do not tell the whole picture. Other important avenues of future research include emerging blood-based biomarkers such as: 1) exosomal microRNAs (miR), which are small non-coding RNAs that modulate mRNA stability and post-transcriptional gene regulation that often become dysregulated in numerous conditions, including in the pathological process of AD, 2) novel neuronal injury biomarkers, such as those associated with endothelial damage and blood-brain barrier disruption, and 3) unbiased systems biology approaches (genomics, proteomics, lipidomics, and metabolomics). Ultimately, all of these approaches may be useful to explore shared mechanisms that contribute to delirium and AD.

4. Proposed Conceptual Model:

We propose a conceptual model (Figure 1) illustrating how biomarker studies might advance our understanding of the interrelationship of delirium and AD. This model builds on the concept of *vulnerability*, the degree to which the brain adversely reacts to a stressor, *resilience*, which we describe as the ability of the brain to withstand and recover from the impact of stressors⁹, and the severity of the stressor. The model is simplified to represent the most likely pathways. For example, a patient with a resilient brain may be capable of withstanding relatively mild stressors, resulting in no delirium or only a mild delirium with a good chance of full recovery; this same resilient brain when faced with a severe stressor (e.g. a young otherwise healthy patient in the intensive care unit with severe sepsis), may manifest a severe delirium with persistent cognitive symptoms. Conversely, a patient with a vulnerable brain (e.g., a patient with cognitive impairment or an underlying inflammatory state) may need only a mild stressor to precipitate a severe delirium with persistent symptoms.

The model also considers changes in biomarkers over time from baseline, to acute delirium, to convalescence, and then over the long-term. The time course is of critical importance, particularly in delirium which itself fluctuates in terms of clinical presentation and symptom severity. In this model, *risk* biomarkers reflecting a baseline vulnerability (i.e., inflammation, oxidative stress, or chronic neurodegeneration) may be predictive of delirium incidence and outcome. During the acute phase of delirium, there is an emergence of new *disease* biomarkers, reflecting diverse processes that might include inflammation, alterations in neurotransmitter function, neuronal or microglial dysfunction, or acceleration of underlying chronic processes. Finally, *outcome* biomarkers indicating the end-product of disease processes, such as neuronal injury or death, appear after delirium and may persist over the long term. We hypothesize that the occurrence of neuronal injury, as shown in our model, is critical to linking delirium and dementia.

5. Mechanisms and pathophysiology at the Interface of Delirium and AD

Within the framework of our proposed conceptual model (Figure 1), we hypothesize that there are common baseline risk biomarkers and outcome biomarkers for delirium and AD, and that these represent shared mechanisms and pathophysiology. Moreover, biomarkers of AD (which may be either risk markers or disease markers for AD depending on whether or not the AD is symptomatic), could also serve as risk biomarkers for delirium, and thus identify individuals who are vulnerable in the face of stressors to developing delirium. Neuronal injury, as reflected by outcome biomarkers, may represent a final common pathway for disparate pathophysiologic processes that occur during acute delirium. These outcome markers for delirium may serve as risk markers for cognitive decline or AD following an episode of delirium. For example, systemic inflammation may lead to neuronal inflammation which then results in direct neuronal injury¹⁰. Thus, longitudinal studies are needed¹¹ and we include this in our conceptual model. In the setting of underlying brain vulnerability, such as neurodegeneration or aging, systemic inflammation may lead to an exaggerated central inflammatory response¹², and therefore potentially greater neuronal injury. It may also be possible that in the setting of AD pathology (which again may or may not be clinically symptomatic), neurons are more vulnerable to injury and cell death with even modest levels of neuroinflammation. Whether neuronal injury from delirium can then subsequently initiate or accelerate AD pathology is not known, but we hypothesize that neuronal injury and death is a critical step connecting delirium and AD. Therefore, biomarkers that reflect neuronal injury or death, in addition to biomarkers of AD, may yield important insight into the shared mechanisms between delirium and AD. Below we review selected literature, with a focus on biomarkers reflecting neuronal injury that have been examined in both delirium and AD: 1) AD biomarkers and 2) biomarkers of neuronal injury. We also discuss important issues in designing future biomarker studies.

6. AD biomarkers and delirium:

Reduced CSF levels of amyloid β ($A\beta$)42 and elevated CSF levels of total tau (T-tau) and phospho-tau (P-tau) compared with controls has been established as an “AD-signature” for diagnosing cognitive impairment due to AD pathology. A recent meta-analysis of biomarker literature in AD and mild cognitive impairment (MCI) supports the association of this CSF AD-signature with AD and MCI¹³. Elevated levels of CSF T-tau have been described in traumatic brain injury, acute stroke, and other neurodegenerative conditions, and likely reflects the intensity of neurodegeneration and disease progression. Elevated CSF P-tau, a measure of the phosphorylation state of tau appears to be more specific with AD¹⁴.

Plasma levels of T-tau correlate poorly with CSF T-tau, however plasma T-tau has been found to be associated with AD. To date, plasma findings have been less reproducible than those in CSF, at least using technology available up to this point¹⁴.

Studies of AD biomarkers in delirium have been mixed. Several studies have associated the “CSF-AD signature” described above with delirium. Patients with post-operative delirium have a reduced CSF $A\beta$ 42/Tau ratio¹⁵ and a recent study¹⁶ found patients without dementia who developed delirium had lower CSF $A\beta$ 42 levels, higher T-tau levels, and lower ratios of

A β 42 to T-tau and P-tau relative to those without delirium. In contrast, other studies did not find significant differences between preoperative CSF Abeta1 β 42, tau, and P-tau levels in participants who did and did not develop delirium¹⁷.

Another AD-related biomarker that has been examined in delirium is apolipoprotein E (ApoE). Two different aspects of ApoE have been examined, the ApoE genotype, particularly the E4 allele, which has been strongly associated with AD, and absolute levels of the ApoE protein measured in plasma and CSF. The presence of an E4 allele of apolipoprotein E (ApoE) genotype has been associated with delirium in some studies¹⁸, but others did not observe this relationship^{19,20}. In meta-analyses the ApoE E4 allele is associated with longer duration of delirium but not with delirium incidence¹⁸. Plasma ApoE levels are reduced in AD²¹ and it is hypothesized that ApoE plays a role in neuronal maintenance and repair. In patients with delirium, compared to AD, ApoE levels in CSF are even lower during delirium. This study observed no significant differences in ApoE in plasma between AD and delirium, nor did plasma and CSF ApoE levels correlate, suggesting that blood-based ApoE levels do not reflect brain dysfunction in delirium as well as they do in dementia²². Despite the conflicting findings, the potential role of ApoE in the relationship between delirium and dementia remains intriguing and worthy of further investigation.

7. Neuronal Injury/Death Biomarkers in AD and Delirium

7.1. Neuron Specific Enolase (NSE):

Neuron specific enolase (NSE) is one of the five isozymes of the glycolytic enzyme, enolase and is released into the CSF when neural tissue is injured. In dementia, CSF NSE findings have been variable. NSE in the CSF has been shown to be increased in AD²³, increased in both AD and vascular dementia²⁴, unchanged in AD²⁵, or reduced in AD²⁶. There were no differences in serum or plasma concentrations of NSE in patients with AD compared to controls in a number of studies¹³.

NSE has also been examined in delirium, and overall, the findings are also mixed. Compared with participants with dementia, patients with delirium demonstrated lower levels of CSF NSE²⁷. Delirium is associated with higher plasma NSE concentrations and mortality in critically ill patients²⁸. A trend towards an association between persistently elevated plasma NSE levels and cognitive impairment at discharge in patients following cardiopulmonary bypass surgery²⁹ has been reported. Others found no significant difference in plasma NSE between delirium and control groups³⁰.

7.2. S100B

S100B is a calcium-binding protein secreted by astrocytes that is released from injured cells into the bloodstream and has been proposed as a marker of the acute phase of brain damage, blood-brain barrier (BBB) permeability, and serious central nervous system (CNS) injury. S100B serum levels are high during inflammation, and after trauma or surgery. Among patients with AD, some studies report higher CSF levels of S100B in AD patients compared to controls³¹, and other studies report that S100B levels correlate with AD disease severity

(Clinical Dementia Rating or Mini Mental State Exam score)²⁵. Others have found higher CSF S100B levels in mild-to moderate AD, which then decreased as the disease worsened³².

There is significant literature examining the association of S100B with delirium or outcomes after delirium. A number of studies have shown high plasma S100B levels in delirium^{33,34} or elevated CSF S100B levels measured at the time of hip fracture surgery in patients with delirium vs. without delirium³⁵. In keeping with these observations, a low concentration of S100B has been proposed to be used as a risk stratification marker to rule out delirium³⁶. However, there are studies that did not detect any difference in plasma S100B levels in patients with and without cognitive impairment following cardiopulmonary bypass^{28,29}, or found that CSF S100B levels were lower in patients with persistent delirium compared to those with probable AD²⁷. A recent study of older hip fracture patients found serum S100B was not associated with postoperative delirium, and although S100B was associated with cognitive decline or death in the first year after hip fracture, this was observed only in participants without perioperative delirium³⁷.

7.3. Glial fibrillary acidic protein (GFAP)

Glial fibrillary acidic protein (GFAP) is expressed by astrocytes and is used as a marker of astrocytosis in neurodegeneration. CSF concentration of GFAP has been shown to be elevated in AD, as well as in other neurodegenerative dementias³⁸ though other studies found no difference between AD and controls or between AD and other neurodegenerative conditions³⁹. GFAP has not been demonstrated to be increased in delirium⁴⁰.

7.4. Brain derived neurotrophic factor (BDNF)

Brain derived neurotrophic factor (BDNF) functions to help support neuron survival and encourage the growth and differentiation of new neurons and synapses. Advanced age and low education has been associated with decreased serum BDNF levels, with the lowest levels in patients with AD, which also corresponded to the severity of cognitive impairment⁴¹. Others have observed that at early stages of AD, BDNF significantly increased in comparison to control groups although levels then declined in later stages of the disease whereas another study found no change in BDNF⁴². BDNF has been found to be elevated in delirium in one study²⁸ and not elevated compared with controls in another study⁴³. BDNF has not yet been studied as a resilience factor following an episode of delirium, which would correspond to its putative physiological role.

7.5. Neurofilament light (NfL)

Neurofilament light (NfL), is intermediate filament protein that is expressed in neurons and believed to function primarily to provide structural support for the axon⁴⁴. NfL is a general marker of neuronal injury and neurodegeneration and has also been detected in CSF and blood in multiple conditions including stroke, traumatic brain injury, multiple sclerosis, progressive supranuclear palsy, and frontotemporal dementia. In AD, serum NfL has been shown to be increased in AD and MCI patients compared to controls, with the highest serum levels in cases with positive amyloid PET scans. Serum NfL also correlated with poorer cognition and greater changes in neuroimaging⁴⁵. In the CSF, NfL has been shown to predict

neurodegeneration in older adults with very low AD risk. To date, NfL has not been examined in delirium.

7.6. Ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1)

Ubiquitin carboxyl-terminal hydrolase (UCH-L1) is an important component of the ubiquitin-proteasome system (UPS), which functions to remove and degrade misfolded proteins. Impairment of the UPS results in the accumulation of mis-folded proteins in the cell, and a decrease in UCH-L1 activity has associated with Parkinson's and AD. UCH-L1 is found in neuronal cell bodies and is thought to be a highly specific marker of neuronal injury. UCH-L1 can be detected in CSF and serum in patients with traumatic brain injury, hypoxic-ischemic encephalopathy, and seizures⁴⁶. Post-mortem studies of brains from patients with sporadic AD show a down-regulation of UCH-L1⁴⁷. In TBI UCH-L1 levels are increased within one hour⁴⁸. Despite this potential promise as a neuronal injury biomarker, UCH-L1 has not been examined in any large dementia or delirium studies.

8. Micro RNA as potential biomarkers for delirium

MicroRNAs (miR) are small non-coding RNAs that regulate the expression of mRNAs post-transcriptionally by inhibiting translation or degradation of their mRNA targets. Abnormal expression of miRNAs has been observed in diverse disease and altered physiological states⁴⁹. While most miRNA are found intracellularly, circulating miRNA or extracellular miRNA, have also been detected in different biofluids, including serum and plasma, and as such hold potential as biomarkers in aging and age-related disorders⁵⁰. Circulating miRNA are believed to be released and then protected from extracellular degradation through transport via exosomes (cell-derived extracellular vesicles), microvesicles, and other mechanisms⁴⁹. Freely circulating disease-specific or dysregulated miRs have been linked to pathogenic states⁵⁰.

In AD, miRNA have been investigated in blood, serum, serum or plasma exosomes, and CSF, and are both upregulated and down regulated (for review, see ⁵⁰). Studies have suggested that miRNAs serve as critical regulators in signaling pathways such as in amyloid metabolism, tau pathology, neuroinflammation, and apoptosis. Dysregulated miRs may influence gene transcription, protein expression and induce the spread of neurodegeneration⁵¹. The most consistently dysregulated miRNA markers for AD include miR-29b, miR-181c, miR-15b, miR-146a, and miR-107 where uniform results have been observed in at least two independent studies⁵².

In delirium, a recent pilot study⁵³ among older patients who underwent total knee or hip replacement under spinal anesthesia, several miRs (miR-146a, miR-125b, and miR-181c) known to modulate both neuronal and immune processes were examined. Among patients who developed delirium, an up-regulation of miR-146a and miR-181c in CSF and down-regulation of miR-146a in the serum was observed. Additionally, lower CSF miR-146a and lower CSF/serum miR-146a ratios were significantly associated with milder delirium severity. Taken together, these findings support a potential role for miRs as delirium risk, disease, or end product biomarkers. miRNA's may likewise contribute to our understanding of shared delirium and dementia pathophysiology.

9. Discussion: Recommendations for Future Research

Understanding the interface between delirium and AD is a high-priority focus of aging research. Biomarkers can play important roles in confirming diagnosis, measuring severity, and stratifying risk, and may also be used to achieve a greater understanding of shared pathophysiology between delirium and AD and ultimately to find more effective treatment strategies. Biomarkers shared by both delirium and AD are potential “linkage” points whereby one condition may influence the other, and could potentially explain for example, how delirium accelerates the rate of cognitive decline in patients with AD.

Biomarkers of AD pathology and neuronal injury have been found in both delirium and AD (Table 1), however the results across studies have been somewhat inconsistent. This in part may be due to study design, for example the use of small sample sizes and cross-sectional designs⁵⁴. For logistical reasons, CSF biomarker studies frequently rely on collecting CSF at the time of surgery, which can limit the patient population to those undergoing emergency surgery for acute hip fracture or other procedures performed under spinal anesthesia. Other methodologic issues include a lack of standardization of biomarker sample collection, processing, storage, and assays across labs, or lack of quality control of assays within labs.

Specific issues should be considered when designing a study targeted towards biomarker discovery at the interface between delirium and AD (Table 2). Studies will need to be conducted in multiple, large-scale multi-center cohorts including diverse clinical populations to validate and assure generalizability of the findings. Careful inclusion/exclusion criteria, and detailed baseline assessment can help ensure the appropriateness of the control group. Matched case-control studies may be more feasible and efficient, particularly if resources are limited. Biomarkers for delirium are likely to include both static baseline risk markers as well as dynamic disease biomarkers that fluctuate over the course of the delirium episode and recovery period. Careful consideration will need to be made for which time points delirium, cognitive function, and/or biomarkers will be measured in the study; the temporal relationship between biomarkers and the course of delirium – including the time before, during, and after the delirium episode - will be critical in understanding at which point(s) delirium may connect with dementia.

Carefully characterized clinical phenotypes are essential for effective biomarkers studies. Consistent use of validated delirium measures is a must and both the occurrence and severity of delirium should be measured. Baseline cognitive function should be assessed and included in the analysis. If AD is used as inclusion criteria, how AD will be characterized in the study – i.e., using a reference standard, clinical criteria, AD imaging or CSF biomarkers, an expert consensus panel, or a combination thereof – should also be considered.

Biomarker discovery generally takes one of two general approaches – either hypothesis-derived screening of candidate biomarkers, or broad-based laboratory screens. A particular advantage of multiplex assays is the identification of hundreds to thousands of proteins from a single sample across a wide assay dynamic range (pg/mL to ng/mL), with reasonable sensitivity, reproducibility, and high throughput. Examination of biomarkers over time is critical given the dynamic nature of delirium, as evidenced by the observation that IL-6

change over time in patients with delirium^{54,55}. In addition, due to the fluctuating and changing time course of delirium, ideally biomarkers should be measured at multiple time points, to understand how biomarkers levels align with the course of delirium (e.g., its onset, peak, duration, and resolution).

As delirium and AD often affect frail and medically complex older adults, attrition should be anticipated. Data analysis must consider possible flaws in the study design, confounding factors, and handling missing data. Lastly, standardization of assay platforms across laboratories, and careful quality control within laboratories will allow for comparisons across studies.

10. Limitations

Because this review is focused on biomarkers reflecting neuronal injury, a number of putative biomarkers shared between delirium and dementia were not discussed. It is likely that there are multiple mechanisms (and biomarkers) that are involved in the interface between delirium and dementia and unfortunately it is not possible to include all within this review. However, other putative biomarkers can still be integrated into our conceptual model, as risk or disease markers that are contributory along the pathway to neuronal injury. For example, although the association of C-reactive protein and dementia has been mixed⁵⁶, CRP has been shown, as defined in our model, to be a baseline (risk biomarker) IL-6 to be an acute phase (disease biomarker)^{55,56} in delirium. Anemia and hypoproteinemia are considered to be precipitating factors for delirium and anemia been associated with dementia⁵⁷, and lowered levels of melatonin are associated with MCI and delirium⁵⁸ all could fit into our model as biomarkers reflecting brain vulnerability (i.e., risk biomarkers).

11. Conclusions

Delirium and AD have been closely linked epidemiologically, yet the pathophysiology underlying this relationship remains largely unknown, and under-explored. Examining established biomarkers of AD in delirium studies, and emerging biomarkers of neuronal injury and microRNA's in both studies of delirium and AD, may help to shed light on the shared, complex pathophysiology underlying both syndromes. Careful consideration of study design including eligibility criteria, rigorous measurement of delirium, AD, and the biomarkers of interest, and sophisticated analytic strategies to address confounding and attrition, will be important to achieve these goals. Through improved understanding of the pathophysiology of delirium and AD derived from such studies, interventions can be designed to reduce the impending epidemic of late-life cognitive impairment.

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Key points:

1. The interrelationship between delirium and Alzheimer's disease (AD) is complex and poorly understood.
2. Advances in cerebrospinal fluid (CSF) and blood-based biomarkers, including development of ultra-sensitive immunoassays to measure protein biomarkers, and novel biomarkers such as exosomal microRNA, may lead to discovery of biomarkers common to delirium and AD, potentially representing shared pathophysiology.
3. We propose a conceptual model illustrating how biomarker studies might advance our understanding of the interrelationship of delirium and AD.
4. Important issues in designing future biomarker studies include careful consideration of study design, sophisticated statistical analytic strategies, and standardization of assay platforms.

Figure 1. Conceptual model for the interrelationship between delirium and AD.

Grey boxes indicate the baseline brain status (far left panel, BASELINE) delirium “state” (middle panels, ACUTE and CONVALESCENT), or outcome (far right panel, OUTCOME); white boxes indicate corresponding (hypothesized) biomarker level. Solid arrows indicate hypothesized pathways for development of delirium (gray), complicated delirium (black), or no delirium (white); dashed arrows indicate where exceptions can occur. ¹This figure is intended to represent the most likely pathways for outcomes but there are exceptions. For example, a patient with a resilient brain (upper box, far left panel) could develop a severe delirium, if the delirium trigger was sufficiently noxious (lower box, second panel from left) and ultimately develop long-term cognitive decline or ADRD; likewise someone with a vulnerable brain (lower box, far left) who is resilient to the delirium trigger because of high cognitive reserve might develop a mild delirium (middle box, second panel from left) and go on to recover (upper box, far right panel)

¹ Delirium can be triggered by a range of insults including surgery, infections, hypoxia, metabolic abnormalities, stroke, drugs, or anesthetics, and these insults can vary in severity and duration

² Abnormal *risk* biomarkers (at baseline) of a vulnerable brain might reflect inflammation, oxidative stress, or chronic neurodegeneration present at basal level

³ Abnormal biomarkers triggered by delirium might reflect inflammation, alterations in neurotransmitter function, neuronal or microglial dysfunction, or neuronal death, or acceleration of underlying chronic processes. As biomarkers become increasingly abnormal, delirium severity may increase as well.

⁴ Abnormal end product (i.e., neuronal injury/cell death) biomarkers emerge in the convalescent phase when disease processes are sufficient during the acute phase to trigger neuronal injury. Note: This model will accommodate multiple putative biomarkers. For example, anemia can still be integrated into our conceptual model, as a risk or disease marker that is contributory along the pathway to neuronal injury.

abbreviations: AD=Alzheimer's disease; ADRD=Alzheimer's disease and related dementias; LTCD=long-term cognitive decline; MCI=mild cognitive impairment

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Table 1.

Summary of Selected Biomarkers at the Interface of Delirium and Dementia

Biomarker	Fluid	Biomarker level in Dementia	Biomarker level in Delirium	Biomarker level in Other Neurological Conditions
Alzheimer's disease (AD) associated biomarkers				
amyloid β ($A\beta$)42	CSF	Decreased	Decreased (some studies)	
t-Tau	CSF	Increased	Increased (some studies)	Increased in TBI, stroke, neurodegeneration
p-Tau	CSF	Increased (specific for AD dx)	Unchanged	
p-Tau	Plasma	Poor correlation with CSF t-tau but increased levels associated with AD	NA	
ApoE genotype	plasma	Strong association	Inconsistent association	
ApoE level	CSF		Decreased	
ApoE level	Plasma	Decreased	Does not correlate with CSF levels	
Neuronal Injury/Death Biomarkers				
BDNF	Plasma	Increase then decrease/variable	Increased/ variable	
GFAP	CSF	Increased/variable	Not increased	
NfL	CSF	Increased	NA	Increased in Stroke, TBI, MS, PSP, FTD
NfL	Plasma	Increased	NA	Increased after surgery and anesthesia
NSE	CSF or plasma	Variable	Variable	
S100B	CSF	Increased, then decreased in later stages of disease	Increased/variable	Increased with trauma, surgery, or inflammation
S100B	Plasma	NA	Increased/variable	
UCH-L1	CSF or plasma	Increased (limited studies)	NA	Increased in PD, TBI, HIE, seizures
microRNA				
miR	CSF	miR-29a, miR-125b (upregulated); miR-146a (downregulated)	miR-125b, miR-146a, miR-181c (upregulated)	
miR	Plasma	miR-146a (upregulated); miR-29b, miR-181c, miR-15b, miR-107 (downregulated)	miR-146a (downregulated)	

ApoE=apolipoprotein E; BDNF=brain derived neurotrophic factor; CSF= cerebrospinal fluid; FTD= frontotemporal dementia; GFAP= Glial fibrillary acidic protein; HIE= hypoxic ischemic encephalopathy; miR= microRNA; MS= multiple sclerosis; NA= no published reports; NfL= Neurofilament Light; NSE = neuron specific enolase; PSP= progressive supranuclear palsy; TBI= traumatic brain injury; UCH-L1= Ubiquitin carboxyl-terminal hydrolase L1

Table 2.**Checklist for Biomarker Studies Examining the Interface Between Delirium and AD**

Section/Topic	Questions to Address
Study Design	What is the optimal study design to maximize biomarker discovery? Who should be included in the study population? Are exclusion and inclusion criteria well defined and justified? Is an appropriate control group included? Are credible sample size calculations performed on main study hypotheses, such that adequate number of participants are enrolled? Which time points will delirium, cognitive function, and/or biomarkers be measured? Is there an intervention as part of the study? If so, is the intervention double-blinded?
Assessment of Methods	What instruments will be used to measure delirium and delirium severity? What instruments will be used to measure baseline cognitive function? What methods will be used to diagnose AD and AD severity? Are instruments standardized and validated? How will biomarkers be collected (blood, CSF)?
Outcomes	Which outcomes are most relevant – delirium incidence and severity? Cognitive function? Incident MCI or AD? (i.e. is the potential biomarker being examined as a risk, disease, or outcome biomarker?)
Data Analysis	Has a biostatistician been consulted to advise on the project? What analytic approach is optimum? What is the expected attrition for the study, and is this realistic? How will missing data and nonresponses be handled? Are there weaknesses in the study design that will compromise the data analysis? How will potential confounding be controlled (design/analysis)? Consideration of biological variables of interest, such as sex-stratification
Validation Reproducibility of Findings	Is there independent validation of findings? What methods will be used? Split sample, independent sample?, etc.
Summary	What is the clinical relevance of the findings? What additional steps are required before the biomarkers can be applied to clinical care?