Cerebrospinal Fluid Biomarkers in Alzheimer’s Disease and Related Disorders Research

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Learning Objectives

1. Compare observational studies and interventional studies
2. Identify 2 biomarkers of interest in AD
3. Discuss importance of diversity in research on ADRD

Overview

- Define key terms
- Discuss:
  - CSF and what it tells us about brain health
  - Emerging evidence about inflammation, immunity
  - New uses of existing drugs
  - ACTRU research studies
  - Recruitment challenges
    - Diversity in research participants
    - Access to research studies
Definitions

• Dementia
• Alzheimer’s Disease (AD) and related dementias (ADRD)
  • Beta amyloid plaques
  • Tau tangles
• Lewy Body Dementia (LBD) – alpha-synuclein deposits
• Frontotemporal Dementia (FTD)
• Vascular Dementia
• Mixed Dementia

Expanding focus of ADRD research

• Hallmark features of tau tangles and amyloid plaques
  • Not well correlated with cognition
  • People with high burden of tau or amyloid in their brains functioning normally
  • People without significant tau or amyloid displaying impairment
• Towards inflammation and immune system
  • Trying to put out the “fire”
  • Are buildups of tau tangles and amyloid plaques the “smoke”? 
  • Increasing attention paid to the ancillary “nursemaid” cells
    • Microglia
    • Astrocytes

Cerebrospinal Fluid (CSF)

• Clear, colorless fluid occupying subarachnoid space and ventricular system around and inside the brain, spinal cord
• Produced by ependymal cells in choroid plexus
• Cushions/buffers cortex
• Provides basic mechanical and immunological protection to the brain inside the skull
• Vital to cerebral autoregulation and blood flow
Basic Functions of CSF

- Buoyancy
- Protection
- **Chemical stability**
  - Removes metabolic waste from CNS through BBB, allows for homeostatic regulation of neuroendocrine factors
- **Waste removal**
  - Flows throughout ventricles and absorbed back into bloodstream
- Prevention of brain ischemia – related to ICP and blood perfusion

Why focus on CSF?

- Gives us meaningful information about the brain behind the BBB
- Measuring biomarkers is critical to understanding pathology in living people
- Important for ruling out other pathologies such as MS, infection, etc.
- Changes in biomarkers typically occur before symptom onset
- Well studied in millions of people across disease spectrum
  - Not ethnically diverse samples!
- **Significant sensitivity** to diagnose AD (~90%):
  - Amyloid levels typically low
  - Tau and phospho-tau elevated
- **Decent specificity** to rule out AD (~70-80%)
  - Could have prodromal AD?

Lumbar Puncture (LP)

- No anticoagulation (Aspirin 81mg is OK)
- Outpatient procedure takes about 30 min
- Lidocaine to numb the skin
- People typically recover in 2-24 hrs
- Monitor for headaches
Biomarkers

“A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions” – FDA-NIH

- Reliable indicators of presence of disease
- Combination of fluid and imaging (current)

Challenges:
- Patients may be reluctant to have LP
- Insurance may deny covering “fancy” imaging
- Timing: the disease process has already begun by the time these abnormal biomarkers are discovered

A/T/N Classification

- 7 major biomarkers of interest in AD/AD research
- A: value of β-amyloid
  - Either amyloid PET or CSF Aβ-42
- T: value of tau
  - Either tau PET or CSF phospho-tau
- N: biomarkers of neurodegeneration or neuronal injury
  - Either FDG-PET, structural MRI, or CSF total tau
- Each category is either (+) or (-)
  - Example: Individual results would appear as A+/T+/N-, or A+/T-/-N-
Microglia

- “First responders”
- Small with “thorny” processes which can touch neighboring neurons
- Can transform into macrophages to clear debris, waste
  - Clear Aβ and tau
- Monitor health of neurons by detecting injuries to neurons

Astrocytes

- Star-shaped glial cells
- Cover nearly all capillaries in CNS
  - Support BBB
  - Keep toxins out of brain
- Provide nutrients to neurons
- Repair tissue after injury
- Regulate neuronal communication by recycling neurotransmitters released during synaptic transmission
- Regulate external chemical environment by removing excess ions

Biomarkers of Synapse or Neuronal Loss

- Neurofilament Light Chain (NfL)
  - Very sensitive to AD onset
  - Released into extracellular space when neurons degenerate
- Neurogranin (Ng)
  - Post-synaptic protein concentrated in dendritic spines, hippocampus
  - Elevated early in disease progression
  - Localized at epicenter of pathogenic events in AD
Biomarkers of Inflammation and Microglia “Dysfunction”

• “Chicken or the egg”
  • Part of original pathogenesis?
  • Or reaction to amyloid and tau deposition?
• Soluble TREM2
  • Triggering Receptor Expressed on Myeloid Cells 2
  • Expressed on microglia in the brain
  • Regulates immune cell activation after ligand binding (including APOE and Aβ)
  • Regulates cytokines and microglia activation
• YKL-40
  • Glycoprotein expressed in astrocytes and microglia
  • Plays a role in inflammation and tissue remodeling

Biomarkers of Related Disorders

• TAR DNA-Binding Protein 43 (TDP-43)
  • Present in up to 50% of AD cases
  • Main feature of FTD and ALS
• Alpha-synuclein
  • Key component of Lewy Bodies, Parkinson’s Disease, multi-system atrophy (MSA)
  • Involved in pre-synaptic signaling
• Vascular Damage and BBB
  • Vascular damage is large component of AD
  • Microvascular damage often seen (Mixed dementia)

Key Point

• Although we cannot control our genetics or history, we can control blood pressure, diet, exercise
• Aggressive BP control to prevent microvascular damage!
Observational Studies

- No intervention
- Pro: generally lower time commitment, no new drugs or s/e, great for “healthy controls”
- Con: no change to disease trajectory
- May include:
  - Collection of body fluids (LP)
  - Imaging (MRI, PET-CT)
  - Cognitive testing
  - EEG
  - Wearable technology (FitBit)

Interventional Studies

- Testing investigational drug/device
- Pro: may benefit patient, feeling of hope
- Con: false hope, may receive placebo, can be time-intensive, strict I/E criteria
- May include:
  - Oral, IV, or SQ medications
  - Placebo vs. “active” drug
  - Activities from observational studies

New research on old drugs

- Thinking outside the box
- New drugs are expensive and time-consuming to develop
- How can we repurpose already FDA-approved meds to treat ADRD?
  - Metformin
  - Methylphenidate (Concerta®)*
  - Nicotinamide riboside (Niagen)
  - Bacille Calmette-Guerin (BCG) vaccine*

Methylphenidate Study (Concerta®)

- Participants wear a FitBit, play Lumosity games, answer questions about their sleep, mood, etc.
- Great way to determine whether a drug helps an individual
- Double-blind multi-crossover design allows for participant to serve as their own control
BCG Vaccine Pilot Study

- Bacillus Calmette-Guérin (BCG) has “off-target” effects
  - Bladder cancer
  - Type 1 Diabetes
- Influences regulatory T-cells (Tregs) of the innate immune system
- Can BCG increase neurotrophins and decrease neurotoxins?

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Describe Skin Lesions

- Induration: 2-4 weeks after vaccine
- Pustule formation: 5-7 weeks
- Scar formation: 2-3 months

Importance of Diversity in Research

- Most studies include primarily white patients
- Skewed towards more affluent patients
- How does this influence our data?
  - We don’t know how incomplete the picture is
  - Without representation, drugs that could help diverse patients may not “perform” well enough
Trusting Relationships

- Crucial to develop trusting relationships with the community
- Working against challenges of institutionalized racism and history of mistreatment by the medical community
- Takes time but it’s worthwhile!
- Community service that can be sustained
- Meet people where they are - church, grocery store, community centers

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