Neuro-ophthalmic Manifestations of Alzheimer’s Disease

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Disclosure Statement:
Neuro-ophthalmic Manifestations of Alzheimer’s Disease
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- King Devick Technologies (scientific advisory board)
- Heidelberg Engineering (scientific advisory board)

Key Points
- Types of dementia
- Pathophysiology of Alzheimer’s Disease (AD)
- Non-ocular findings with AD
- Neuro-ophthalmic findings with AD
- Comparison between AD & Chronic Traumatic Encephalopathy (CTE)
- Role of ocular structure and function as surrogate biomarkers of disease activity/progression

Definition of Dementia
- Dementia is a loss of brain function that occurs with certain diseases. It affects memory, thinking, language, judgment, and behavior.

Common Types of Dementia
- Alzheimer’s disease (60-80%)
- Vascular dementia
- Dementia with Lewy bodies
- Frontotemporal lobular degeneration
- Mixed dementia
- Parkinson’s disease
- Creutzfeldt-Jakob disease
- Normal pressure hydrocephalus

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Alois Alzheimer, MD (1906)
• South-West German Psychiatrists' Meeting presentation on pre and post-mortem findings of Auguste Deter - "On a Peculiar Disease of the Cerebral Cortex"

Alzheimer’s Disease
• Progressive dementia with loss of neurons and the presence of two main microscopic neuropathological hallmarks: extracellular amyloid plaques and intracellular neurofibrillary tangles

Epidemiology of Alzheimer’s Disease (AD)
• 5.2 million Americans with AD (24 million world-wide)
• 96% > 65 years
• 5th leading cause of death > 65 years
• Increasing incidence and prevalence (est. American prevalence of 13.8M by 2050)

Risk Factors for AD
• Older age
• Genetics (APOE4 allele)
• Prior history of TBI

APOE & AD

<table>
<thead>
<tr>
<th>Allele</th>
<th>Normal Population</th>
<th>in AD</th>
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<tbody>
<tr>
<td>E2</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>E3</td>
<td>79%</td>
<td>40-50%</td>
</tr>
<tr>
<td>E4</td>
<td>14%</td>
<td>40-50%</td>
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• APOE4
  — Impaired sequestration of cholesterol (atherosclerosis)
  — Impaired glucose transport to the brain (type 3 diabetes)
  — Impaired removal of β amyloid (Alzheimer’s disease)
  — Allele frequency is twice as high in Africans/African Americans as compared to Caucasians

Increased Risk of AD with APOE4 & TBI
• 2 fold increase of AD with APOE4 alone
• 10 fold increase in AD with APOE4 & history of TBI
**Pathology of AD (Beta-Amyloid Cascade Hypothesis)**

- Mitochondrial dysfunction (cytochrome oxidase pathway)
- Up-regulation of amyloid precursor protein (APP)
- Extracellular β-amyloid neuritic plaques
- Intracellular neurofibrillary tau tangles

**Brain Under Attack!**

- Extracellular neuritic plaques activate microglia & astrocytes
- Upregulation of complement molecules, pro-inflammatory cytokines & other inflammatory mediators
- Progressive neurodegeneration
- ? Role of anti-inflammatory agents

**Clinical Presentation of AD (non-ocular)**

- Early:
  - Difficulty remembering names and recent events
  - Apathy and depression
  - Problems with vision and sense of smell
- Later:
  - Impaired judgment, disorientation, confusion, behavior changes, difficulty walking, speaking, swallowing → death (pathology/degeneration of bulbar structures)

**Polling Question #1**

What is the genetic marker associated with Alzheimer’s disease?
- a. Factor V Leiden mutation
- b. APOE4 allele
- c. CRB1
- d. RHO

**Stage 1: Preclinical AD (Asymptomatic with Positive Biomarkers)**

- Accumulation of CNS Aβ
  - CSF analysis
  - Brain imaging
- Marker of neuronal injury
  - Accumulation of tau within CSF
  - Abnormal brain glucose metabolism (PET scan)
- Subtle cognitive changes
Stage 2: Prodromal AD / Mild Cognitive Impairment (MCI)

- Evidence of CNS biomarkers
- Evidence of early cognitive decline

Stage 3: Dementia due to AD

- Mild
- Moderate
- Severe

Mild Dementia due to AD

- Impaired short-term memory
- Impaired problem solving abilities (e.g. math/numbers, judgment tasks)
- Personality changes (e.g. irritability & anger)
- Difficulty with thought organization and expression
- Unfamiliarity with environment

Moderate Dementia due to AD

- Increasingly poor judgment and confusion
- Increased memory problems - inability to remember vital personal information (e.g. inability to remember phone number, address, etc. with repetition of familiar stories)
- Increased need for assistance with daily living activities (e.g. bathing, grooming, bladder and bowel function)
- Progressive personality and behavioral changes (e.g. suspicion of others, late-day agitation, outbursts of aggression)

Severe Dementia due to AD

- Loss of ability to respond to environment
- Inability to communicate
- Loss of motor control & mobility
- Loss of bulbar function (e.g. difficulty with swallowing, bladder/bowel control & breathing)

CNS Biomarkers for Prodromal AD / MCI

- Medial temporal lobe atrophy on MRI
- CSF abnormalities (β-amyloid, phosphorylated tau)
- Temporoparietal hypometabolism on 18 F-fluorodeoxyglucose PET
- Positivity on amyloid ligand imaging with PET

Brain PET in AD

- FDG-PET
  - Decreased cortical metabolism of glucose with AD
- Amyloid PET
  - Increased signal associated with uptake of amyloid ligand

Preliminary Results of IDEAS Study

- Amyloid PET allows for more accurate detection or exclusion of AD as compared to metabolic imaging and/or CSF analysis
  - Pre-scan diagnosis of AD with positive aPET associated with 99% accuracy of AD
  - Pre-scan diagnosis of non-AD with negative aPET associated with 99% accuracy of non-AD
  - Pre-scan diagnosis of non-AD with positive aPET associated re-assessment as AD in 60% of cases
  - Pre-scan diagnosis of AD with negative aPET associated with exclusion of AD in 54% of cases

Ocular Manifestations of Alzheimer’s Disease

- 1986 study post mortem study of optic nerves in patients with AD
- Wide-spread axonal degeneration in 8/10 optic nerves
- Specificity for larger M-cell degeneration

Neuro-ophthalmic Findings with AD

- Functional
  - Visual Dysfunction (contrast sensitivity / low contrast acuity)
  - Visual-motor dysfunction (abnormal saccades)
- Structural (OCT)
  - RNFL/GCC thinning
Visual Dysfunction

Reduced Contrast Sensitivity / Low Contrast Acuity with Alzheimer’s Disease


- Impaired contrast sensitivity (particularly at low spatial frequencies) with AD vs. healthy elderly controls
- Implication of disease involving primary and association visual cortex vs. retina/optic nerve


- Study of visual deficits in patients with AD (N = 10) other dementias (N = 10) age-matched controls (N = 11) & young controls (N = 10)
- Assessment of color vision (D-15), contrast sensitivity (Pelli-Robson) & stereo acuity (RANDOT)
- Low spatial frequency contrast sensitivity deficits most specific for AD vs. other visual measures


- Contrast sensitivity (frequency doubling technology) assessment in individuals with AD (n = 10), mild cognitive impairment (n = 28), cognitive complaints (n = 20) & healthy controls (n = 29)
- CS evaluation as a function of cognitive performance
- Reduced contrast sensitivity specific for AD and parallels the course of cognitive impairment with AD

Posterior Cortical Atrophy (Benson’s Syndrome)

- Approx. 5% of AD patients (earlier age of onset)
- Preserved cognitive function
- Beta amyloid/tau infiltration & atrophy of visual cortex
  - Progressive vision loss (without obvious clinical correlation)
  - Difficulty reading / inability to follow printed words
  - Photophobia
  - Problems with depth perception
  - Hemianopic field loss / Visual neglect
  - Difficulty with visual processing (recognition of familiar objects/faces)

Visual-motor Dysfunction with AD

Impaired Saccades
Types of Saccades

- Voluntary - FEF
- Predictive - DLPFC, FEF
- Memory - DLPFC, FEF
- Reflex - Parietal
- Antisaccade - DLPFC, FEF - direct eyes away from a target

Challenges to Brain

- Saccades must be fast (300-500 deg/sec, up to 900-1000 deg/sec) and brief (100-200 msec)
- Saccades must be accurate
- Saccade-generating “burst neurons” in the brainstem must discharge vigorously
- Prone to malfunction in neurodegenerative disease & TBI

Visual-motor Dysfunction with AD: Impaired Saccades

- Impaired eye tracking while reading with AD vs. age-matched controls (Fernandez G, et al. Invest Ophthalmol Vis Sci 2013)
- Impaired microsaccades with mild cognitive impairment & AD (Kapoula Z, et al. Age (Dodr) 2014)
Ocular Structural Changes with AD

OCT Findings

- RNFL & paramacular thinning in AD vs. controls (Polo V, et al. Eye 2014)
- RNFL thinning (superior quadrant selectivity with mild cognitive impairment/early AD) parallels dementia progression in AD (Liu D, et al. BMC Neurol 2015)

Meta-analysis of 25 studies involving 887 AD patients, 216 MCI patients and 864 health controls
- AD & MCI patients had thinner RNFL (p < 0.0001) & macular thickness (p = 0.0001) as compared to healthy controls

Polling Question #2

All of the following are ocular findings with Alzheimer’s disease EXCEPT:
- a. Eye movement abnormalities
- b. Retinal nerve fiber layer thinning
- c. Macular edema
- d. Impaired contrast sensitivity

OCT Findings in AD

- OCT Angiography in AD

- Enlargement of foveal avascular zone (FAZ) in patients with preclinical AD vs. health controls
- Reduction in retinal vascular density in patients with AD vs. Health controls

Pharmacotherapy for AD

- Cholinesterase inhibitors
- NMDA antagonists
- Aβ sequestration agents / disease modifying therapy

6-12 month delay of symptoms
Cholinesterase Inhibitors

- Donepezil (Aricept)
  - All stages
- Galantamine (Razadyne)
  - Mild-moderate AD
- Rivastigmine (Exelon)
  - Mild-moderate AD

NMDA Antagonists

- Memantine (Namenda)
  - Moderate to severe AD
  - Alone or in combo with cholinesterase inhibitors
- Namzeric (Namenda/Aricept combo)

Disease Modifying Therapy

- Aducanumab (Aduhelm™)
  - Monoclonal antibody designed to clear beta amyloid
  - Monthly infusions
  - FDA approval 6/7/21 for early AD

Bloomberg News 6/7/21

- Aducanumab binds to amyloid molecules
- Infusion Tx q 4 weeks (est. annual cost: $50K)
- Benefit described as “fairly small” based on Mini-Mental State Examination (MMSE)

### Non-pharmacologic Therapy

- **Exercise** — increase in **brain-derived neurotrophic factor (BDNF)**
  - Released from astrocytes — repair of adjacent neurons ("brain fertilizer")
- **Mediterranean diet**
- **Turmeric (curcumin)**
  - Improved cognitive function
  - Degradation of plaques (animal models)

*Nonaka S, et al. Ann Indian Acad Neurol 2020*

### Chronic Traumatic Encephalopathy (CTE)

### Historical Perspective of CTE

- **Martland** — “Punch drunk”
  — JAMA 1928
- **Millspaugh** — “Dementia pugilistica”
  — US Naval Medical Bulletin 1937
- **Critchley** — “Medical aspects of boxing particularly from a neurological standpoint”
  — Psychological Bulletin 1957
- **Corsellis** — “Chronic traumatic encephalopathy”
  — Psychological Medicine 1973

### Mike Webster (1952-2002)

- 16 years in NFL
- Died in 2002 (age 50)
- Significant history of depression and memory loss prior to death
- Autopsy of brain by Bennet Omalu MD (Pgh Medical Examiner)
- Pathology slides reviewed by Steven DeKorsky (Univ. Pittsburgh) with diagnosis of CTE
- Controversy as to relationship with NFL career / repetitive head trauma

### Neuropathology of CTE

- Atrophy of cerebral hemispheres, temporal lobe, mammillary bodies & brainstem
- Ventricular dilatation
- Fenestration of septum pelucium
- **Marked accumulation of tau-immunoreactive astrocytes**

**Pathophysiology of CTE**

- Repetitive head trauma
- Up-regulation of amyloid precursor proteins (APP)
  - $\beta$ synthesis
  - Phosphorylation of Tau
  - Microtubular disarrangement
  - Perivascular liberation of Tau involving base of cortical sulci

DeKosky S. AAN-SCCC 2015

**Prominent NFL Players with CTE**

- Mike Webster
- Andre Waters
- Junior Seau
- Dave Duerson


**Mr. Duerson’s Clinical History**

- Long-standing complaints of headaches since NFL and onward.
- Over the ~5 years prior to death, he had worsening short-term memory difficulties, as well as problems with language and “vision”
- Increasingly out of control:
  - Short fuse
  - Hot tempered
  - Physically abusive
  - Verbally abusive
Owen Thomas
- Co-Captain of 2010 Penn Football Team
- Began playing football at 9 years old
- Committed suicide April 26, 2010, at the age of 21
- No history of concussion
- No history of mental illness
- Mentioned doing poorly in two classes to his parents the day before hanging himself in his off-campus apartment

18 y/o male with CTE

APOE 4 & CTE
- Increased chronic neurologic deficits in boxers with APOE4 (Jordan BD, et al. JAMA 1997)
- APOE4 identified within early cohort of biopsy-proven CTE (Omalu BI, et al. Neurosurgery 2011)
The Search for Surrogate Biomarkers

- FDDNP PET scans on 5 retired NFL players with history of mood & cognitive dysfunction
- Comparison of PET signals with age-matched norms
- FDDNP signals higher in NFL players (subcortical regions and amygdala)

Analysis of Florataucipir PET in 26 former NFL players vs. 31 controls
- Former NFL players with cognitive and neuropsychiatric symptoms had higher tau levels measured by PET than controls in brain regions that are affected by CTE and did not have elevated amyloid-beta levels
- Elevated tau levels not significantly different as compared to controls

Evidence for Ocular Surrogate Biomarkers in CTE

- Study of 78 former NFL players & 16 health age-matched controls
- The NFL group had higher exosomal tau than the control group (p < 0.0001)
- Exosomal tau discriminated between the groups, with 82% sensitivity, 100% specificity, 100% positive predictive value, and 53% negative predictive value
- Within the NFL group, higher exosomal tau was associated with worse performance on tests of memory (p = 0.0126) and psychomotor speed (p = 0.0093)

Preliminary Study of Plasma Exosomal Tau as a Potential Biomarker for Chronic Traumatic Encephalopathy

- Multi-center study of 46 collision sport athletes as compared to age-matched healthy controls
  - Illinois Eye Institute/Illinois College of Optometry
  - NYU Langone Medical Center/Department of Neurology
- Comparison of OCT, low contrast acuity, rapid number naming & quality of life among boxers/retired NFL players vs. age-matched controls
Results: Visual Pathway Structure

- Controls
  - Boxing Athletes (n=14, 28 eyes)
  - Football Athletes (n=29, 58 eyes)

Average RNFL thickness, µm, mean ± SD:
- Boxing: 83.5 ± 2.8
- Football: 81.2 ± 1.2

Average GCC thickness, µm, mean ± SD:
- Boxing: 79.7 ± 4.6
- Football: 78.2 ± 1.2

p < 0.001


Visual Function: Low Contrast Acuity

- Controls
  - Boxing Athletes (n=14, 28 eyes)
  - Football Athletes (n=29, 58 eyes)

Binocular 2.5% mean (letters/70):
- Controls: 38.6 ± 0.5
- Boxing: 31.7 ± 2.1
- Football: 36.6 ± 0.8

p = 0.002

Monocular 2.5% mean (letters/70):
- Controls: 30.8 ± 0.6
- Boxing: 24.4 ± 2.0
- Football: 29.2 ± 1.1

p = 0.003


OCT Findings in Military Veterans with TBI vs. Healthy Controls

- Longitudinal OCT study of veterans with mTBI vs. controls
- Significant progression of RNFL thinning among mTBI cohort (1.25 microns/year) as compared to controls (0.1 microns/year)

Kardon R, et al. NANOS Meeting 2019

Polling Question #3

What is the diagnostic brain biomarker for chronic traumatic encephalopathy?
- a. Tau
- b. Blood
- c. Beta amyloid
- d. Lipofuscin

Comparison of Clinical & Neuropathology Findings in CTE vs. AD

- Both associated with TBI & genetic factors (APOE4 allele)
- Older age of onset with AD
- Differences in psych and behavioral findings
  - Early depression / loss of executive function → CTE
  - Early short term memory impairment → AD
- Neuritic plaques & neurofibrillary tau tangles with AD
- Predominance neurofibrillary tau tangles with CTE (perivascular distribution at base of sulci)
- Superficial (layers II & III) pathology with CTE vs. deeper (layers V & VI) with AD

Key Points

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Thank you!