Course #

511

Understanding Alzheimer's
Understanding Alzheimer’s

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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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Epidemiology of Alzheimer’s Disease (AD)

• 5.2 Americans with AD
• 96% > 65 years
• 5th leading cause of death > 65 years
• Increasing incidence and prevalence (est. prevalence of 13.8M by 2050)

Risk Factors for AD

• Older age
• Genetics (APOE4 allele)
• Prior history of TBI

APOE & AD

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<tr>
<th>Allele Frequency</th>
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<td>Normal Population</td>
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• APOE4
  – Impaired sequestration of cholesterol (atherosclerosis)
  – 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

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

"Amyloid Cascade" Hypothesis

Medial Temporal Lobe
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

Staging of Alzheimer’s Disease
1. Preclinical Alzheimer’s Disease (AD risk state)
2. Prodromal AD / Mild Cognitive Impairment
3. Dementia due to Alzheimer’s Disease

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

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
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)

Pharmacotherapy for AD

• Cholinesterase inhibitors
• NMDA antagonists
• Aβ sequestration agents / disease modifying therapy (clinical trials)

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)

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

Visual Dysfunction in Alzheimer’s Disease: Relation to Normal Aging
• 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

Vision in Aging & Dementia
• 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) & stero acuity (RANDOT)
• Low spatial frequency contrast sensitivity deficits most specific for AD vs. other visual measures

Visual Contrast Sensitivity in Alzheimer’s Disease, Mild Cognitive Impairment, and Older Adults with Cognitive Complaints
• 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

Visual-motor Dysfunction with AD: Impaired Hand-Eye Coordination
• Impaired hand-eye coordination in AD vs. age-matched health controls→degeneration of posterior parietal cortex vs. purely cognitive impairment (Verheij S, et al. J Alzheimers Dis 2012)

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 900-100 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 (Dordr) 2014)


- Analysis of saccadic eye movements during reading in patients with early AD (n = 20) vs. health age-matched controls (n = 20)
- Impaired eye-tracking with early AD vs. controls
- Potential role of saccades for early diagnosis & long-term surveillance of AD

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Visual eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability

- Prospective analysis of 36 PCS subjects vs. healthy controls
- PCS associated with worsening of anti-saccades, self-paced saccades, memory-guided sequences & smooth pursuits
- Eye movement dysfunction showed higher correlation with symptom load as compared to neuro-psych testing
- Biological substrate for concussion-related symptoms

Postfight K-D scores (n = 39 participants) were significantly higher (worse) for those with head trauma during the match (59.1 ± 7.4 vs 41.0 ± 6.7 seconds, p < 0.0001, Wilcoxon rank sum test)

- Those with loss of consciousness showed the greatest worsening from prefight to postfight. Worse postfight K-D scores (rs = -0.79, p < 0.0001) and greater worsening of scores (rs = 0.90, p < 0.0001) correlated well with postfight MACE scores
- Worsening of K-D scores by ≥5 seconds was a distinguishing characteristic noted only among participants with head trauma
- High levels of test-retest reliability were observed (intraclass correlation coefficient 0.97 [95% confidence interval 0.90-1.0])
Distinctive Features of Microsaccades in Alzheimer’s Disease and in Mild Cognitive Impairment (Kapoula Z, et al. Age (Dordr) 2014)

- Study of microsaccades during attempted fixation in patients with AD, mild cognitive impairment and health age-matched controls
- Impaired microsaccades among AD and MCI groups (implication of square-wave jerks as indicator of AD / MCI)


- Evaluation of saccades & anti-saccades as a function of neuropsych testing among individuals with aMCI (n = 22), mild AD (n = 24) & age-matched controls (n = 76)
- Impaired antisaccades with amnestic mild cognitive impairment & AD → impaired executive function

Diagnosis of Mild Alzheimer Disease Through the Analysis of Eye Movements During Reading (Fernandez G, et al. J Integr Neurosci 2015)

- Eye movement/saccade analysis of individuals with AD (n = 20) vs. age-matched controls (n = 40)
- Abnormal “reading saccades” with AD as compared to controls suggesting disease of pre-frontal cortex

Ocular Structural Changes with AD

OCT Findings

77 y/o AA Man

- Complaint on non-specific visual problems
- BVO:
  - 20/20 OD
  - 20/25 OS
- History of AD
OCT Findings in AD

- 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)
- OCT as potential surrogate marker of disease progression with AD

Reliability and Validity of Cirrus and Spectralis Optical Coherence Tomography for Detecting Retinal Atrophy in Alzheimer's Disease (Polo V, et al. Eye 2014)

- Analysis of macular cube and optic disc OCTs among individuals with AD (n = 75) vs. age-matched controls (n = 75)
- Significant parafoveal retinal and RNFL thinning for AD vs. controls
- Correlation between RNFL and disease duration


- Analysis of RNFL thickness with MCI & AD vs. age-matched controls
- RNFL thinning (superior quadrant selectivity with mild cognitive impairment/early AD) parallels dementia progression in AD

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)
  - Aβ synthesis
  - Phosphorylation of Tau
  - Microtubular disarrangement
  - Perivascular liberation of Tau involving base of cortical sulci

DeKosky S. AAN SCC 2015

Criteria for Pathological Diagnosis of CTE

- NHG Consensus Conference (Boston, Feb 2015)
  - In CTE, the tau lesion considered pathognomonic was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci.

Koroshetz W. AAN SCC 2015

Prominent NFL Players with CTE

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

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

Comparison with other former NFL players

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
Stage 1: headache and loss of attention and concentration
Stage 2: depression, explosivity and short-term memory loss
Stage 3: loss of executive dysfunction and cognitive impairment
Stage 4: dementia, word-finding difficulty and aggression


Clinical “Spectrum” of CTE
• Boston University study of 36 male subjects with histopathologically documented CTE
• Retrospective interviews with next-of-kin
  – 61% Behavioral/mood disturbances (younger age)
  – 31% Cognitive impairment/dementia (older age)

Stein RA, et al. Neurology 2013

CTE Masquerades
• Alzheimer dementia
• Progressive supranuclear palsy
• Parkinsonism
• Amyotrophic lateral sclerosis (Lou Gehrig's Disease)

Wally Hilgenberg
1942-2008
APOE4 Allele

- APOE facilitates normal sequestration of cholesterol and Aβ
- APOE4 allele results in faulty accumulation of Aβ and hyperlipidemia
- 40-50% prevalence of APOE4 with AD (vs. 14% normal population)
- Allele frequency is 2X as high in African American as in Caucasian populations

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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

- PET scans of retired NFL players reveals FDDNP signals in areas of presumed Tau deposition (Small GW, et al. Am J Geriatr Psychiatry 2013)

FDDNP Binding (NFL v. Control)

- 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)

Comparison of FDDNP – PET Findings in retired NFL Players vs. AD

**NFL Players (n = 14)**
- High signal lesions within amygdala and subcortical regions responsible for learning, mood, emotions & behavior

**AD (n = 24)**
- High signal lesions within medial temporal lobe with minimal to no involvement of subcortical regions (cognitive regions)


The Search for Ocular Surrogate Biomarkers

- Retinal deposition of hyperphosphorylated tau (McKee A. personal communication 2012)
- Potential for OCT and other visual tests as surrogate biomarkers of CTE

VICTORS Study

- Comparison of OCT, low contrast acuity and rapid number naming among boxers/retired NFL players vs. age-matched controls
- Thinning of nerve fiber layer/GCC (greatest among boxers)


OCT Findings Among Collision Sport Athletes vs. Controls (VICTORS Study)


Shively S, et al. *Arch Neurol* 2012
CTE vs. Alzheimer’s

### Comparison of Clinical & Neuropathology Findings in CTE vs. AD

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<tr>
<th>Clinical</th>
<th>CTE</th>
<th>AD</th>
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<td>Short term memory deficits early in the course</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Depression early in the course</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Abrupt mood swings / explosive behavior</td>
<td>++</td>
<td>+/-</td>
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<tr>
<td>Substance abuse</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Late-stage Parkinsonism</td>
<td>+++</td>
<td>+/-</td>
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<tr>
<td>Suicidal behavior</td>
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### Summary: 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!