

Canine Cognitive Dysfunction (CCD)



CW Dewey, DVM, MS, CTCVMP
DACVIM (Neurology), DACVS

Brutus

- 14 yo MC Pug
- "Slowing down" recently
- Seems like he is going "senile"
- Acute onset of balance loss



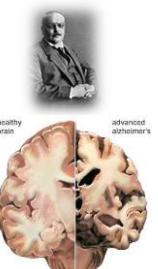
Brutus' MRI Results



T2-weighted T2*-weighted

Human Alzheimer's Disease (AD) and Canine Cognitive Dysfunction Syndrome (CDS)

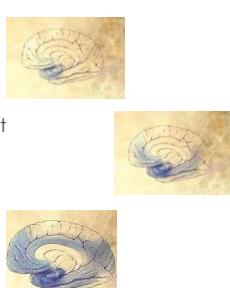
- Analogous disorders
- Senile dementia
- Progressive deterioration
- Multiple theories
- Multiple treatment options
- No cure



The top right corner features a portrait of a man, likely a historical figure related to Alzheimer's research. Below the portrait is a split-brain diagram showing a healthy brain on the left and an advanced Alzheimer's brain on the right, illustrating the structural changes associated with the disease.

Categories of Cognitive Function in Aging Patients

- Successful aging
- Mild cognitive impairment
- Severe cognitive impairment (dementia)



The middle section contains three small brain diagrams arranged vertically. The top diagram shows a brain with yellow highlights, the middle one shows a brain with blue highlights, and the bottom one shows a brain with both yellow and blue highlights, representing different levels of cognitive function in aging patients.

Diagnosis of CDS (or CCD)

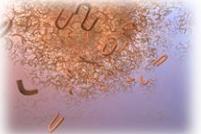
- Probably more difficult than diagnosing AD
- Based primarily on historical complaints
- Ruling out other causes of encephalopathy
- Neurologic examination findings
- Brain imaging
- Histopathology



The bottom right corner features a photograph of a dog's head, specifically focusing on the ear area, which serves as a visual metaphor for the diagnosis of Canine Cognitive Dysfunction Syndrome.

Similarities Between AD and CDS

- Disease of the elderly
- Similar structural brain changes
- Progressive accumulation of beta-amyloid (A_β) protein
- Progressive accumulation of tau protein
- Microvascular changes in brains similar



Neurofibrillary Tangles (NTs)

- Form in humans, not dogs
- Amino acid sequence of tau protein different in canine vs humans
- Dogs may not live long enough for NTs to form
- Significance of NTs unclear



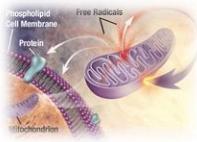
Dissimilarities between AD and CCD

- Primarily in degree of clinical severity
- Also societal role expected with successful management
- CCD should be considered a unique disorder, despite mechanistic similarities with AD



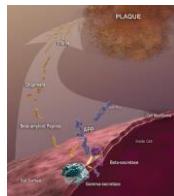
Pathogenesis of AD/CDS

- Multifactorial
- Some genetic risk factors
- Toxic effect of A β : Amyloid-dependent effects
- Microvascular damage
- Oxidative damage
- Mitochondrial dysfunction
- Excitotoxic damage (glutamate)
- Inflammatory damage (cytokines)



Amyloid-Dependent vs Amyloid-Independent Processes

- A β deposition clearly part of process, may not be primary
- Initial damage may be oxidative injury to small blood vessels
- Ischemic injury may lead to inflammatory mediator increase
- Ischemia may also alter A β metabolism
- Increased A β also adds to oxidative stress



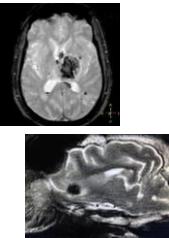
Neurochemical Changes in AD/CDS

- Acetylcholine
- Dopamine
- Norepinephrine
- GABA
- Glutamate
- Lactate
- Pyruvate
- Potassium

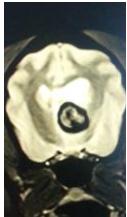


Spontaneous Intracranial Hemorrhage in CDS/AD

- Microhemorrhages well documented in both disorders
 - Suspected due to amyloid deposition
 - Macrohemorrhages in dogs-related to aging process?



Recent Focus on Vascular Phenomena and AD



- VCID
 - Genetic risk factors for both
 - Cerebral amyloid angiopathy (CAA)
 - “Chicken or the egg” scenario
 - Dog MRI investigation

Clinical Features of CDS in Dogs

- Elderly, usually >9 yrs
 - Inattentiveness
 - Inactivity
 - Anxiety
 - Aimless wandering (often pacing at night)
 - Demented behavior
 - Abnormal sleep/wake cycle



Clinical Features of CDS in Dogs

- Urinary and/or fecal incontinence
- Difficulty navigating stairs
- Becoming lost in previously familiar surroundings
- Failure to recognize people or other pets
- Decreased interaction with family
- Apparent hearing loss
- Excessive vocalization (especially at night)



Other Clinical Features of CDS in Dogs

- Seizures
- Vestibular dysfunction
- Also occur in humans with AD
- May have a vascular basis-TIAs
- Seizures not well documented in CDS literature-clinical experience



Four Key Clinical Features of CDS

- Anxiety
- Abnormal sleep/wake cycle
- Decreased interaction with owners
- Apparent confusion



Recent Links Between Seizure Activity and AD

- Seizure activity may precede obvious dementia
 - APP linked to seizure activity
 - Some genetic forms of AD associated with seizures
 - Some seizures are non-convulsive
 - Late-onset/cryptogenic canine epilepsy?



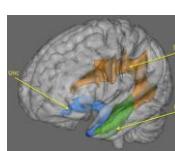
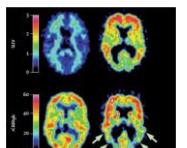
Checklist for CDS in Dogs

- DISHAAL acronym
 - Disorientation
 - Interactions
 - Sleep/wake cycle
 - Housesoiling
 - Activity (repetitive or decreased)
 - Anxiety
 - Learning and memory

Section	Topic	Age/Time Available	Source & F
1. General Information	Demographic information, medical history, social history, toxicology screen, physical examination, laboratory evaluation, imaging studies, and treatment.	Initial visit	Textbook of Veterinary Internal Medicine, 7th edition, by Ettinger and Feldman, W.B. Saunders Company, Philadelphia, 2010.
2. Clinical Signs	Classification of clinical signs, common clinical signs, and differential diagnosis of common clinical signs.	Initial visit	Textbook of Veterinary Internal Medicine, 7th edition, by Ettinger and Feldman, W.B. Saunders Company, Philadelphia, 2010.
3. Diagnostic Tests	Common diagnostic tests, interpretation of test results, and use of test results in differential diagnosis.	Initial visit	Textbook of Veterinary Internal Medicine, 7th edition, by Ettinger and Feldman, W.B. Saunders Company, Philadelphia, 2010.
4. Therapeutic Agents	Common therapeutic agents, pharmacokinetics, pharmacodynamics, and adverse effects.	Initial visit	Textbook of Veterinary Internal Medicine, 7th edition, by Ettinger and Feldman, W.B. Saunders Company, Philadelphia, 2010.
5. Learning Objectives/Tests/Comments	Learning objectives, tests, and comments for each section.	Initial visit	Textbook of Veterinary Internal Medicine, 7th edition, by Ettinger and Feldman, W.B. Saunders Company, Philadelphia, 2010.

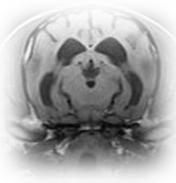
Diagnosis of AD

- Historical features
 - Clinical findings
 - Advanced imaging: MRI, PET scan, SPECT, others
 - CSF biomarkers-tau protein, A β protein



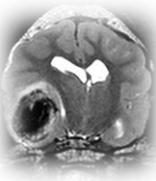
Diagnosis of CDS

- Historical features
 - Clinical signs
 - Advanced imaging-MRI only, so far
 - Ruling out other causes of encephalopathy



Differential Diagnoses of CDS in Dogs (Prior to Imaging)

- Brain tumor - #1
 - Inflammatory/infectious disease
 - Metabolic encephalopathy



Assessing Cognitive Impairment in Dogs

- In clinical setting, history and examination
 - In research setting, standardized testing apparatus with a battery of specific tasks to procure objective data
 - Tasks include
 - Landmark discrimination
 - Oddity discrimination
 - Object, size, black/white discrimination
 - Reversal tasks
 - Spatial memory tasks



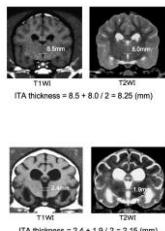
General MR Imaging Characteristics of the Aging Brain

- Generalized cerebral atrophy
- Enlarged (compensatory) lateral ventricles
- Prominent sulci
- Widened CSF space
- Medial temporal lobe atrophy



Interthalamic Adhesion Thickness in Older Dogs with and without CDS

- Significantly smaller in dogs with CDS
- Thickness size of 5.0 mm or less consistent with CDS

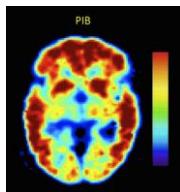


ITA thickness = $8.5 + 8.0 / 2 = 8.25$ (mm)

ITA thickness = $2.4 + 1.9 / 2 = 2.15$ (mm)

Imaging Studies for AD Diagnosis in Humans

- MRI, including functional MRI and DTI
- PET scans, including glucose-utilization
- A_{Beta} markers
- SPECT



Treatment of AD in People

- Multifactorial disease process
 - Multifaceted treatment approach
 - Many treatments evaluated by placebo-controlled studies



Treatment Options for AD

- Acetylcholinesterase inhibitors
 - NMDA receptor antagonists
 - Anti-inflammatory drugs
 - Antidepressant drugs
 - Anti-seizure drugs
 - Disease-modifying therapy
(mainly targeting A β protein)
 - Nutritional and supplement
therapy (anti-oxidants)



Proposed Treatments for CDS

- Selegiline-most often prescribed
 - Anti-oxidant fortified diet (b/d, others)
 - Gabapentin/pregabalin
 - Carprofen
 - Environmental enrichment



Proposed Treatments for CDS

- Phosphatidylserine
- Diet rich in MCTs
- S-adenosyl-L-methionine (SAMe) tosylate
- Apoaequorin (Neutricks)
- Propentofylline
- Others-levetiracetam



Levetiracetam for AD

- Several mechanisms involved (improved synaptic function, mitochondrial effects, decreased glutamate release)
- Experimental rodent studies
- Human clinical trials



Medium Chain Triglycerides (MCTs) for AD/CCD

- Improved cognition
- Traditionally thought due to increased ketone levels
- Recent evidence- direct effects of MCTs on brain function



Chinese Herbs with Efficacy for AD

Chinese herb/latin name	TCM Mer name and action
Sheng Jiang (Sugarcane)	Cools Heat and Phlegm
Rehmannia (Shen Cao Ni)	Cools Heat, removes toxins
Cervi Cornu (Deer Antler)	Cools Heat, cools Blood
Sinensis (Bee Stew)	Tonifies Qi
Corydalis (Yi Xing Zi)	Cools Heat, Compels
Polygonum multiflorum (Tuscan) (He Shou Wu)	Calms Shen, transforms Phlegm
Salvia miltiorrhiza (Dan Shen)	Cools heat & activates Blood
Anemone (Ai Mu) (Dang Gui)	Stimulates and moves Qi, Blood, rectifies Stagnation
Cocculus indicus (Zhi Ling Zi)	Invigilates Blood, invades Stagnation
Spatholobus root (Dan Ke Zi)	Cools Internal Wind, subdues wind Yang
Berberis chinensis (Shi Zi Huang)	Neutralizes Kidney Yin and Jing
Fructus Cornus officinalis (Huang Jing)	Invigorates Kidney Jing and Jing
Magnolia officinalis (Xin Rui Zi)	Moves Qi, resolves Stagnation
Trichosanthes (Lu Guo) (Huang Qin)	Cools Heat, detoxifies
Comandra (Chu Hu)	Cools Heat, drains Damp

Chinese Herbs in Conventional Terms

Latin and Chinese (in parentheses) herbot name	Mechanism of action
Ginkgo biloba (Ba Gu)	Antioxidant; anti-platelet; anti-inflammatory
Huperzia serrata (Gong Ceng Tzi)	Pro-cholinergic (IMDA ontogenetica)
Cucurbita longa (Yu Jin)	Inhibits AA production; antioxidant; anti-inflammatory
Ginseng (Ren Shen)	Antioxidant; anti-glucomafe (IMDA ontogenetica); decreases AA
Coptis chinensis (Huang Lian)	Inhibits AA production; pro-cholinergic; antioxidant; anti-inflammatory
Foliarlykehuo (Yan Yan Zi)	Inhibits AA production; anti-platelet
Sakura millefolium (Duo Shui)	Inhibits AA aggregation; antioxidant; anti-inflammatory
Anemone sinensis (Dong Qu)	Antioxidant; anti-inflammatory
Cicuta suaveolens (Zhang Heng Wu)	Antioxidant; anti-platelet
Ginkgo biloba (Ba Gu)	Pro-cholinergic; antioxidant
Kalmia glaucescens (Hu Shi Lingzhi)	Pro-cholinergic; antioxidant
Salvia miltiorrhiza (Tie Gou Cao)	Antioxidant; anti-platelet
Magnolia officinalis (Xin Yi Huo)	No-cholinergic; antioxidant
Eclipta prostrata (Huang Qian)	Inhibits AA aggregation; antioxidant; anti-inflammatory; anti-platelet
Camellia sinensis (Chao Huo)	Reduces AA levels; antioxidant; anti-inflammatory; anti-platelet

Selegiline for Dogs with CDS

- Questionnaire-based studies
 - Proposed mechanism:
increase brain dopamine levels
 - Also increases brain catecholamine levels
 - Evidence of ineffectivity in dogs and humans



Natural Phytochemicals for Treatment/Prevention of AD/CDS

- Resveratrol
- Curcumin
- Catechins

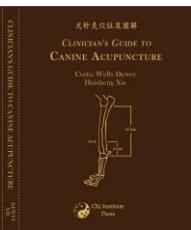


Environmental Enrichment



- Toys—especially those requiring some task
- Exercise
- Social interaction
- Experimental and clinical proof of efficacy
- Concept of “cognitive reserve”

Acupuncture for CCD?



- Experimental evidence of efficacy in rodent AD models
- Clinical evidence of efficacy in human AD
- Multiple mechanisms, including improved synaptic plasticity

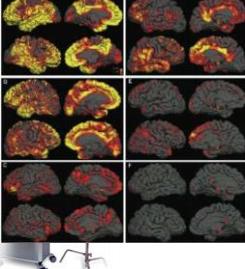
Prognosis for AD and CDS

- Poor for resolution
- Mild to moderate improvement with therapy
- Progressive neurologic deterioration
- Death within 8-10 yrs with AD; Fair prognosis for control and quality of life in aged dogs



Potential Areas of Investigation for AD and CDS

- Functional imaging studies
- Search for genetic markers
- Gene therapy
- Clinical drug trials



Questions?