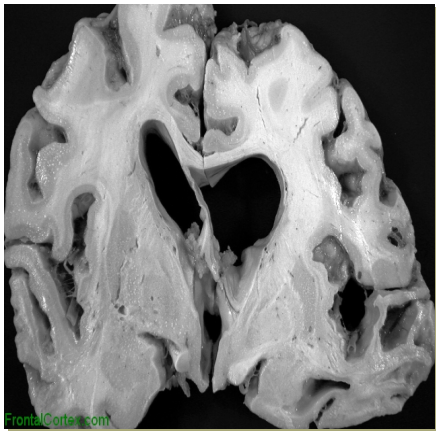
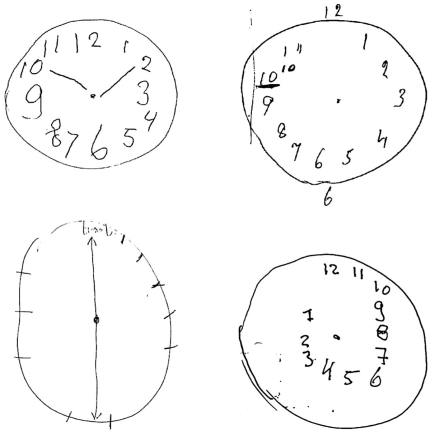




Dementia

Alzheimer's

Characteristics, causes, pathology, clinical features, progression, diagnosis, and treatment

Characteristics

- Dementia – not caused by other disease e.g. Parkinson's
- Significant cognitive deficit
- PROGRESSIVE
- Consciousness not affected
- Pt. 40-90 yrs old

Causes

Environmental

- Lifestyle
- Head injury

Risk Factors

- Down's
- Family history
- Advanced age
- ε4-allele of apolipoprotein E-Gene
- Female gender

Familial/Genetic theory

- Genetics 60-80% causation
- Familial (<5%)
  - Presinilin I (ch. 14)
  - Presinilin II (ch. 1)
  - APP (ch. 21)
- Late onset (non-familial)
  - ApoE (Ɛ4, Ɛ2)

Pathology

Macroscopic: atrophy
Disturbance in neurotransmitters; marked cholinergic deficit

Neurofibrillary tangles

- Cytoskeletal protein
- Hyperphosphorylated Tau protein
  - Tau maintains microtubules within axons
  - Hyperphosphorylated no more supports microtubules
  - Collapse of transport system
- Elevated in CSF

Neuritic (Amyloid) Plaques

- Extracellular compacted insoluble amyloid protein
  - Collection of waste products of dead neurons around amyloid core
- Aß$_{42}$ peptide – abnormal secretase cleavage
- Neurotoxic properties
- Reduced in CSF

Clinical Features and Progression

Mild

- Date disorientation
- Naming difficulties
- Recent recall problems
- Poor concentration
- Social withdrawal
- Irritability – mood/ personality changes
- Problems managing finances
- Poor performance at work

Moderate

- Disorientation for date and place
- Comprehension difficulties
- Impaired learning
- Impaired calculation
- Getting lost
- Delusions, hallucinations
- Agitation, aggression
- Aphasia
- Apraxia

Severe

- Disorientation for person
- Unintelligible verbal output
- Remote memory gone
- Agraphia
- Unable to feed
- Total apraxia
- Unable to walk
- Incontinent

Average time from onset to death is ~5-10 years

Diagnosis

DSM-IV Criteria

1. Development of cognitive deficits, manifested by both:
   - Impaired memory
   - Aphasia, apraxia, agnosia & disturbed executive function
2. Significantly impaired social & occupational function
3. Gradual onset & continuing decline

Investigations

- Clinical Dx; by exclusion
- Definitive Dx: biopsy/autopsy
- Radiological
  - CT: exclude multiple-infarcts or mass lesion
  - MRI: shows atrophy
  - SPECT: shows temporofrontal hypoperfusion

Treatment

HRT found to lower risk of developing AD

- Acetylcholine inhibitors:
  - Avoid anticholinergic medications!
  - Use donepezil, a **cholinesterase inhibitor [1st line]**
  - Tacrine (older); currently not used because of 4 times/day dosing and marginal improvement in cognition + more SE

- Dietary supplements > not beneficial

- Vitamin E: slows disease progression and preserves function in people with moderately severe Alzheimer's disease. *Full benefit is yet to be determined.*

Treatment

Category	Name	Action
Anticholinesterase	Tacrine	↑ available estrogen
Nerve growth factor	No trade name	Stimulate nerve growth
Glutamate enhancers	Labazimide	Facilitate glutamate
Antioxidants	Seligiline	Stop free radicals
Anti-inflammatory	Advil	Unknown
HRT	Estrogen	Unknown

Vascular Dementia

Characteristics, clinical features, diagnosis, and management

Characteristics

Multi-Infarct Dementia

- Overdiagnosed; 10% of dementia cases
- Cause: multiple strokes (cortical and subcortical lesions)
  - Damage to blood vessels through areteriosclerosis
  - Silent strokes; progression stroke by stroke (focal damage ↑)
- Stroke profile: HTN, DM, atherosclerosis, etc
- Dx from Hx and confirmed by CT and MRI
- Occurs in middle and later life (50-70 yrs)
- Incidence higher in men
- 1st sign: delerium

MRI Imaging:
•Periventricular hyperintensities
•Ventricular capping
•"Small vessel ischemia"

Clinical Presentation

Multi-Infarct Dementia

- ABRUPT onset

Binswanger's disease-insidious onset, due to diffuse subcortical white matter degeneration, most commonly seen in patients with long-standing HTN and atherosclerosis

- Step-wise deterioration (course is variable; may plateau)
- History of HTN, CVA
- Emotional incontinence e.g. inappropriate sense of humor
- Mood lability
- Somatic complaints
- Focal neurological signs and symptoms

Multiple medications and comorbid illnesses associated with the vascular risk factors increase vulnerability to delirium (confusion)

Diagnosis: DSM-IV Criteria

- Development of cognitive deficits manifested by both:
  - Impaired memory
  - Aphasia, apraxia, agnosia, and disturbed executive function
- Significantly impaired social and occupational function

BUT with

- Step-wise deterioration (after each event)
- Focal neurologic symptoms & signs/evidence of CVD or multiple CVD risk factors:
  - HTN, DM, hypercholisterolemia, obesity, CAD

Management

- Risk assessment
  - Age, hypertension, smoking, diabetes, history of stroke/TIA
- Reduction of risk of further damage
  - Management of stroke and risk factors
- Treatment of secondary conditions
  - Depression, anxiety, agitation
- Treatment of dementia symptoms
  - Cognition, global function, activities of daily living

Focal neurodegenerative dementias

Fronto-temporal degenerative dementia

General Characteristics

Chr. 17 abnormality

- Frontal/temporal lobar atrophy on MRI
- Pathology: Pick's bodies = tau protein
- Diagnostic criteria = AD, BUT
  - Onset at young age; presenile (<65 yrs)
  - Predominant changes in behavior; occur early and progress
  - Non-fluent aphasia
  - Memory loss and visuospatial abnormalities occur later
- SPECT > anterior defects
- Normal EEG

Types:
1. Pick's
2. Non-specific frontal degeneration
3. Frontal degeneration with anterior spinal neuron loss

Clinical Presentation

- Mean age is 53 yrs
- Familial aggregation
- Predominantly males
- Cognitive impairement mostly in executive functions e.g. planning, judgement etc and attention
- Speech may be economical (mutism) or increased (in disinhibited pts)
- Behavioral
  - Emotional blunting
  - Inertia, lack of initiative
  - Social disinhibition – loss of insight
  - Impulsivity, overactivity
  - Stereotyped, preserved behavior

Normal Pressure Hydrocephalus

- Triad of symptoms:
  - Gait instability (apraxic gait): wide-based, shuffling with poor coordination
  - Urinary incontinence; includes urgency (follows gait disturbance)
  - Dementia: slow thinking/response, decreased spontaneity
- May appear similar to AD
- Reversible with treatment
- DEFENITE DIAGNOSIS: MRI
  - Enlarged ventricles BUT no evidence of atrophy

Dementia with Lewy Bodies

- Involves subcortical structures
- Overlap with AD and PD
- Etiology:
  - Accumulation of cytoplasmic inclusions (Lewy bodies)

- Decline in
  - Memory
  - Language
  - Planning, judgement (executive functions)
- Visual hallucinations
- Parkinsonism signs (rigidity, slowness, unexplained falls)
- Alterations of alertness/attention
- Early incontinence
- Neuroleptic hypersensitivity:
  - Do not give anti-psychotics > worsens parkinsonism symptoms

AIDS Dementia Complex

- ~ 2/3 of patients with AIDS develop dementia; mostly due to AIDS-dementia complex
  - In some HIV is found in the CNS post-mortem
  - In others, an immune mechanism/ unidentified pathogen is blamed
- Initially subcortical
- Dx:
  - CT: atrophy
  - MRI: increased T2 signal from white matter
- Rx with Zidovudine halts and partially reverses neuropsychological deficit

Other Dementias

- Parkinson Dementia
  - Age: 50-80
  - Survival 8-15 yrs
  - Dementia occurs **later**
  - Neuropsychiatric symptoms
  - Dysphagia, dysphonia

- Parkinson with Dementia
  - Dementia occurs **early**
  - + physical symptoms:
    - ++ frontal lobe symptoms
    - Poor response to L-dopa
    - Rapid course

- Progressive Supranuclear Palsy (Dudley Moore)
  - Age: late 50's to mid 60's
  - Survival 10 yrs
  - Initially: ~ Parkinson's symptoms e.g. falls
  - Difficulty with vision
  - Inability to look down
  - Mental slowness, frontal lobe dysfunction
  - Dysarthria, dysphagia

Other Dementias

- Alcoholic Dementia
  - Direct effects
  - Secondary effects
  - Wernicke-Korsakoff syndrome
- Vitamin Deficiency
  - Vit. B12, folate, niacin, thiamine
- Toxic Metal & Gas Exposure
  - Lead, mercury, manganese, arsenic, carbon monoxide, carbon disulfide
- Organic Causes
  - Organ failure (liver, kidneys)
  - Endocrine (hypothyroidism, DM)
  - Inflammatory (SLE)
  - Neurodegenerative

Differential

Delirium	Dementia
Rapid onset	Insidious onset
Fluctuating course	Slowly progressing course
Attention disturbance	Memory deficit
Confusion	Consciousness intact
Clouded consciousness	Subtle behavioral changes
Marked behavioral changes	Can be irreversible
Can be reversible	

Management

Symptom Management

Other cognitive enhancers: estrogen, NSAIDs, ginkgo, vit E

Non-Pharmacologic

- Cognitive enhancement
- Individual and group therapy
- Environmental modification
- Regular appointments
- Communication with caregivers
- Attention to safety

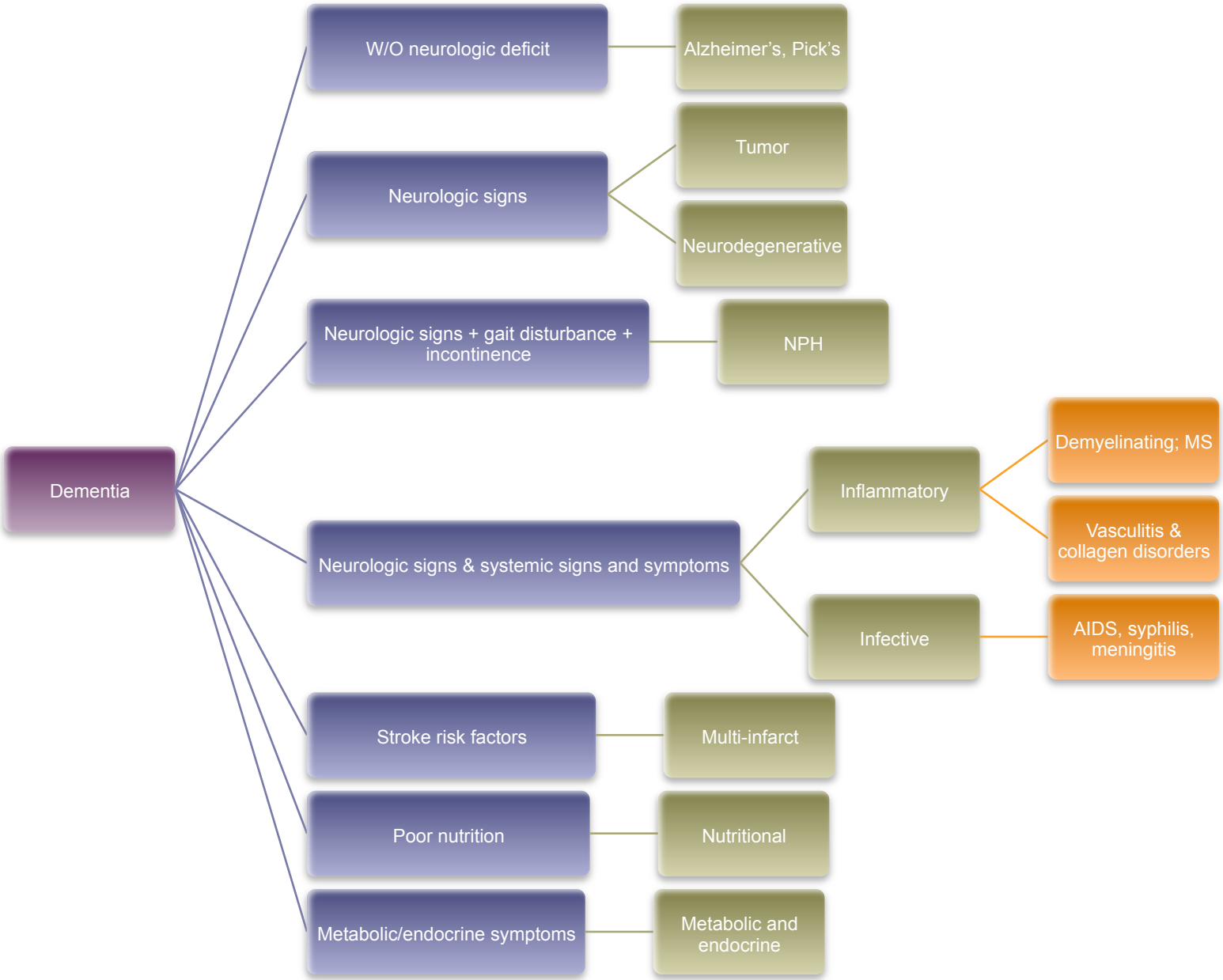
Pharmacologic

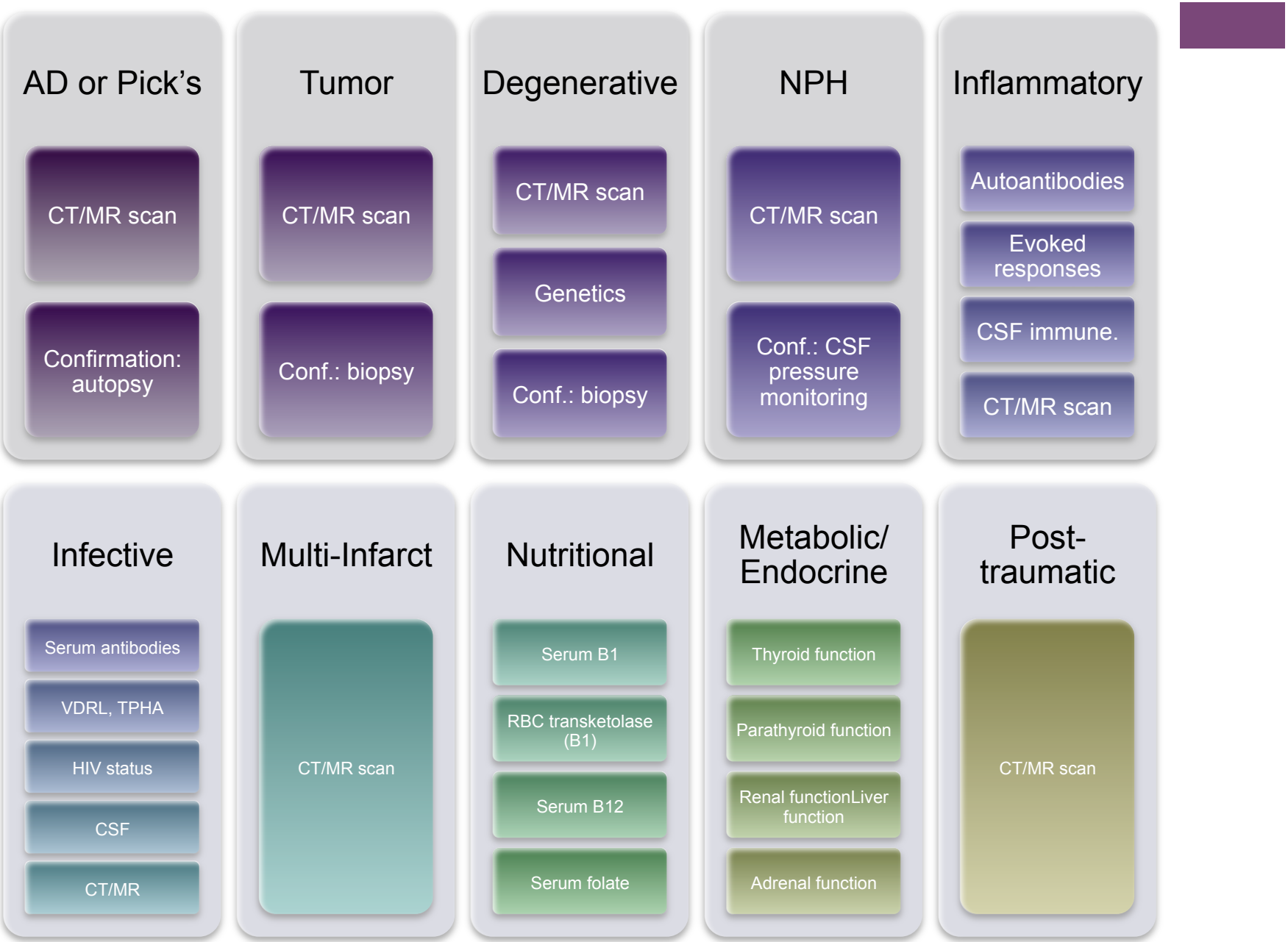
- Cholinesterase inhibitors
  - Small improvement of cognition and ADL
  - Donepezil, rivastigmine, galantamine
- Memantine *Alone or in combination*
  - NMDA (receptor activated by glutamase) antagonist
  - Excessive NMDA = excitotoxicity & transmitter damage
  - Neuroprotective & disease modifying (in moderate-severe)

Symptom Management

- **Managing Sleep Disturbances**
  - Improve sleep hygiene
  - Daytime activity – prevent daytime sleeping
  - Bright-light therapy
  - Treat associated depression
  - If the above did not work
    - Trazodone
    - Nefazodone
    - Zolpidem
  - Avoid benzodiazepines & antihistamines

- **Managing Psychosis**
  - Medication SE
    - High potency e.g. haloperidol: extrapyramidal
    - Lower potency e.g. thioridazone: anticholinergic
    - Atypical: clozapine, resperidone, olanzapine
- **Managing Agitation**
  - Behavioral interventions e.g. routine
  - Behavioral modification using rewards
  - Pharmacologic e.g. buspirone
  - Avoid physical restraints


Dementia
W/O neurologic deficit
Alzheimer's, Pick's
Neurologic signs
Tumor
Neurodegenerative
Neurologic signs + gait disturbance + incontinence
NPH
Neurologic signs & systemic signs and symptoms
Inflammatory
Demyelinating; MS
Vasculitis & collagen disorders
Infective
AIDS, syphilis, meningitis
Stroke risk factors
Multi-infarct
Poor nutrition
Nutritional
Metabolic/endocrine symptoms
Metabolic and endocrine


AD or Pick's
CT/MR scan
Confirmation: autopsy
Tumor
CT/MR scan
Conf.: biopsy
Degenerative
CT/MR scan
Genetics
Conf.: biopsy
NPH
CT/MR scan
Conf.: CSF pressure monitoring
Inflammatory
Autoantibodies
Evoked responses
CSF immune.
CT/MR scan
Infective
Serum antibodies
VDRL, TPHA
HIV status
CSF
CT/MR
Multi-Infarct
CT/MR scan
Nutritional
Serum B1
RBC transketolase (B1)
Serum B12
Serum folate
Metabolic/ Endocrine
Thyroid function
Parathyroid function
Renal functionLiver function
Adrenal function
Post-traumatic
CT/MR scan