

# CHAPTER 2

## Dementia

### I. Delirium

#### A. Definitions

1. **Confusional state:** characterized by inability to think with proper speed and clarity, impaired immediate recall, and *diminution of attention and concentration*
2. **Delirium:** an *acute confusional state*, marked by *prominent alterations in perception and consciousness* and associated with vivid hallucinations, delusions, heightened alertness and agitation, hyperactivity of psychomotor and autonomic functions, insomnia, etc.
3. **Dementia:** a syndrome characterized by deterioration of function in *memory, plus two other cognitive domains* (e.g., executive functioning, praxis, language, etc.); compared to previous baseline cognitive ability, *severe enough to interfere with usual social functioning and activities of daily life*

#### B. Etiology of delirium

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<i>Intoxication</i>	<i>Drugs:</i> alcohol, anticholinergics, sedative hypnotics, opiates, digitalis derivatives, steroids, salicylates, antibiotics, anticonvulsants, antihypertensives, H <sub>2</sub> blockers, antineoplastics, lithium, antiparkinsonian agents, indomethacin, etc.  <i>Inhalants:</i> gasoline, glue, ether, nitrous oxide, nitrates  <i>Toxins:</i> carbon disulfide, organic solvents, bromide, heavy metals, organophosphates, carbon monoxide, plants and mushrooms, venom
<i>Withdrawal syndromes</i>	Alcohol  Sedatives/hypnotics: barbiturates, benzodiazepines, glutethimide, meprobamate, etc.  Amphetamines
<i>Metabolic disorders</i>	Hypoxia  Hypoglycemia  Hepatic, pulmonary, renal, pancreatic insufficiency  <i>Errors of metabolism:</i> porphyria, carcinoid, Wilson's disease
<i>Nutritional disorders</i>	Vitamin deficiencies: B <sub>12</sub> , nicotinic acid, thiamine, folate, pyridoxine  <i>Hypervitaminosis:</i> vitamin A and D intoxication  Fluid/electrolyte disorders: dehydration or water intoxication; alkalosis/acidosis; excesses or deficiencies of Na, Ca, Mg, etc.
<i>Hormonal disorders</i>	Hyper-/hypothyroidism  Hyperinsulinism  Hypopituitarism

	Addison's disease
	Cushing's syndrome
	Hypo-/hyperparathyroidism
<i>Infection</i>	Systemic (especially pneumonia and urinary tract infection)
	Intracranial: encephalitis, meningitis, herpes, rabies, etc.
<i>Neoplasms</i>	Metastases, meningeal carcinomatosis
	Paraneoplastic
	Primary tumors of the temporal lobe, parietal lobe, or brain stem
<i>Inflammatory</i>	Central nervous system vasculitis
<i>Trauma</i>	Subarachnoid hemorrhage
	Postconcussive delirium
	Cerebral contusions or lacerations
<i>Miscellaneous</i>	Postconvulsive
	Postoperative/intensive care unit
	Mixed
	Poststroke

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## II. Dementia

### A. Etiology of dementia.

<i>Trauma</i>	Dementia pugilistica
	Diffuse axonal injury
	Chronic subdural hematoma
	Postconcussion syndrome
<i>Inflammatory/ infection</i>	Chronic meningitis (tuberculosis, cryptococcus, cysticercosis)
	Syphilis ( <i>general paresis of the insane, gumma, vasculitic</i> )
	Postherpes simplex encephalitis
	Focal cerebritis/abscess
	Human immunodeficiency virus dementia and opportunistic infections
	Progressive multifocal leukoencephalopathy
	Creutzfeldt-Jakob disease (CJD)
	Lyme disease
	Parenchymal or cerebral sarcoidosis
	Subacute sclerosing panencephalitis
	Whipple's disease of the brain
<i>Neoplastic</i>	Benign and malignant tumors
	Paraneoplastic limbic encephalitis
<i>Metabolic</i>	Hypothyroid
	Vitamin B <sub>1</sub> deficiency ( <i>Wernicke-Korsakoff</i> )
	Vitamin B <sub>12</sub> deficiency
	Vitamin E deficiency ( <i>neuropathy, ataxia, encephalopathy in celiac disease</i> )

	Nicotinic acid deficiency ( <i>pellagra</i> )
	Uremia/dialysis dementia
	Chronic hepatic encephalopathy
	Chronic hypoglycemic encephalopathy
	Chronic hypercapnia/hyperviscosity/hypoxemia
	Chronic hypercalcemia/electrolyte imbalance
	Addison's/Cushing's diseases
	Hartnup's disease
<i>Vascular</i>	Multi-infarct dementia
	Binswanger's encephalopathy
	Amyloid dementia
	Specific vascular syndromes (thalamic, inferotemporal, bifrontal)
	Triple borderzone watershed infarction
	Diffuse hypoxic/ischemic injury
	Mitochondrial disorders (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes)
	<i>Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, migraine</i>
<i>Autoimmune</i>	Systemic lupus erythematosus
	Polyarteritis nodosa
	Temporal arteritis
	Wegener's granulomatosis
	Isolated angiitis of the central nervous system
<i>Drugs/toxins</i>	Medications: $\beta$ -blockers, neuroleptics, antidepressants, histamine receptor blockers, dopamine receptor blockers
	Substances of abuse: alcohol, phencyclidine, mescaline, marijuana psychosis, etc.
	Toxins: lead, mercury, arsenic
<i>Demyelinating</i>	Multiple sclerosis, Schilder's disease, Baló concentric sclerosis
	Electric injury-induced demyelination
	Decompression sickness demyelination
	Adrenoleukodystrophy
	Metachromatic leukodystrophy
	Other inflammatory/infectious processes
<i>Obstructive</i>	Normal pressure hydrocephalus
	Obstructive hydrocephalus
<i>Degenerative—adult</i>	Alzheimer's disease (AD)
	Pick's disease
	Parkinson's disease (PD)
	Huntington's disease
	Frontotemporal dementia
	Progressive supranuclear palsy

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	Dementia with Lewy bodies (DLB)
	Multiple systems atrophy
	Corticobasal ganglionic degeneration
	Hallervorden-Spatz disease
	Primary progressive aphasia
<i>Degenerative— pediatric</i>	Mitochondrial diseases (myoclonic epilepsy with ragged red fibers and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes)
	Adrenoleukodystrophy
	Metachromatic leukodystrophy
	Kufs' disease ( <i>neuronal ceroid lipofuscinoses</i> )
	GM <sub>1</sub> and GM <sub>2</sub> gangliosidoses
	Niemann-Pick II-C
	Krabbe's disease ( <i>globoid cell leukodystrophy</i> )
	Alexander's disease
	Lafora's disease
	Cerebrotendinous xanthomatosis

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B. *Diagnostic workup.*

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Basic	Complete blood cell count, erythrocyte sedimentation rate, creatinine, electrolytes, glucose, calcium, magnesium, liver function tests, thyroid-stimulating hormone, B <sub>12</sub> , folate, VDRL, antinuclear antibodies, human immunodeficiency virus, chest x-ray, urinalysis, computed tomography of the head (with contrast if suspecting an enhancing lesion), electroencephalography, neuropsychologic testing, psychiatric consultation (if indicated), spinal tap (if indicated)
Expanded	Magnetic resonance imaging with gadolinium <i>Spinal tap—cells, protein, glucose, fungus, tuberculosis, virus, cytology, oligoclonal banding, immunoglobulin G, 14-3-3, glutamine, lactate</i> Schilling test Arterial blood gas Toxic screen (drugs, poisons, metals) Hemoglobin A1c, insulin B <sub>1</sub> , B <sub>6</sub> , vitamin E Porphyrins Vascular workup: lipid profile, anticardiolipin antibodies, carotid ultrasound, Holter monitor, echocardiogram Quantitative plasma amino acids Quantitative urine amino acids <i>Vasculitis workup: anti-double-stranded DNA, Ro, La, Sm, ribonucleoprotein, antineutrophil cytoplasmic antibodies, C3, C4, CH50</i> Tumor screen, paraneoplastic serum antibodies
If necessary	Positron emission tomography/single-photon emission computed tomography Cerebral angiography for vasculitis Biopsy: brain, meninges, nerve, muscle, skin, liver, kidney

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C. *Suggested evaluations for dementia of undetermined cause.*

Low-serum ceruloplasmin and copper, high-urine and liver copper	<i>Wilson's disease</i>
Plasma very-long-chain fatty acids	<i>Adrenoleukodystrophy</i>
White blood cell count arylsulfatase A	<i>Metachromatic leukodystrophy</i>
Serum hexosaminidase A and B	<i>Tay-Sachs disease</i> <i>Sandhoff disease</i>
Muscle biopsy (ragged red fibers on trichrome; polysaccharide nonmembrane bound structures)	<i>Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes</i> <i>Myoclonic epilepsy with ragged red fibers</i> <i>Lafora bodies</i>
White blood cell count for galactocerebroside $\beta$ -galactosidase	<i>Krabbe's disease</i>
Serum cholestanol or urine bile acids	<i>Cerebrotendinous xanthomatosis</i>
White blood cell count for $\beta$ -galactosidase	<i>GM<sub>1</sub> gangliosidosis</i>
Skin biopsy for biochemical testing of fibroblasts	<i>Niemann-Pick II-C</i>
X-ray of hands for bone cysts, bone or skin biopsy for fat cells	<i>Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy</i>
Urine mucopolysaccharides elevated, serum $\alpha$ -N-acetyl glucosaminidase deficient	<i>Mucopolysaccharidoses</i>
Indications for biopsy	<i>Focal, relevant lesion(s) of undetermined etiology</i> <i>Central nervous system vasculitis</i> <i>Subacute sclerosing panencephalitis, CJD, progressive multifocal leukoencephalopathy</i> <i>Krabbe's disease (periodic acid-Schiff-positive histiocytes)</i> <i>Kufs' disease (intranuclear fingerprint pattern)</i> <i>Neuronal intranuclear (eosinophilic) inclusion disease</i>

D. **AD:** the most common degenerative disease of the brain; incidence increases sharply with age after 65; age is the most important and common risk factor (10% of patients >65 y/o, 50% of patients >85 y/o); other risk factors: Down syndrome (patient 30–45 y/o shows similar pathologic changes), mother's age at birth, head injury, excess aluminum intake, apolipoprotein E genotype; reported protective factors: smoking, education, inheritance of apolipoprotein E2 allele.

1. *Clinical features:* common words, tasks, places, and events are forgotten; remote memory is also affected, difficulty remembering words, echolalia (repetition of spoken phrase), difficulty balancing checkbook; may progress to acalculia, difficulty parking car, putting arms in sleeves, lost on way to home; initially little change in behavior but later with paranoid delusions, anxiety, phobias, akinesia, mutism; day–night pattern changes; parkinsonian look; rigidity and fine tremor, myoclonus
2. *Pathology:* brain volume is decreased in advanced case up to 20% or more; ventricles enlarge proportionally; extreme hippocampal atrophy; atrophic process involves temporal, parietal, and frontal, but cases vary a lot; microscopically: senile or neuritic plaques,

*neurofibrillary tangles, granulovacuolar degeneration of neurons most prominent in pyramidal cell layer of hippocampus; Hirano bodies*

- a. *Cholinergic neurons of the nucleus basalis of Meynert (substantia innominata), locus ceruleus, medial septal nuclei, and diagonal band of Broca are reduced; with resulting deficiency of acetylcholine*
  - b. *Neurofibrillary tangles are composed of clusters of abnormal tubules, and senile plaques contain a core of amyloid; tangles and plaques are found in all association cortex; CA1 zone of the hippocampus disproportionately affected*
3. *Genetics: familial in 10%*
- a. *A defective gene was identified on chromosome 21 near the  $\beta$ -amyloid gene that codes for an errant AAP (amyloid precursor protein) gene.*
  - b. *Chromosome 14, for the protein called presenilin-1; accounts for 80% of the familial cases.*
  - c. *Gene mutation on chromosome 1 for the protein presenilin-2; age of onset for all familial cases is earlier.*
  - d. *Apolipoprotein E4 on chromosome 19 is associated with tripling the risk of acquiring AD.*
4. *Treatment*
- a. *Cholinesterase inhibitors: pharmacologic characteristics*

	<b>Tacrine</b>	<b>Donepezil</b>	<b>Rivastigmine</b>	<b>Galantamine</b>
Year available	1993	1996	2000	2001
Brain selectivity	No	Yes	Yes	Yes
Reversibility	Yes	Yes	Yes/slow	Yes
Chemical class	Acridine	Piperidine	Carbamate	Phenanthrene alkaloid
Enzymes inhibited:				
Acetylcholinesterase	Yes	Yes	Yes	Yes
Butyrylcholinesterase	Yes	Negligible	Yes	Negligible
Nicotinic receptor modulation	No	No	No	Yes
Doses per day	4	1	2	2
Initial dose (mg/day)	40	5	3	8
Maximum dose (mg/day)	160	10	12	24
Given with food	No, unless nausea occurs	No	Yes	Yes
Plasma half-life (hrs)	2–4	~70	~1	~6
Elimination pathway	Liver	Liver	Kidney	50% Kidney 50% Liver
Metabolism by cytochrome P450	Yes	Yes	Minimal	Yes

- b. *Memantine: a low to moderate affinity to noncompetitive N-methyl-D-aspartate receptor antagonist (N-methyl-D-aspartate receptors, by the excitatory amino acid glutamate, have been hypothesized to contribute to the symptomatology of AD); U.S. Food and Drug Administration–approved for the treatment of moderate to severe dementia in AD; titrate doses up to 20 mg/day*

- NB:** Early in the disease, AD patients are characterized by impaired word recall and normal digit span.
- NB:** *Mild cognitive impairment* refers to mild memory impairment or subtle changes in cognitive function that do not interfere with daily activities for which no underlying cause can be found.
- E. Frontotemporal dementia:** syndrome characterized by *prominent frontal lobe symptoms*, in contrast to the more pronounced amnesic symptoms in AD; reduced frontal cerebral blood flow; there is symmetric frontal and anterior temporal atrophy with frontal ventricular enlargement; striatum, amygdala, or hippocampus is usually spared.
1. *Frontotemporal dementia of the frontal lobe degeneration type:* microscopically: microvacuolation and gliosis predominantly over the outer three laminae of cerebral frontal cortex; no Pick bodies, ballooned neurons, or Lewy bodies (LBs)
  2. *Frontotemporal dementia of the Pick type:* more pronounced *frontal lobe atrophy and in addition to microvacuolation, gliosis, neuronal loss, have ballooned or inflated neurons and Pick bodies;* Pick bodies are most frequent in the medial parts of temporal lobes; clinically: gradual onset of confusion with personal neglect, apathy, focal disturbances, such as aphasia and apraxia, personality changes, abulia, frontal release signs
  3. *Frontotemporal dementia of the motor neuron type:* previously described clinical and neuropathologic findings are *coupled with spinal motor neuron degeneration; motor neuron loss is most severe in the cervical and thoracic segments;* may be identical to amyotrophy-dementia complex
- F. DLB:** the syndrome of DLB is characterized by the clinical *triad of fluctuating cognitive impairment, recurrent visual hallucinations, and spontaneous motor features of parkinsonism.* In an attempt to define DLB as a distinct clinical syndrome, separate from AD and PD with dementia, a consensus workshop established a new set of diagnostic criteria.

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<i>Mandatory</i>	Presence of dementia, PLUS Core features (at least two out of three for probable DLB): Fluctuation of cognition, function, or alertness Visual hallucinations Parkinsonism
<i>Supporting features</i>	Repeated falls Syncope Transient loss of consciousness Neuroleptic sensitivity Systematized delusions Nonvisual hallucinations Depression Rapid eye movement sleep behavior disorder

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1. *Clinical:* the degree to which an individual patient exhibits cognitive impairment, behavioral problems, and parkinsonian features is variable.
2. *Pathology:* the essential hallmark of DLB pathology is *the LB; these LBs are observed in the brain stem nuclei, subcortical regions, and cerebral cortices;* in the brain stem, pigmented neurons often present with the classic morphology of intracellular LBs, comprising an eosinophilic core with a peripheral halo; immunohistochemistry using antibodies

against ubiquitin or  $\alpha$ -synuclein has been shown to be more sensitive and specific in the detection of cortical LB; the clinical overlap of AD, DLB, and PD with dementia similarly extends to their pathology—most cases of DLB have varying degrees of AD pathology, including deposits of  $\beta$ -amyloid protein and neurofibrillary tangles.

3. *Neurochemistry*: substantial loss of cholinergic neurons in the nucleus basalis of Meynert, suggesting a cholinergic mechanism of cognitive impairment in DLB, similar to that of AD; deficits in acetylcholine,  $\gamma$ -aminobutyric acid, dopamine, and serotonin neurotransmission have also been described in DLB; neocortical choline acetyltransferase, a synthetic enzyme for acetylcholine, is decreased significantly, similar to that seen in AD or PD with dementia; reduced dopamine and its metabolites have been shown in DLB brains, possibly accounting for its parkinsonian features.
4. *Treatment*: must be individualized.
  - a. Although there are no officially approved drugs for DLB, limited experience from clinical trials, as well as past experience with treatment of AD and PD patients, provide some basis for making drug choices; the cholinergic deficit seen in DLB makes *cholinesterase inhibitor* drugs the mainstay of treatment for cognitive impairment; this class of drugs has also shown therapeutic benefit in reducing hallucinations and other neuropsychiatric symptoms of the disease.
  - b. Patients with DLB are exquisitely sensitive to the extrapyramidal side effects of neuroleptic medications; thus, only *atypical antipsychotic agents*, such as quetiapine, should be considered as alternative treatment for psychosis.
  - c. Anxiety and depression are best treated with *selective serotonin reuptake inhibitors*, whereas rapid eye movement sleep behavior disorder may be treated with low-dose *clonazepam*.
  - d. Parkinsonism responds to dopaminergic agents; however, precipitation or aggravation of hallucinosis may occur; *levodopa* is preferred over dopamine agonists owing to its lower propensity to cause hallucinations and somnolence.

**NB:** DLB may present as parkinsonism with early-onset visual hallucinations and dementia; they are extremely sensitive to neuroleptics.

**G. Multi-infarct dementia:** history of one or more strokes is usually clear; deficit increases with strokes, and focality of deficits may indicate the type and location of strokes; multiple lacunar infarcts may also give rise to a pseudobulbar palsy with a history of stroke; **Binswanger's disease:** multi-infarct state of cerebral white matter associated with dementia; **cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy** treatment: may respond to cholinesterase inhibitors.

**H. Other dementias.**

1. *Mesolimbocortical dementia of non-Alzheimer's type*: memory, initiative, and attention are affected more and early; histologically with cell loss and gliosis in hippocampi, caudate nuclei, thalami, and the ventral tegmental area of the mesencephalon
2. *Thalamic dementia*: rapidly progressive (over few months) dementia associated with choreoathetosis; relatively pure degeneration of the thalamic neurons; myoclonus may be present; should be differentiated from CJD
3. *Hypoxic encephalopathy and acute inclusion body (herpes simplex) encephalitis*: these two conditions may cause injury to the inferomedial portion of both temporal lobes and may leave the patient with memory and learning difficulties
4. *Severe trauma*: especially in conditions when prolonged coma and stupor follow the injury, causes well-established cerebral deficits

5. *Primary progressive aphasia*: a linguistic syndrome of *progressive aphasia without initial dementia*; may exhibit neuropathologic features identical to frontotemporal dementia of the frontal lobe degeneration type except that speech areas are more heavily involved; progressive aphasia has also been described in the context of AD, CJD, corticobasal ganglionic degeneration, and classic Pick's disease
6. *Prion disorders*: CJD, *Gerstmann-Straussler-Scheinker*
7. *Hydrocephalic dementia*: normal pressure hydrocephalus—dementia, gait disturbance (magnetic gait), and urinary incontinence
8. *Dementia pugilistica (punch drunk)*: long-recognized sequelae of multiple head injuries in boxing; pathology: demonstrate  $\beta$ -amyloid protein-containing plaques and neurofibrillary tangles

## ADDITIONAL NOTES