Behavior, Cortical Function, and Dementia (Dr. Merchut)

Neurobehavioral Syndromes from Focal Cerebral Lesions

1. Aphasia (see "Language")

2. Amnesia

Memory is the ability to learn and then recall information after different periods of time. **"Immediate" memory** is somewhat of a misnomer, as it actually pertains to the pre-requisite state of attentiveness required for learning something. A patient should be **alert and awake enough to immediately repeat or recite** a sequence of 5 numbers spoken out loud. Patients too inattentive for this task may be excessively sleepy, are sedated from medications, have a systemic illness diffusely inhibiting cortical function, or have lesions affecting the reticular activating system more directly. Impaired attention precludes any reliable testing of recent or remote memory as well as other cortical functions. **Recent or short-term memory** is the ability to recall information after several minutes of retention. A patient would be given 3 items to repeat out loud, and instructed to recall them 5 minutes later on command. **Remote or long-term memory** is the ability to recall past events hours, weeks, or even years afterward. The examiner could ask about a prior address or anniversary date for which the correct answer is known.

Memory function depends on bilateral circuits or pathways involving the **temporal lobe and thalamus**, specifically the hippocampus → fornix → mammillary body → anterior thalamic nucleus. Amnesia is caused by bilateral thalamic and mammillary body lesions in **Wernicke-Korsakoff syndrome**, a state of thiamine deficiency often seen in malnourished alcoholics. Bilateral hippocampal lesions cause amnesia as sequelae of **anoxia** (cardiac arrest survivors) or *Herpes simplex* **encephalitis**. A milder memory impairment of gradual onset may occur with normal aging or represent the earliest symptom of dementia and thus is one of the most common complaints of elderly patients seeking medical attention.

3. Apraxia

Apraxia is the inability to conceptualize and perform a skilled, learned, motor act on command. There must be no existing significant or severe impairments of sensation, strength, comprehension or attention to prevent performance of the task. On request, an apraxic patient would be unable to follow commands such as "comb your hair" or "salute the flag" but may spontaneously carry out these actions at another time. It is as if a computer file containing all the elements to execute a task exists but cannot be opened or accessed. A patient with a prefrontal lobe lesion may exhibit **gait apraxia**, the inability to walk on command as if both feet were "glued to the floor" or "stuck in the mud." Posterior cortical lesions, especially involving the parietal lobe, may cause **constructional apraxia**, where the patient cannot "draw a house" or copy a simple drawing, and **dressing apraxia**, where the patient cannot put on and button a shirt.

4. Agnosia

Agnosia is the impaired recognition of perceived stimuli caused by lesions of sensory association cortex. The same familiar object not identified solely by one sensory modality often is recognized by different sensory stimuli or characteristics. In visual agnosia, a patient cannot identify a "bell" by seeing it, but does recognize it by hearing it rung or touching it. Tactile agnosia is the inability to recognize objects solely by "feel" or "with eyes closed," although accurate visual identification of the same objects is normal. Tactile agnosia can thus be considered a severe degree of astereognosis.

5. Focal cerebral syndromes

Lesions of particular lobes of the cerebral hemispheres often involve head trauma, stroke, tumor, or dementia. Patients with the **prefrontal or frontal lobe syndrome** are listless, apathetic, and unconcerned, with poor hygiene and incontinence. Poor judgment and disinhibition lead to impolite outbursts, rude humor, and inappropriate sexual behavior. Executive functions are impaired, with poor planning and performance of multistep or novel tasks, lack of creative thinking and creativity, limited attention, and motor perseveration (aimless repetition of simple motor acts). Gait apraxia may be present. **Gegenhalten or paratonia** may be noted on examination, where increased limb tone or resistance is felt as the examiner moves the patient's limb more rapidly. There may be the abnormal reappearance of **frontal lobe release signs,** which were previously normal findings during infancy when myelination of descending inhibitory pathways was incomplete. Stroking lightly around the mouth causes the lips to "suck" and "snout," or seek out and "root" to the stimulus. Palmar and plantar grasp responses consist of the fingers or toes "latching onto" the examiner's finger when the palm or sole is rubbed.

Syndromes of the temporal lobes may include amnesia (bilateral hippocampal lesions), cortical deafness (bilateral auditory cortex lesions), and the Klüver-Bucy syndrome (see "Limbic System"). A unilateral lesion of the superior-posterior dominant temporal lobe produces Wernicke's aphasia (see "Language").

Parietal lobe syndromes affecting sensory cortex produce astereognosis, agraphesthesia, and extinction on double simultaneous stimulation (see "Neurological Examination"). **Lesions of the nondominant parietal lobe cause impairment of spatial relationships between the body and its surroundings**. A patient with **anosognosia** is unaware of his or her hemiparesis, which in its extreme form consists of a "denial" of that half of the body, or **hemispatial neglect**. Patients with a right parietal infarction may fail to dress or groom the left side of the body, even ignoring injuries or harm there. Spatial confusion may also be exhibited as dressing apraxia or constructional apraxia. A lesion of the supramarginal or angular gyrus of the dominant parietal lobe produces Gerstmann's syndrome, consisting of agraphia, right-left disorientation, dyscalculia (difficulty with calculations), and finger agnosia (inability to identify one's fingers).

Occipital lobe syndromes may involve enough bilateral visual cortex to produce cortical blindness, which is sometimes accompanied by a denial or unawareness of visual

loss, Anton's syndrome. Bilateral temporo-occipital lesions may produce visual agnosia, a subtype of which is prosopagnosia, the inability to recognize previously known faces. A dominant temporo-occipital lobe lesion may cause color anomia, the inability to name colors.

Neurobehavioral Syndromes from Diffuse or Multiple Cerebral Lesions

1. The acute confusional state (delirium)

Global, extensive cognitive impairment, abnormal behavior, and cortical dysfunction occur if several lobes of the cerebral hemispheres are simultaneously or progressively affected. If this occurs abruptly over a short period of hours to days, it is known as the **acute confusional state or delirium**, a common clinical problem in neurology. Typical here are **fluctuating levels of attention and motor activity**, with the patient alternating from overly-excitable agitation and often purposeless hyperactivity "as if high on drugs" to periods of obtundation and stupor. Moods and emotions may vary and hallucinations are often reported. Other prominent findings include tremulousness, asterixis, myoclonus, ataxia, and dysarthria. There are multiple causes of the acute confusional state, many of which are treatable or reversible if diagnosed early. The brain may be directly involved, as in viral encephalitis or the post-ictal state after a seizure, or it is indirectly involved, as from systemic illness like kidney failure, metabolic abnormalities, or the effects of medications or illicit drugs. Often any chronic, focal deficits in patients with a previous stroke, head trauma, multiple sclerosis, or other neurological disease may appear worse if such systemic problems indirectly affect the brain and cause the acute confusional state.

2. Dementia (organic brain syndrome)

Dementia is the general term for a diffuse impairment of cortical function which usually evolves less abruptly over a longer period of months to years, and impedes the daily function of a patient. Since this is a loss of previously acquired mental and intellectual ability, it differs from mental retardation or learning disorders where such capabilities were never attained. Memory loss is often the first deficit noted, but changes in judgment and intellect also occur. The intellectual decline of a college trained professional may take longer to manifest than that of an unskilled worker lacking any formal education. Aphasia, apraxia, and agnosia may be found on examination. Personality changes may include suspiciousness, mistrust, and paranoia, with behaviors varying from childishness to unprovoked anger or agitation. As dementia progresses, the patient gets disoriented to time and place, fails to recognize family and friends, and becomes unable to perform basic tasks of dressing, bathing, and eating.

The **diagnosis of dementia relies heavily on the observations of family and friends** since the patient may deny or be unaware of any cognitive trouble. A detailed history is imperative to find the cause of dementia, emphasizing the early discovery of a treatable or reversible etiology. Effective interventions could be made for patients **abusing alcohol or drugs, taking medications incorrectly, or lacking vitamins** from malnutrition. A history and physical findings of stepwise, focal neurological deficits

make a vascular cause of dementia more likely. Elderly depressed patients may appear to be demented, so screening for **depression** is always worthwhile. On rare occasions, the presence of dementia in several, particularly younger, family members raises the possibility of a **hereditary** dementia.

The evaluation for dementia should include some **standardized cognitive testing**, such as the brief **Mini-Mental State Examination (MMSE),** or a more detailed neuropsychological profile. This latter provides a baseline comparison for future testing, helps determine the type of dementia involved, and may reveal any elements of depression. A **brain scan, preferably an MRI**, serves to determine if dementia is caused by chronic subdural hematomas, brain tumors or abscesses, multiple infarctions or hemorrhages, or normal pressure hydrocephalus. Focal findings or asymmetries of the bedside neurological examination should prompt a more urgent brain MRI scan. Unexplained fever and headache may be signs of a chronic meningitis causing dementia, where **lumbar puncture** may be necessary. **HIV** infection should be suspected in a younger patient with dementia. All patients with memory or cognitive impairment should have a **complete blood count, chemistry profile, vitamin B12 level and thyroid functions** checked. An unremarkable diagnostic workup, including nonspecific age-related brain atrophy on an MRI scan, is typically found in patients with Alzheimer's dementia, which historically has been a diagnosis of exclusion.

Alzheimer's Disease

1. Pathogenesis of Alzheimer's Disease

The **most common type of dementia in the United States** is Alzheimer's Disease (AD). AD is a degenerative disease, where specific types of neurons are gradually destroyed by metabolic changes unrelated to infection, ischemia, or immune system abnormalities. Most cases are sporadic, with prevalence increasing with age. It is estimated that about 50% of those surviving to 85-90 years of age will develop AD. Rare familial forms occur, with disease onset earlier in adult life. The earliest or most predominant deficit, memory loss, reflects the initial pathological changes in the medial temporal lobes and hippocampi. Excessive accumulation of the protein **β-amyloid** in the form of **extracellular amyloid or senile cortical plaques** appears to be a pathological hallmark of AD, although what triggers this process is unknown (Fig. 1). β-amyloid is a fragment of the larger transmembrane β-amyloid precursor protein (β-APP) coded on chromosome 21. Patients with trisomy 21 (Down's syndrome) virtually all develop AD at the early age of 40-50 years. Familial types of AD have been associated with other gene mutations affecting β-APP. β-amyloid deposition leads to formation of **intraneuronal neurofibrillary tangles**, consisting of microtubule-associated **tau protein**. Abnormal tau formation occurs in other, rarer neurodegenerative diseases (progressive supranuclear palsy (PSP), corticobasal degeneration, and frontotemporal lobar dementia), collectively termed "tauopathies." A cascade of other neurotoxic events leads to cellular death, especially but not exclusively affecting cholinergic neurons.
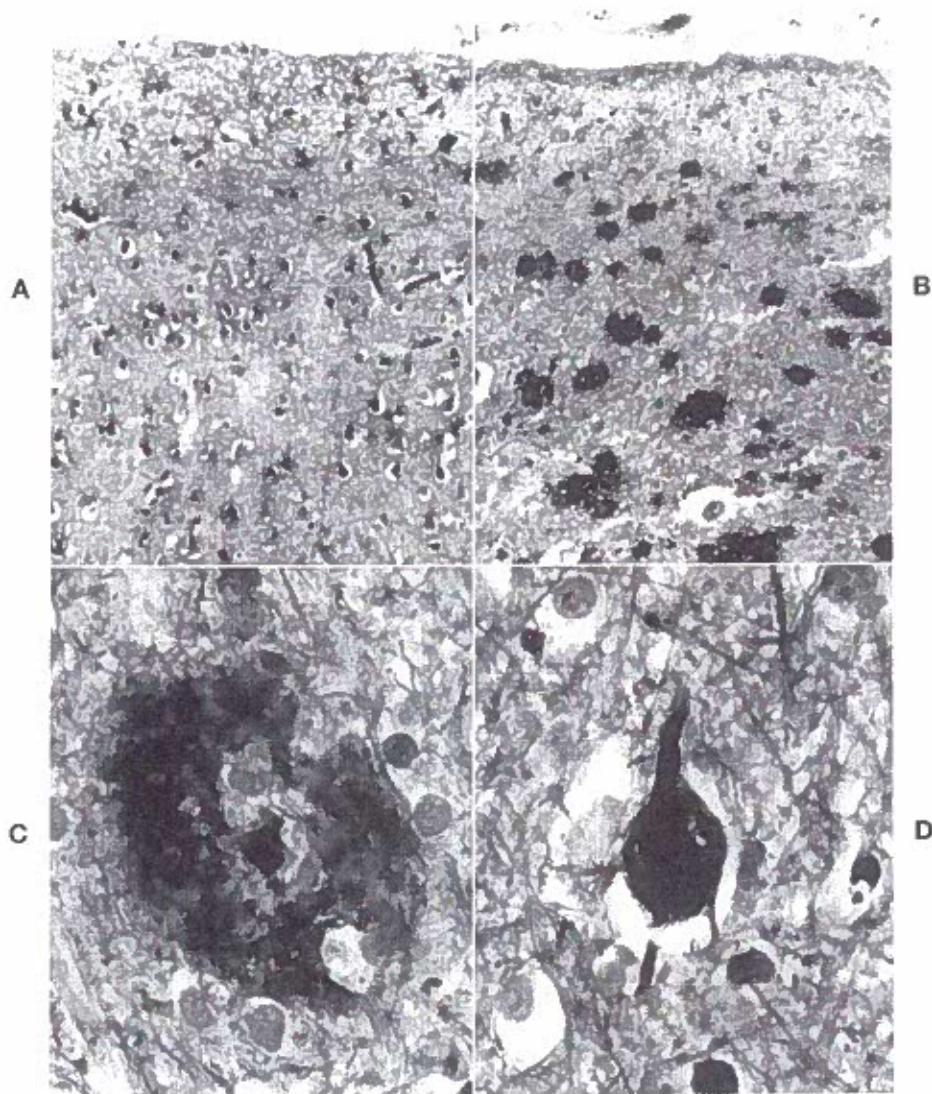
Fig. 1
Section of normal cerebral cortex (A) compared with section showing abundant senile amyloid plaques (B) in a patient with Alzheimer's disease. High-power light microscopic view of senile amyloid plaque (C) and intracellular neurofibrillary tangle (D), shown with a Bielschowsky silver stain. (Courtesy Dr. John M. Lee, Department of Pathology, Loyola University Stritch School of Medicine.)

2. Diagnosis and treatment of Alzheimer's Disease

Memory loss is typically the initial symptom, followed by other features of cognitive decline. Formal neuropsychological testing may be needed to detect or confirm these expected findings. Behavioral changes and parkinsonian signs are relatively minor and usually occur later in the course of AD. Focal, asymmetrical neurological deficits such as hemiparesis, hemisensory loss, hemianopsia, or cerebellar signs are more typical of vascular dementia from multiple, bilateral cerebral ischemic infarctions. However, some elderly patients are found to have co-existing vascular dementia and Alzheimer's disease. In the absence of cerebral infarctions, CT or MRI brain scans show only age-related atrophy in AD patients. Functional neuroimaging with positron emission tomography (PET) or single photon emission computed tomography (SPECT) may show hypoperfusion of temporal and parietal cortex, reflecting the underlying hypometabolism in these areas from AD. **PET scans utilizing Pittsburgh Compound B (PIB), which selectively binds to β-amyloid, apparently show the typical AD uptake** in the prefrontal, temporal, and sensory association cortex, sparing the occipital and primary sensorimotor cortex. These newer imaging tests may now allow the premortem diagnosis of Alzheimer's disease, formerly a clinical diagnosis "of exclusion" (eliminating other possibilities), and confirmed only at postmortem examination of the brain.

Unfortunately there is no curative treatment for Alzheimer's disease. Its deteriorating course can be slowed down by enhancing the cholinergic system with **central acetylcholinesterase inhibitors (AChE-I) such as donepezil, rivastigmine, or galantamine**. As the dementia worsens, memantine can be added to or used in place of an AChE-I drug. **Memantine is an *N*-methyl-D-aspartate (NMDA) antagonist** which opposes the excitotoxic effects of glutamate in the central nervous system. Sedatives and antipsychotic medications may also be needed to control agitation and behavioral symptoms in AD patients. It is also important to provide support and "time off" for the caregivers of AD patients, who gradually assume their total daily care. After years of AD, patients eventually become helpless and bedbound, dying from the medical complications of aspiration pneumonia, pulmonary emboli, and malnutrition.