Medical Progress

Treatable Dementias

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Dementia is an acquired impairment of intellect produced by brain dysfunction. In the past, dementia was regarded as inevitably chronic, progressive and irreversible. More recently dementia has been viewed as a clinical syndrome that may be produced by both irreversible and reversible conditions. Recognition of the presence of a dementia syndrome should be followed by an evaluation for potentially treatable causes of the intellectual deterioration. Dementia treatment includes therapy for reversible or curable dementias and nonspecific interventions that may improve the condition of patients with progressive dementia syndromes.

(Mahler ME, Cummings JL, Benson DF: Treatable dementias. West J Med 1987 Jun; 146:705-712)

Dementia is defined as an acquired, persistent impairment of intellectual function with deficits in at least three of the following five spheres of mental activity: memory, language, visuospatial skills, cognition (abstraction, mathematics, judgment and so forth) and personality.[1] This definition distinguishes dementia from conditions in which the deficit is limited to a single neuropsychological domain such as memory or language as in amnesia or aphasia, respectively. It also contrasts dementia with acute confusional states (delirium), which are characterized by an abrupt onset, brief duration of hours to days and predominantly attentional deficits. (Confusional states lasting weeks to months are properly classified as dementias.) Dementia is also distinguished from mental retardation where the deficits are congenital rather than acquired in origin. Dementia, using this definition, is a clinical syndrome that may result from many different disease processes that interfere with brain function to compromise intellectual abilities.

In the United States, the size of the population over age 65 will increase from 22 million in 1978 to 51 million in 2030, and 5% to 15% of these persons will have a dementia syndrome.[2] The inevitable growth in the prevalence of dementia is accompanied by the need for expensive medical and social services, hospital and nursing home beds, day care facilities and prescription medications. The increasing size of the elderly population and the concomitant increase in the number of patients with dementia has made the search for treatable causes of the syndrome more imperative.[3]

The precise frequency of treatable dementia has been difficult to determine because of the different referral sources, research methods and definitions of dementia used in investigating the causes of dementia. Cummings and Benson reviewed seven case series in which the causes of dementia had been reported.[4] They found that potentially reversible dementias included metabolic disorders (0% to 17%), obstructive hydrocephalus (1% to 8%), infections (1% to 4%), toxic conditions (1% to 8%), subdural hematomas (1% to 2%) and cerebral neoplasms (1% to 8%). Thus, between 5% and 47% of patients referred with a diagnosis of dementia had a potentially reversible structural, toxic or metabolic condition. An additional 2% to 28% of patients had treatable psychiatric disorders, primarily depression, accounting for their intellectual impairment. Of the remaining patients, 30% to 40% had treatable if not reversible conditions such as multi-infarct dementia, alcoholic dementia and progressive extrapyramidal syndromes with dementia, such as Parkinson's disease and Huntington's disease. Chronic progressive disorders such as Alzheimer's disease affected 25% to 50% of patients.

An emphasis on detecting and ameliorating treatable causes of intellectual impairment applies to all patients with dementia. In some cases a completely curable disorder such as hypothyroidism or vitamin B_{12} deficiency may be discovered. In others, such as neurosyphilis or multi-infarct dementia, intervention may modify the course of the illness, sparing a patient further deterioration without reversing existing deficits. Treatment may lessen related symptoms without altering the intellectual difficulty, as in Huntington's disease. Even in chronic, progressive dementias, such as Alzheimer's disease, evaluation may reveal treatable complications such as electrolyte imbalances, pulmonary and urinary tract infections or drug toxicities that may be exacerbating the mental state and behavioral changes.[5]

A potential criticism of an emphasis on reversible dementias is that, even when a theoretically reversible cause is found, therapy for the underlying cause may not fully restore intellectual function.[5] This is particularly so if the dementia has been present for several years before the cause is discovered. Intervention, however, may halt the progression of mental decline, and treatment may prevent the need for placement in a nursing home, reduce the level of dependence or allow for a higher quality of life.

The evaluation of patients with dementia has been made more rewarding by the development of new technologies. Contemporary clinicians in most areas have access to computed x-ray tomography, magnetic resonance imaging, cisternography, serum drug assays and automated serum metabolic assessments that aid in the discovery of intracranial as well as systemic disorders affecting brain function. At the same time, clinical criteria for the diagnosis of irreversible disorders have been clarified making it more obvious which

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TABLE 1.—*Reversible Dementias*

Disorder	*Clinical Characteristics*	*Treatment*
Intracranial Disorders		
Meningioma, low-grade astrocytoma, solitary metastasis	Headache; seizures; papilledema; gradually progressive focal signs	Surgical removal
Pituitary adenoma	Visual field deficits; headache; endocrinologic changes	Surgical removal; radiation therapy, or bromocriptine mesylate
Hydrocephalus	Dementia; incontinence; gait disturbance	Ventricular shunting
Subdural hematoma	Headache; fluctuating course; psychomotor slowing; decreased alertness (may occur without focal signs, without known trauma)	Surgical drainage; antiedema agents
Cerebral abscess	Headache; fever; focal signs; multiple CT lesions; CSF leukocytosis, cultures usually negative	High-dose penicillin, chloramphenicol; steroids; surgical aspiration or excision in some cases
Tuberculous meningitis	Subacute course; lethargy; fever (may be absent in elderly); stiff neck; CSF: increased lymphocytes, decreased glucose, positive cultures or acid-fast bacilli; tuberculoma mass may occur	Isoniazid, ethambutol HCl, rifampin combination; ventricular shunt if hydrocephalus occurs
Cryptococcal meningitis	Immunocompromised host, may have mass lesions; organisms in CSF seen in india ink; CSF antigens	Amphotericin B (intravenous or intrathecal); flucytosine
Toxoplasmosis	Immunocompromised host; mass lesions and focal signs; antibody titers	Sulfadiazine and pyrimethamine
Cerebral malaria	Stupor; fevers; brain edema; *Plasmodium falciparum*	Quinine (steroid use controversial)
Whipple's disease	Constitutional symptoms; malabsorption; uveitis; supranuclear gaze palsy; multiple low-density CT lesions; PAS-positive GI or brain biopsy	Penicillin; tetracycline; chloramphenicol
Giant cell arteritis	Headache; vision loss; polymyalgia rheumatica; elevated sedimentation rate (ESR)	Steroids
Systemic lupus erythematosus	Neuropsychiatric syndromes; seizures; systemic manifestations	Steroids
Cerebral arteritis	Headache; strokelike signs; systemic signs of arteritis; inflammatory CSF; elevated ESR; "beading" arteriogram	Steroids
Sarcoidosis	Cerebral mass lesion; may be without pulmonary disease	Steroids
Systemic Illnesses		
Cardiac disease	Heart failure; arrhythmia; other causes of decreased cerebral perfusion; lethargy; chronic confusional state	Diuretics; digoxin; antiarrhythmic agents
Hypertensive encephalopathy	Pronounced elevation of blood pressure; headache; retinopathy; nephropathy; seizures	Antihypertension drugs
Anemia	Fatigue; lethargy; impaired concentration	Transfusion; correct underlying condition
Hyperviscosity syndrome	Polycythemia; Waldenström's macroglobulinemia	Blood removal; plasmapheresis
Pulmonary disease	COPD; pneumonia; other causes of chronic hypercapnia or hypoxia; headache; papilledema; tremor; myoclonus	Ventilation; oxygen; correct acidosis if present; treat underlying condition
Sleep apnea	Loud snoring; daytime lethargy; nocturnal O_2 desaturation, apnea, arrhythmia	Tracheostomy; protriptyline HCl for central type apnea
Chronic renal failure	Uremia and other metabolic derangements; fatigue; apathy; irritability; tremor; asterixis; myoclonus; neuropathy; EEG may have paroxysmal slowing	Dialysis; kidney transplantation
Hepatic encephalopathy	Liver disease stigmata; asterixis; tremor; myoclonus; hyperammonemia frequent; EEG triphasic waves; exacerbated by diuretics, sedatives, GI tract bleeding, dietary protein	Lactulose; neomycin; reduce dietary protein; correct exacerbating factors
Hypernatremia	Usually dehydration; diabetes insipidus	Rehydration; vasopressin snuff
Hyponatremia	Weakness; lethargy; seizures; often inappropriate antidiuretic hormone secretion	Fluid restriction
Hypercalcemia	Weakness; fatigue; mood changes; increased calcium due to hyperparathyroidism, multiple myeloma, bone metastases, ectopic parathyroid hormone	Hydration and diuretics; plicamycin (mithramycin); treat underlying disorder
Hypocalcemia	Tetany; seizures; may result from hypoparathyroidism, renal failure, hypomagnesemia; basal ganglia may calcify with extrapyramidal syndrome	Calcium and vitamin D supplements; phosphate binders
Hypomagnesemia	Similar to hypocalcemia; often associated with alcoholism	Magnesium sulfate
Hypothyroidism	May present with dementia; signs of myxedema; delayed reflexes; elevated thyroid-stimulating hormone	Thyroid hormone replacement
Hyperthyroidism	Restlessness, anxiety; tremor; tachycardia; exophthalmic ophthalmoplegia; may be masked in elderly	Propranolol HCl; propylthiouracil; surgical procedure; radioiodine therapy
Cushing's syndrome	Central obesity; striae; hypertension; diabetes mellitus; irritability, depression; exogenous or endogenous corticosteroid excess	Treat underlying cause
Addison's disease	Weakness; hypotension; pigment change; hyponatremia; hyperkalemia	Corticosteroid replacement
Hyperglycemia	Diabetes mellitus; hyperosmolar state with stupor; may have minor focal signs	Hydration; hypoglycemic agents; diet
Hypoglycemia	Excess hypoglycemic agents; chronic or recurrent from insulinoma	Glucose; correct underlying disorder
Porphyria	Abdominal pain, GI symptoms; neuropathy; personality change; agitation; confusion	Avoid the use of barbiturates, sulfa drugs, other precipitants

COPD=chronic obstructive pulmonary disease, CSF=cerebrospinal fluid, CT=computed tomography, EEG=electroencephalogram, GI=gastrointestinal, HCl=hydrochloride, PAS=periodic acid-Schiff

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patients require more thorough investigations. The diagnosis of Alzheimer's disease, the principal cause of irreversible dementia, now depends on both inclusionary and exclusionary clinical criteria.[6,7] Patients whose symptoms differ significantly from the characteristic syndrome of Alzheimer's disease must be evaluated carefully for potentially reversible dementing disorders, and those diagnosed as having Alzheimer's disease clinically should be evaluated for possible supervening treatable conditions. This reliance on a simultaneous "rule-in/rule-out" approach guides the selection of appropriate laboratory assessments in each case.

Finally, the emphasis on treatable causes of dementia provides a framework capable of including the therapeutic advances of the future. Diseases now viewed as untreatable and irreversible may become reversible with the development of appropriate interventions in the same way that hypothyroidism, neurosyphilis and obstructive hydrocephalus were once irreversible and progressive but are now recognized as treatable causes of dementia.

The treatable dementias are divided below into those that may be completely reversed with timely, appropriate treatment; those in which specific treatment may alter the course of the dementia or provide symptomatic relief, and those in which treatment is limited to preventing secondary complications of the disorder.

Reversible Dementias

Reversible dementias include a variety of intracranial disorders and a heterogeneous array of metabolic and toxic encephalopathies. Table 1 summarizes these disorders, their principal associated clinical characteristics and the appropriate therapeutic interventions.

Intracranial Conditions

Among the intracranial conditions are mass lesions such as cerebral neoplasms, granulomas, abscesses and gummas. These space-occupying masses often cause focal sensorimotor signs and symptoms. Seizures may result from local destructive effects of the lesions, and lethargy, headache, vomiting and papilledema may be produced by increased intracranial pressure. Symptoms due to surgically resectable meningiomas, low-grade gliomas, solitary metastases and pituitary adenomas are more reversible than those resulting from other more malignant neoplasms.

Obstructive hydrocephalus is a special case of a space-occupying process. Hydrocephalus may be of the noncommun-

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TABLE 1.—*Reversible Dementias (Continued)*

Disorder	*Clinical Characteristics*	*Treatment*
Systemic Illnesses (Continued)		
Vitamin B_{12} deficiency	Memory loss may precede anemia; myelopathy and neuropathy; pernicious anemia, other GI disorders; positive Schilling's test	Vitamin B_{12} injections
Folate deficiency	Syndrome similar to vitamin B_{12} deficiency; alcoholism, malabsorption, phenytoin	Folate supplementation
Thiamine (vitamin B_1) deficiency	Memory disorder; ophthalmoplegia; ataxia; neuropathy	Thiamine supplementation
Niacin deficiency	Pellagra; weakness and lethargy; dermatitis; diarrhea, other GI symptoms	Niacin supplementation
Toxic Disorders		
Major tranquilizers	Chronic confusional state; parkinsonism	Lower dose or discontinue medication
Antidepressants	Chronic confusional state; tremors; anticholinergic effects	Lower dose or discontinue medication
Sedative-hypnotics	Lethargy, confusional state; withdrawal syndromes	Lower dose or discontinue medication (taper dose)
Narcotics	Pupillary constriction; constipation; respiratory depression; elderly sensitive to low doses	Lower dose or discontinue; give naloxone HCl for acute condition
Anticholinergics	Memory loss; confusional state; psychosis; dilated pupils; dry skin; tachycardia; wide variety of medications involved	Discontinue medication; give physostigmine in acute state
Antihypertensives	Psychomotor slowing, depression; methyldopa, reserpine, clonidine, propranolol use	Switch to other agents for blood pressure control
Anticonvulsants	Sedation from barbiturates; phenytoin use may give cerebellar signs; toxic levels	Switch to another drug
Digoxin	GI and cardiac side effects; confusional state	Adjust dose
Antiparkinsonian	Levodopa, amantadine, bromocriptine use; confusional state; psychosis	Reduce medication dose
Antibiotics	Penicillin, chloramphenicol use; high doses, often from decreased clearance in elderly	Adjust dose
Gastrointestinal agents	Chronic confusional state; cimetidine use; metaclopramide may cause extrapyramidal syndrome	Adjust or discontinue medication
Antineoplastic agents	Asparaginase; intrathecal administration of methotrexate	Discontinue medication
Lead	Encephalopathy; motor neuropathy; headache; seizures; anemia; lead lines	Edetate chelation; eliminate exposure
Arsenic	Somnolence; sensory neuropathy; GI symptoms; Mees' lines	Chelation; eliminate exposure
Organic solvents	Headache; lethargy; poor concentration; peripheral neuropathy	Eliminate exposure
Insecticides	Irritability; forgetfulness; organophosphates	Avoid exposure
Psychiatric Disorder		
Depression	Psychomotor retardation; neurovegetative changes; altered mood; prior depression history; may be masked in elderly; may be associated with other illnesses or drugs	Psychotherapy; antidepressants; electroconvulsive therapy

COPD=chronic obstructive pulmonary disease, CSF=cerebrospinal fluid, CT=computed tomography, EEG=electroencephalogram, GI=gastrointestinal, HCl=hydrochloride, PAS=periodic acid-Schiff

TABLE 2.—*Features That Distinguish Between Toxic-Metabolic Dementias and Alzheimer's Disease*

Feature	*Toxic-Metabolic Dementia*	*Alzheimer's Disease*
History		
Onset	Acute or subacute	Insidious
Course	Fluctuating	Progressive
Mental state		
Arousal	Fluctuating	Normal
Language	Anomia	Aphasia
Speech	Slurred	Normal
Memory	Inattentive and forgetful	Amnesia
Hallucinations	Common	Less common
Motor system	Tremor, asterixis	Normal until late
Electroencephalogram	Diffusely slow	Normal early, mildly slow late
Computed tomographic scan	Normal or shows atrophy	Normal or shows atrophy

icating variety due to intraventricular blockage by a mass lesion or chronic infection or the communicating variety (normal-pressure hydrocephalus) that may follow trauma, infection or subarachnoid hemorrhage.[8] The ventricular dilatation is associated with a triad of clinical signs including dementia, incontinence and gait disturbance. Although ventricular shunting does not reverse all cases, most patients with abnormal cisternograms and a compatible clinical syndrome have improvement following the surgical procedure.

Subdural hematomas, especially when bilateral, cause dementia that may be reversible with surgical drainage. Headaches, psychomotor slowing and a fluctuating course are more characteristic than focal signs. Subacute and chronic hematomas are revealed by brain imaging studies.

Infections such as chronic meningitis (tuberculous, fungal or parasitic), cerebral abscesses, granulomas and Whipple's disease are also among the intracranial disorders that may cause reversible dementia. In some cases these may be complicated by the development of a secondary obstructive hydrocephalus that requires separate treatment.

A number of inflammatory conditions such as systemic lupus erythematosus, giant cell arteritis, sarcoidosis and Behçet's syndrome affect intracerebral structures. These disorders may cause cerebral ischemia in addition to inflammation to produce dementia. Steroid therapy may help ameliorate the intellectual deficits in these conditions.[9,10]

Toxic, Metabolic and Systemic Disturbances

Toxic and metabolic disorders frequently present as acute confusional states, and if the cause is not identified and corrected immediately, a chronic state ensues that must be differentiated from other causes of dementia. The clinical manifestations of toxic and metabolic disorders may vary with the underlying condition, but they often share common features that allow them to be distinguished from degenerative dementias such as Alzheimer's disease. Table 2 lists the features that may help differentiate between the two types of dementia. Systemic, toxic and metabolic disorders are more likely to have an acute or a subacute onset and to show a fluctuating course with exacerbations and remissions. Patients may exhibit decreased or increased arousal and variable attention to external stimuli. Although difficulty with naming is common, other aphasic symptoms are rare in chronic confusional states but common in Alzheimer's disease. Memory difficulties are prominent in both. Slurred speech, tremor and asterixis are motoric features of toxic-metabolic encephalopathies, whereas in Alzheimer's disease the motor system is normal until late in the clinical course. An electroencephalogram usually shows more pronounced slowing early in the course of a toxic-metabolic encephalopathy in comparison to that seen in Alzheimer's disease.

A wide variety of systemic and metabolic disorders can produce reversible dementia syndromes. The elderly suffer disproportionately from systemic illnesses and, because of a reduced capacity for homeostasis, are most vulnerable to the metabolic dementias. About 86% of persons older than 65 years have one chronic illness and 50% have two or more chronic medical conditions.[11] Changes in mental function may be the initial manifestation of systemic and metabolic illness in the elderly.[12] Table 1 lists the principal systemic causes of dementia, including cardiac and pulmonary disease, anemia, uremia, hepatic encephalopathy, electrolyte disturbances, endocrinopathies, vitamin deficiencies, systemic infections and inflammatory diseases. In most cases, treatment of the underlying condition restores mental function except when conditions such as vitamin B_{12} deficiency or pronounced hypoxia produce structural neurologic damage that persists following treatment and leads to a more chronic dementia syndrome.

Toxic causes of dementia include heavy metal encephalopathies, organic solvent and pesticide exposure and a large number of over-the-counter and prescription medications (Table 1). The high frequency of medical illnesses in the elderly results in the use of multiple medications and a high potential for iatrogenic dementia.[13] Those older than 65 years, representing 11% of the US population, receive 30% of all prescribed medications. A similar disproportionate use occurs with over-the-counter medications: 70% of the elderly, compared with only 10% of young patients, regularly uses proprietary drugs.[14] Drug metabolism is altered in the elderly because of changes in the ratio of body fat to lean mass, decreased blood flow to detoxifying organs and changes in the absorption and serum protein binding of drugs. These alterations render the elderly more vulnerable to drug interactions and to the accumulation of toxic concentrations at doses recommended for younger patients. In addition, with advanced age, the brain may be more sensitive to the effects of many drugs even if routine dosages are administered.

These changes make it prudent to be conservative when prescribing medicines for the elderly. This includes eliminating unnecessary drugs, discouraging the excessive use of over-the-counter agents and using pharmacokinetic principles and serum drug assays whenever possible to avoid toxicity. It is always important to consider a prescribed drug as a poten-

tially reversible cause of dementia. In most patients, decreasing or eliminating exposure to the offending agent is sufficient to reverse the dementia syndrome. An interval of several weeks may be required between the identification and treatment of a toxic-metabolic disorder and the resolution of symptoms of intellectual decline.[15]

Depression

A final highly reversible type of dementia is that due to psychiatric disease, especially depression.[16,17] This is sometimes referred to as pseudodementia. These patients meet the criteria for dementia given above, however, and there is nothing false about their impairments in intellectual function. The course of dementia due to an affective disorder tends to be short, and there will often have been a prior episode of depression. Psychomotor slowing and changes in neurovegetative function may suggest a depression even when a patient does not admit to a sad mood. The patient performs poorly on psychometric tests and gives frequent "I don't know" responses. A depressed patient tends to be aware of his or her

TABLE 3.—*Treatable Dementias*

Disorder	*Clinical Characteristics*	*Treatment*
Malignant gliomas; metastases	Headache; nausea; papilledema; seizures; progressive focal signs	Surgical decompression; steroids; irradiation
Multi-infarct dementia	Abrupt onset; fluctuating course; focal signs and symptoms; cardiovascular risk factors	Control hypertension, other risk factors; antiplatelet therapy; anticoagulation
Angular gyrus syndrome	Gerstmann's syndrome plus anomia, alexia; nonverbal memory and daily activities preserved	Treat underlying stroke or tumor
Post-trauma dementia	Closed head injury; memory loss; personality changes; focal signs; postconcussion syndrome	Rehabilitation program
Dementia pugilistica	Repeated blows to head; psychomotor slowing; extrapyramidal signs	Antiparkinsonian drugs
Neurosyphilis	General paresis; frontal lobe personality; 20 years after primary infection; positive serology, positive CSF; meningovascular lues, gummas, tabes dorsalis	High-dose intravenous administration of penicillin
Coccidioidomycosis	Pulmonary disease; Southwest US; erythema nodosum; basilar meningitis	Prolonged amphotericin B (intravenous or intrathecal); shunt hydrocephalus
Other fungal disease	Histoplasmosis; *Candida; Aspergillus;* mucormycosis; blastomycosis	Amphotericin B; flucytosine; ketaconazole
Amebiasis	Fulminant meningoencephalitis	Amphotericin B; rifampin; miconazole
Cysticercosis	*Tinea soleum;* basilar meningitis; parenchymal calcified cysts; seizures; hydrocephalus	Praziquantel; steroids; anticonvulsants
Progressive multifocal leukoencephalopathy	Immunocompromised host; focal signs; headache; multiple white matter lesions; papovavirus	Cytarabine; treat underlying disorder
Herpes encephalitis	Headache; fever; psychosis; seizures; hemorrhagic temporal lesions; EEG has focal repetitive spikes; residual amnesia	Vidarabine
Acquired immunodeficiency syndrome	Opportunistic infections of the CNS and systemically; encephalitis; T-cell abnormalities; lymphadenopathy	Treat infections
Multiple sclerosis	Fluctuating course; multiple lesions affecting vision, spine, bladder function; mood changes; memory loss	Steroids; immunosuppression
Epilepsy	Postictal confusion; myoclonic epilepsy; brain damage	Control seizures with optimal anticonvulsants
Parkinson's disease	Tremor; rigidity; bradykinesia	Levodopa-carbidopa combination; anticholinergics; amantadine HCl; bromocriptine mesylate
Huntington's disease	Familial chorea; psychiatric symptoms	Haloperidol for chorea and psychosis; antidepressants
Progressive supranuclear palsy	Decreased voluntary gaze, especially vertical; axial rigidity; gait difficulty	Antiparkinsonian drugs
Wilson's disease	Familial; dysarthria, dystonia, tremor; liver disease; Kayser-Fleischer rings; low serum ceruloplasmin; high urinary copper excretion	Penicillamine; low copper diet
Basal ganglia calcification	Parkinsonism or chorea; may be familial or associated with hypoparathyroidism	Treat endocrine disorder and movement disorder
Post-cardiac arrest anoxic encephalopathy	Acute cerebral hypoxia, carbon monoxide poisoning; myoclonus; seizures; spasticity; amnesia residual	Seizure control
Dialysis dementia	Dysarthria; agitation; myoclonus; EEG: slow wave bursts; aluminum toxicity	Diazepam
Acquired hepatocerebral degeneration	Chronic hepatic encephalopathy; dysarthria; ataxia; asterixis; choreoathetosis	Reduce dietary protein; lactulose; neomycin
Behçet's syndrome	Uveitis; oral and genital ulcers; aseptic meningitis with cranial nerve palsies	Steroids; immunosuppression
Cancer complications	Metastases; endocrine and metabolic effects; infections	Treat underlying malignancy and medical complications
Alcoholic dementia	Prolonged excess alcohol use; memory, abstraction poor; CT atrophy; distinguish from acute intoxication, withdrawal syndromes and Korsakoff's syndrome	Abstinence from alcohol
Mercury	Sensory changes; visual loss; dysarthria; tremors; psychosis	Penicillamine; eliminate exposure
Manganese	Neuropsychiatric and extrapyramidal symptoms	Edetate chelation
MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)	Synthetic heroin contaminant; parkinsonian syndrome	Antiparkinsonian drugs
Schizophrenia	Psychosis; fluctuating course	Neuroleptic agents

CNS=central nervous system, CT=computed tomography, EEG=electroencephalogram

decreased intellectual capacity, and the findings of a neurologic examination and diagnostic evaluations are normal. At times an empiric trial of antidepressants is necessary to establish or to exclude the diagnosis. Depression due to other dementing conditions, such as systemic illnesses, intoxications or hydrocephalus, is a complication that may reverse with treatment of the underlying disorder.

Treatable Dementias

Conditions causing permanent changes of the nervous system cannot be reversed with current medical techniques. Nevertheless, some of these conditions may be considered treatable because appropriate interventions will either alter the course of the dementia or relieve important related symptoms. Most, but not all, of these disorders are primary neurologic illnesses (Table 3).

One of the major causes of treatable dementia is cerebrovascular disease. Multi-infarct dementia may result from several clinically evident strokes or from many small lacunar infarcts in the basal ganglia and deep white matter of the brain. Hypertension, cardiovascular disease, diabetes mellitus, oral contraceptive use, arteritis and familial hyperlipidosis may predispose to strokes and hence to multi-infarct dementia. The Hachinski Ischemia Scale highlights the history, risk factors and focal features usually present in multi-infarct dementia.[18] Treatment is aimed at preventing ischemic events through the use of antiplatelet medications, the selective use of anticoagulants and carotid endarterectomy and reducing risk factors such as hypertension. With prophylaxis against repeat strokes and the natural neurologic recovery processes, there may be significant improvement in the cognitive and the physical difficulties associated with multiple infarcts.

The angular gyrus syndrome, usually caused by an infarct in the dominant parietal lobe, produces a multitude of intellectual deficits and may be confused with a degenerative dementia. The angular gyrus syndrome includes Gerstmann's tetrad—agraphia, acalculia, finger agnosia and right-left disorientation—alexia and anomia. Nonverbal memory, however, will be preserved, an important point distinguishing the condition from Alzheimer's disease.[19]

Posttraumatic dementia is a common cause of intellectual disability,[20] particularly in young people. It tends to be associated with prominent amnesia, focal neurologic signs and personality changes. The clinical features reflect the frontal and temporal preponderance of neuropathologic lesions resulting from closed head trauma. Comprehensive rehabilitation programs are necessary to maximize function. Anticonvulsant medications are used when the trauma is complicated by seizures. Associated neuropsychiatric disorders such as depression or psychosis may be treated with appropriate medications. Dementia pugilistica, a condition resulting from repeated blows to the head in boxers, manifests by psychomotor slowing and extrapyramidal signs such as rigidity, stooped posture and tremor. Antiparkinsonian medications may be helpful for these symptoms.

Most of the diseases of the extrapyramidal system are associated with cognitive and emotional difficulties.[3] Parkinson's disease, Huntington's disease, progressive supranuclear palsy, Wilson's disease and basal ganglia calcification all have distinctive clinical features with movement disorders and distinctive neuropathologic features. In Parkinson's disease, the use of dopaminergic compounds lessens the motor symptoms and may also enhance cognitive function.[21] This treatment is less effective in patients with progressive supranuclear palsy. Wilson's disease may be halted (or reversed if the pathology is not severe) by a regimen of penicillamine and a low copper diet. Basal ganglia calcification may be associated with an underlying endocrinologic disorder, hypoparathyroidism, which can be treated. Although the cognitive decline in Huntington's disease is inexorable, the chorea is reduced by the use of neuroleptic agents. Depression is a frequent accompaniment of Huntington's disease and Parkinson's disease, and treatment of the depression may lead to cognitive improvement. Medications used to treat extrapyramidal syndromes may lead to chronic confusional states, and, therefore, therapeutic interventions need constant monitoring.

Demyelination of subcortical white matter is frequently found in multiple sclerosis, and memory problems and other features of a mild dementia are common.[22] Exacerbations of multiple sclerosis are often associated with a worsening of cognitive function, and steroids or immunosuppressive therapy may be of benefit in altering the progression of symptoms.

Dementia associated with epilepsy may result from anticonvulsant toxicity, underlying brain lesions, frequent seizures or postictal confusion. Subtypes of myoclonic epilepsy cause progressive dementia, and in these cases control of seizures will partially limit cognitive impairment.

Although many infectious causes of dementia are reversible, some infections may produce permanent parenchymal brain damage and chronic dementia even when appropriately treated. For example, *Treponema pallidum* is sensitive to penicillin, but the damage caused in neurosyphilis is more often halted than reversed.[23] Likewise, treatment of fungal meningitis is extremely difficult, often requiring intrathecal administration of amphotericin B and ventricular shunting to relieve hydrocephalus; however, treatment can alter the otherwise fatal progression of these illnesses.

Viral causes of dementia are responsive to treatment. Herpes encephalitis is now managed with vidarabine therapy. Progressive multifocal leukoencephalopathy, a viral condition seen in conjunction with immunosuppression, may respond to treatment or may remit spontaneously.[24] In the current epidemic of the acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV), opportunistic infections affect the brain.[25] AIDS is also frequently associated with an encephalopathy that may be a viral encephalitis.[26]

Various systemic illnesses may secondarily produce permanent neurologic damage. This is true of post-cardiac arrest anoxic encephalopathy. Control of seizures and supportive care are necessary. Chronic hepatic encephalopathy may lead to acquired hepatocerebral degeneration with dementia, dysarthria, ataxia, asterixis and choreoathetosis.[27] Treatment of this condition is similar to that of reversible hepatic encephalopathy, with the goal of halting the progression of the illness. Dialysis dementia results from excess aluminum in hemodialysis. The dysarthria, myoclonus, agitation and dementia may respond transiently to the administration of diazepam.[28]

Most toxic conditions are reversible. Dementia due to excessive alcohol abuse, however, is reversible only when the intake is of relatively short duration. In other cases, the dementia is stabilized by abstinence.[29] MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a potent neurotoxic by-

product of synthetic morphine, causes an irreversible syndrome similar to Parkinson's disease. The use of antiparkinsonian medications is helpful.[30]

Schizophrenia, a psychiatric disorder first described as dementia praecox, must be considered as a treatable dementia when intellectual impairment accompanies an acute psychotic episode.[4] The psychiatric history, the fluctuating course and the response to neuroleptics clarify the nature of the illness. Chronic schizophrenia is sometimes associated with progressive intellectual deterioration late in the course of the disease.

Reversible dementias may sometimes respond only partially to therapy, thus fitting into the treatable category. When this occurs, it may be that the condition persisted to the point of permanent brain damage or that the reserve capacity of an aging nervous system was overwhelmed.

Treatable Aspects of Irreversible Dementias

Even in the case of a progressive, irreversible cause of dementia, there are treatable aspects that may improve a patient's level of function and quality of life.[31] The presence of a degenerative condition, such as Alzheimer's disease, does not confer immunity against the reversible and treatable conditions listed in Tables 1 and 3, and appropriate evaluations for these illnesses should be conducted when indicated.

General health maintenance may prevent medical complications of chronic disability. Medications, especially sedatives used to control the behavior of demented patients, may exaggerate symptoms of confusion and memory impairment. Monitoring medication dosages is essential and may require an aide or family member to supervise the patient. Similarly, it is important to ensure good nutrition. This is particularly true for elderly patients with mild dementia who may be living alone and eating improperly prepared meals and convenience foods with inadequate nutritional value.

Incontinence is frequently the problem that leads to placement of a patient in a nursing facility. Incontinence may result from focal neurologic damage, a side effect of medication, infection or other physical problem. When the incontinence is the result of cognitive impairment, a schedule of frequent toileting in the day and the use of incontinence pads at night may keep the patient clean and dry.

Patients with dementia do not adjust well to novelty; surroundings and schedules should be as consistent as possible. Regular caretakers with whom a patient is familiar are preferable to a constantly changing parade of newcomers. Moves to new homes should be done infrequently, and, if possible, the patient should keep as many personal effects as is practical to enhance the familiarity of the environment. Residences must be kept safe, with locks on cabinets containing dangerous items and medications, locks on doors leading outside and enough nighttime illumination to keep a nocturnal pacer from injury. Ideally the environment will also be stimulating with activities and companions geared to the age and cognitive capacity of a person.

Agitation, violence, hallucinations and delusions that lead to dangerous actions may require treatment. Low doses of major tranquilizers can effectively control these symptoms, with a choice of agents having relatively low sedation (haloperidol) or high sedation (chlorpromazine, thioridazine), as indicated. Short-acting benzodiazepines may help patients who have intermittent anxiety or mild agitation, with constant monitoring for the occurrence of side effects or behavioral worsening. Mild antihistaminic sedatives, low doses of major tranquilizers or short-acting hypnotics are helpful for problematic nocturnal wandering. The use of anticholinergic agents should be avoided. Medications should be used only to control serious behavior problems and not for the convenience of caretakers.

It is the role of a caretaker that ultimately determines the success or failure of all dementia treatment, and the needs of caretakers cannot be ignored. Caring for a patient with dementia creates an emotional, social and financial burden on the spouse or children. Adult day care and respite admissions to hospital may give a caretaker a break from the "36-hour day,"[32] allowing him or her to continue the care for a longer time. Social services, psychological support, financial assistance and legal counsel are often required in addition to medical advice. These needs will change with the stage of dementia.

Evaluating Patients for Treatable Dementia

The number of potential causes for a patient's symptoms of intellectual decline is quite large,[4] and it is undesirable to rely on a series of laboratory tests to exclude systematically each of the possible conditions. Such an approach would be inefficient, expensive and invasive. Clinicians must develop a strategy to guide their selection of tests to arrive most expeditiously at an accurate diagnosis in each case. The primary goal is to identify treatable conditions contributing to the cognitive impairment. Very often the major obstacle to an accurate assessment is the attitude that intellectual decline is normal in the elderly or that all dementia is the result of Alzheimer's disease.

The initial history and general physical examination provide clues to the presence of toxic or systemic illnesses. A detailed neurologic examination alerts a clinician to the presence of localizing signs indicative of focal brain disease or to the existence of an extrapyramidal disorder. Tables 1 and 3 indicate the salient historical, physical and neurologic characteristics associated with various dementia-producing conditions. The presence of one or more of these features would lead a physician to include the relevant specific diagnostic investigations in the assessment.

A properly carried out mental state examination probes each domain of intellectual function as well as the emotional state of a patient. This adds invaluable diagnostic information. For example, in Table 2 the features consistent with a toxic or metabolic confusional state are contrasted with those of dementia of the Alzheimer type. Attention to specific features of a mental state examination can also aid in distinguishing Alzheimer's disease from the angular gyrus syndrome,[19] from the dementia associated with depression[17] and from the dementia syndromes of hydrocephalus and extrapyramidal syndromes.[4]

Certain laboratory investigations should be done routinely in evaluating all dementia patients. Tests that efficiently screen for the common medical illnesses of the elderly and those capable of detecting the most frequent dementias should be done in every case.[5] Complete blood counts, erythrocyte sedimentation rate, serum chemistry analysis, urinalysis, thyroid function tests, syphilis serology, serum B_{12} level, electrocardiogram and a chest x-ray film constitute an initial medical evaluation. In addition, all patients with dementia should be scanned with either computed tomography or magnetic resonance imaging. Imaging the brain allows the detection of

occult tumors, chronic subdural hematomas, hydrocephalus and ischemic lesions. These conditions may be treatable if not reversible, and identifying or excluding them is of great value in establishing diagnostic certainty and in advising patients and families about prognosis. Similarly, an electroencephalogram should be done whenever possible. A normal study is expected in a patient with early Alzheimer's disease and in one with dementia due to depression. Diffuse slowing is indicative of a toxic or metabolic condition, while focal slowing reflects localized structural pathology.[33] Cerebrospinal fluid analysis is important whenever an infectious or inflammatory process is suspected.

Treatable and reversible conditions can be superimposed on degenerative diseases, and the routine workup outlined above should be done even when the presumptive diagnosis is Alzheimer's disease or some other progressive dementia. Specialized or invasive tests are done when there is a specific indication based on the initial evaluation. Two clinical situations routinely requiring more extensive investigation are dementia in a young person and dementia with uncommon or atypical features.

Conclusion

Dementia is a clinical syndrome of acquired persistent intellectual impairment produced by brain dysfunction. The disorders causing dementia entail a spectrum of treatability: in some cases, timely intervention will cure the underlying condition and restore intellectual function; in others, treatment will halt further deterioration or modify important symptoms without reversing the cognitive losses; in still others, appropriate management cannot reverse or halt the disease process, but therapy will maximize remaining abilities and prevent unnecessary complications. Attention to the treatable aspects of all dementing disorders will increase detection of reversible conditions, decrease the burden on a patient's family, enhance the quality of a patient's life and prevent premature nursing home placement.

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