# A Review of the Non-Alzheimer Dementias

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***Objective:*** To review the clinical features, neuropathologic features, clinical course, differential diagnosis, evaluation, and management strategies of the primary non-Alzheimer degenerative and prion disorders that cause dementia.

***Data Sources:*** The PubMed MEDLINE search engine was used to query for all published articles written in English from January 1990 to August 2005 using the keywords *non-Alzheimer*, *tau*, *tauopathy*, *synuclein*, *synucleinopathy*, *prion*, *cognitive impairment*, and *dementia syndrome*. These and related terms were queried on the following additional search engines: On-Line Mendelian Inheritance in Man and GeneTests. Reputable organizations whose aims include promoting education and research in specific syndromes and disorders were queried using the search engine Google.

***Study Selection:*** The original articles on the disorders and syndromes, and subsequent articles and consensus papers that discussed in detail the clinical features, pathologic features, differential diagnosis, evaluation, management strategies, or some combination thereof, were selected for this review.

***Data Extraction:*** Data were extracted from articles that include generally accepted concepts and guidelines on the non-Alzheimer degenerative and prion disorders as viewed by the author.

***Data Synthesis:*** The following data were synthesized and emphasized: the cardinal clinical features, differential diagnosis, findings on ancillary studies most helpful in establishing accurate diagnoses, diagnostic criteria, and key principles of management.

***Conclusions:*** This article provides an up-to-date overview of the primary non-Alzheimer disorders that cause cognitive impairment/dementia to aid the clinician in establishing diagnoses and deciding on appropriate management.

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If one considers that (1) at least 4.5 million Americans have an incurable form of dementia, (2) approximately 20% to 40% of patients with an incurable cause have a non-Alzheimer disorder underlying their symptoms (hence probably over 1 million Americans affected), and (3) the costs associated with Alzheimer's disease and related dementias exceed $100 billion per year,[1] one can appreciate the magnitude and burden of this sizable minority of diseases.

The clinical and neuropathologic terminology in the non-Alzheimer dementias is confusing and still evolving. Because of the considerable heterogeneity between the various diseases and clinical syndromes, we will take a somewhat nontraditional approach and first discuss the non-Alzheimer degenerative and prion diseases that cause dementia, covering the clinical features, neuropathologic features, clinical course, differential diagnosis, evaluation, and management. Those disorders associated with genetic alterations will be referenced to the appropriate section on the Online Mendelian Inheritance in Man (OMIM) Web site (Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=omim). The clinical syndromes associated with each disease will also be discussed. Management strategies for target symptoms will be reviewed as well. This article is designed to provide a focused overview of the most common non-Alzheimer dementia disorders to aid the clinician in establishing diagnoses and deciding on management.

## METHOD

The PubMed MEDLINE search engine (www.pubmed.gov) was used to query for all published articles written in English from January 1990 to August 2005 using the keywords, *non-Alzheimer*, *tau*, *tauopathy*, *synuclein*, *synucleinopathy*, *prion*, *cognitive impairment*, and *dementia syndrome*. These and related terms were

queried on the following additional search engines (last accessed on 8/30/05): On-Line Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=omim) and GeneTests (http://www.geneclinics.org). Reputable organizations whose aims include promoting education and research in specific syndromes and disorders were queried using the search engine Google (www.google.com).

## DEGENERATIVE AND PRION DISORDERS THAT CAUSE DEMENTIA

The pertinent degenerative and prion disorders that cause dementia, grouped by their associated dysfunctional proteins, are shown in Table 1. We will concentrate on the most commonly encountered diseases (asterisked in Table 1); additional details on rare disorders can be found in other resources.[2,3]

### Amyloidopathies

***Alzheimer's disease.*** We will not discuss Alzheimer's disease here, even though it is one of the most commonly encountered diseases, because it is discussed in depth in the article by Caselli et al.[98]

### Tauopathies

***Pick's disease.***

Overview. Arnold Pick[4] first described focal cortical atrophy in a patient with a progressive aphasia syndrome. Decades later, other investigators focused on the neuropathologic features in patients with focal atrophy and termed the ballooned cells as Pick cells and the neuronal inclusions as Pick bodies. While the diagnosis "Pick's disease" has been applied clinically to cases that had focal cortical atrophy and nonspecific neurodegenerative changes with or without Pick cells, there is general consensus that Pick's disease is a pathologic diagnosis that is reserved only for those cases with Pick bodies.[5] Information on Pick's disease can be accessed at these Web sites: http://www.ftd-picks.org/?p=diseases/picks and http://www.pdsg.org.uk/index.php.

Clinical features. Pick's disease typically manifests as frontotemporal dementia, primary progressive aphasia, or semantic dementia (discussed in more detail in the section on cognitive impairment/dementia syndromes later). Rare cases presenting as the corticobasal syndrome have also been reported.

Neuropathologic features. Marked thinning of affected gyri, often termed *knife-edge* in appearance, is the typical macroscopic finding; pallor of the substantia nigra is also common. Histologically, Pick's disease is characterized by the abnormal accumulation of hyperphosphorylated tau in neurons and glia, and as noted above, Pick bodies are required for the neuropathologic diagnosis.[5] The inclusions stain intensely with tau immunocytochemistry.

**Table 1. Dysfunctional Proteins and Associated Neurodegenerative and Prion Disorders That Manifest as Dementia With or Without Parkinsonism With or Without Motor Neuron Disease**

| |
|---|
| Amyloidopathies (dysfunctional protein: amyloid) |
| Alzheimer's disease: sporadic and familial |
| Down's syndrome |
| Familial British dementia |
| Familial Danish dementia |
| Tauopathies (dysfunctional protein: tau) |
| Pick's disease*: sporadic and familial |
| Corticobasal degeneration*: sporadic and familial |
| Progressive supranuclear palsy*: sporadic and familial |
| Argyrophilic grain disease: sporadic and familial |
| Multisystem tauopathy: sporadic and familial |
| Frontotemporal dementia and parkinsonism linked to chromosome 17 with a tau mutation* |
| Synucleinopathies (dysfunctional protein: α-synuclein) |
| Lewy body disease: sporadic and familial (manifesting as the syndromes of Parkinson's disease, dementia with Lewy bodies, or Parkinson's disease with dementia)* |
| Multiple system atrophy (rarely associated with dementia) |
| Prionopathies (dysfunctional protein: prion protein) |
| Creutzfeldt-Jakob disease*: sporadic and familial |
| Gerstmann-Strausser-Schenker: sporadic and familial |
| Fatal familial insomnia: sporadic and familial |
| Other |
| Huntington's disease (dysfunctional protein: huntingtin)* |
| Neurofilament inclusion body dementia (dysfunctional protein: α-internexin) |
| Familial encephalopathy with neuroserpin inclusion bodies (dysfunctional protein: neuroserpin) |
| Frontotemporal dementia, Paget's disease, and inclusion body myositis (dysfunctional protein: valosin-containing protein) |
| Frontotemporal lobar degeneration with ubiquitin-positive inclusions (dysfunctional protein: unknown)*: sporadic and familial |
| Frontotemporal dementia and parkinsonism linked to chromosome 17 with a progranulin mutation (dysfunctional protein: unknown)* |
| Dementia lacking distinctive histopathology (dysfunctional protein: unknown)*: sporadic and familial |
| Hippocampal sclerosis (dysfunctional protein: unknown) |

*The most common non-Alzheimer's disorders, which are discussed in the text.

Clinical course. Most patients succumb to their disease in 3 to 10 years, but durations exceeding 15 years can occur.

Differential diagnosis. Since most cases have findings referable to the frontal or temporal (or both) cortical regions, the clinical manifestations are typically behavior-personality change typical of frontotemporal dementia, aphasia within the progressive nonfluent aphasia/primary progressive aphasia/semantic dementia phenotype, or elements of both. Other disorders that present as frontotemporal dementia and progressive aphasia are described later.

Evaluation. The clinical features, findings on neuropsychological testing, and radiologic findings allow clinical characterization into one of the focal cortical syndromes. At present, there are no antemortem features that reliably predict Pick's disease pathology.

  

Management. Although many agents are currently under investigation in animal models, no human studies have begun yet. Treatment is based on target symptoms.

***Corticobasal degeneration.***

Overview. In 1967, Rebeiz et al.[6] identified 3 patients who had progressive asymmetrical akinetic-rigid syndrome and apraxia and distinctive histopathologic features. The achromatic neurons and degeneration of the cerebral cortex, substantia nigra, and cerebellar dentate nucleus led the investigators to term this entity as *corticodentatonigral degeneration with neuronal achromasia*. Well over 100 cases have been reported since, with most authors now using the term *corticobasal degeneration* and abbreviation "CBD" for such cases. Information on corticobasal degeneration can be accessed at these Web sites: http://www.ftdpicks.org/?p=diseases/corticbasaldegeneration and http://www.tornadodesign.com/cbgd/.

Clinical features. Corticobasal degeneration is usually associated with asymmetric parietofrontal cortical atrophy, and the clinical features reflect this topography, which includes progressive asymmetrical rigidity and apraxia, cortical sensory loss, alien limb phenomenon, dystonia, myoclonus, and tremor—all features of the so-called "corticobasal syndrome"[7] (discussed later). Yet, many patients with underlying corticobasal degeneration have presented with progressive aphasia, frontotemporal dementia, or dementia of the Alzheimer type.[8,9]

Neuropathologic features. Asymmetric parietofrontal or frontotemporal cortical atrophy and pallor of the substantia nigra are the typical macroscopic pathologic findings.[10] The characteristic histologic features are neuronal loss, gliosis, and superficial spongiosis in the maximally affected cortical gyri, tau-positive (tau+) astrocytic plaques and tau+ thread-like lesions in gray and white matter, tau+ oligodendroglial coiled bodies, and ballooned achromatic neurons that are immunoreactive to phosphorylated neurofilament or αβ-crystallin.[10] Four-repeat tau is present in corticobasal degeneration. Most of these pathologic features are indistinguishable from those in frontotemporal dementia and parkinsonism linked to chromosome 17. Thus, knowledge about the family history and molecular genetics is necessary to adequately classify cases with corticobasal degeneration–type pathology.

Clinical course. Duration of symptoms is typically 5 to 8 years, although as few as 2 years and as many as 14 years have been observed.

Differential diagnosis. The unilateral motor findings often lead to suspicion of a stroke or tumor, but neuroimaging studies fail to reveal any infarct or lesion. Corticobasal degeneration must be considered in the differential of any patient with dementia (particularly with atypical features) or parkinsonism.

Evaluation. Neuropsychological testing tends to show subcortical features plus parietofrontal cortical dysfunction corresponding to the hemisphere of maximal involvement. Focal or asymmetric parietofrontal cortical findings (atrophy on computed tomography and magnetic resonance imaging [MRI], hypoperfusion on single photon emission-computed tomography [SPECT], or hypometabolism on positron emission tomography [PET]) are typically present on neuroimaging studies. There are no antemortem features that reliably predict corticobasal degeneration pathology.

Management. Management is symptomatic, depending on the most problematic symptoms and findings. Management for features in the corticobasal syndrome is discussed in the section on corticobasal syndrome.

***Progressive supranuclear palsy.***

Overview. Steele et al.[11] first described the clinical features of the syndrome of progressive supranuclear palsy associated with degeneration of the brainstem, basal ganglia, and cerebellum. Dementia occurs frequently in progressive supranuclear palsy. Additional information on progressive supranuclear palsy can be accessed on the Society for Progressive Supranuclear Palsy Web site at www.psp.org.

Clinical features. The classic presentation of progressive supranuclear palsy is the constellation of supranuclear gaze palsy, postural instability and falls, and parkinsonism; dementia tends to be a middle to late feature of the disorder.[12] Many cases are now appreciated to present as progressive aphasia, frontotemporal dementia, or having obsessive-compulsive features, yet with few or none of the features considered characteristic of progressive supranuclear palsy.[13,14]

Neuropathologic features. The neuropathologic hallmarks of progressive supranuclear palsy are numerous neurofibrillary tangles and neuropil threads in the basal ganglia, diencephalon, and brainstem (e.g., globus pallidus, subthalamic nucleus, and substantia nigra), with tau-immunoreactive tufted astrocytes as a supportive feature.[12,15,16]

Clinical course. The time from onset to death is usually 3 to 7 years, often punctuated by head trauma due to falls and aspiration due to dysphagia.

Differential diagnosis. Other disorders that can mimic progressive supranuclear palsy include vascular disease, Whipple's disease, neurosyphilis, Lewy body disease, Parkinson's disease with argyrophilic grains, familial frontotemporal dementia with parkinsonism, progressive multifocal leukoencephalopathy, corticobasal degeneration, and postencephalitic parkinsonism.[16]

Evaluation. The clinical features make one suspect progressive supranuclear palsy. Other antemortem findings may suggest progressive supranuclear palsy, but there are no antemortem features with 100% specificity.

Management. Management of the cognitive, motor, and gait aspects of progressive supranuclear palsy is challenging. Parkinsonism responds poorly to carbidopa/levodopa, and gait assistance devices or confinement to a wheelchair is often necessary for management of gait impairment. The

topography of cortical dysfunction tends to involve the frontal or frontosubcortical neural networks; thus, apathy and executive dysfunction are often present. Disinhibition, dysphoria, and anxiety are also common. Treatment is directed toward target symptoms. Physical and occupational therapy and gait assistance devices are also indicated in many.

***Frontotemporal dementia and parkinsonism linked to chromosome 17 with a tau mutation.***

Overview. Over 35 different mutations in the microtubule-associated protein tau have been associated with familial frontotemporal dementia and parkinsonism; such cases are often abbreviated "FTDP-17," as the linkage to chromosome 17 was appreciated prior to the identification of mutations in microtubule-associated protein tau.[17] Information on FTDP-17 can be accessed on the Association for the Frontotemporal Dementias Web site http://www.ftdpicks.org/?p=diseases/ftdp17, the OMIM Web site http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=157140, and the GeneTests Web site http://www.geneclinics.org/servlet/access?db=geneclinics&site=gt&id=8888890&key=603N42cEc1vak&gry=&fcn=y&fw=2L2r&filename=/profiles/ftdp-17/index.html.

Clinical features. Most patients with FTDP-17 present with the syndromes of frontotemporal dementia or progressive aphasia, or elements of both.[18] Less commonly, the syndromes of the corticobasal syndrome or atypical parkinsonism are manifested. Some develop features of motor neuron disease as well (an excellent review on the clinical features can be found in reference 19). The age at onset is typically in the 30 to 50 years range, although symptoms presenting before age 30 years have been observed. Importantly, some patients with genetically-confirmed FTDP-17 have no family history of dementia/parkinsonism/motor neuron disease (presumably representing genetic mosaicism),[20] and therefore testing for mutations in microtubule-associated protein tau should at least be considered for any patient presenting with early-onset frontotemporal dementia, progressive aphasia, or atypical parkinsonism.

Neuropathologic features. While all cases with mutations in microtubule-associated protein tau have tau-positive neuronal and/or glial inclusions, the specific histopathologic features can vary, even among relatives with the same mutation.[21] Some cases have findings indistinguishable from sporadic Pick's disease, sporadic corticobasal degeneration, sporadic progressive supranuclear palsy, or sporadic argyrophilic grain disease. Thus, the specific neuropathologic diagnosis rests on not only the specific findings using tau and other immunostains but also genotyping microtubule-associated protein tau.

Clinical course. The clinical features that evolve over time and the rate of progression also vary, even among relatives with the same mutation.[19] Time from onset to death is usually 3 to 8 years, with some surviving well over 10 years from onset.

Differential diagnosis. All of the disorders reviewed in this article are in the differential diagnosis of FTDP-17.

Evaluation. The clinical features, profile of impairment on neuropsychological testing, frontal and/or temporal abnormalities on structural and functional neuroimaging studies, and positive family history of neurodegenerative disease raise suspicion of FTDP-17. Cerebrospinal fluid (CSF) analyses are typically normal except for the occasional patient with elevated protein and/or tau. Genetic counseling is imperative if genetic testing is planned; genetic testing can be carried out in the following Clinical Laboratory Improvement Amendments–certified laboratories: Center for Genetic Testing at Saint Francis (http://www.sfh-lab.com/;), University of California at San Francisco Molecular Diagnostics Laboratory (http://pangloss.ucsfmedicalcenter.org/mdx/), or Mayo Clinic (http://www.mayoclinic.org/laboratorygenetics-rst/molecular.html).

Management. Management is tailored toward target symptoms.

## Synucleinopathies

***Lewy body disease.***

Overview. Friedrich Lewy first described the intracellular neuronal inclusions many decades ago that subsequently came to bear his name. Lewy bodies are easily recognizable in brainstem structures using standard histopathologic techniques, and Okazaki et al. noted similar inclusions in the neocortex in the early 1960s using similar techniques.[22] Yet it was not until the advent of ubiquitin immunohistochemical staining and then α-synuclein immunocytochemistry that Lewy bodies were easily identified in limbic and neocortical structures.[23,24] Most investigators now use the term *Lewy body disease* (abbreviated LBD) as the neuropathologically-defined entity regardless of the clinical phenotype exhibited in life.

Clinical features. Lewy body disease typically manifests as either dementia with Lewy bodies, Parkinson's disease, or Parkinson's disease with dementia. Rarely, other phenotypes have been reported in association with Lewy body disease, including rapid eye movement (REM) sleep behavior disorder or pure autonomic failure.

Neuropathologic features. Most investigators characterize Lewy body disease as brainstem-, limbic-, or neocortical-predominant Lewy body disease based on the consortium description published in 1996.[25]

Clinical course, differential diagnosis, evaluation, and management. See details in sections on dementia with Lewy bodies and Parkinson's disease with dementia later.

## Prionopathies

***Creutzfeldt-Jakob disease.***

Overview. The term *prion* was suggested by Stanley Prusiner, M.D.,[94] for proteinaceous infectious particles that appear to induce conformational changes in prion protein

  

(all humans encode for prion protein on chromosome 20) and ultimately cause neuronal death. There are sporadic, familial, and iatrogenic forms. "New variant Creutzfeldt-Jakob disease" is presumably caused by the ingestion of products from animals that previously had been fed contaminated food. Fatal familial insomnia, Gerstmann-Straussler-Schienker disease, and kuru are the 3 other prion disorders that affect humans. Additional information on Creutzfeldt-Jakob disease can be accessed on the Creutzfeldt-Jakob Disease Foundation Web site at http://www.cjdfoundation.org/, and some excellent reviews on prion disease can be found in references 26 and 27.

Clinical features. The typical clinical features of Creutzfeldt-Jakob disease include rapidly progressive dementia and myoclonus, with the more variable findings being visual disturbance, pyramidal tract dysfunction, extrapyramidal dysfunction, and akinetic mutism. Atypical presentations include frontotemporal dementia, progressive aphasia syndrome, corticobasal syndrome, progressive visuoperceptual/visuospatial impairment syndrome (Heidenhain variant), and various neuropsychiatric presentations.

Neuropathologic features. The characteristic neuropathologic features are spongiform changes and particularly positive staining to prion protein immunohistochemistry.

Clinical course. Although rare cases of Creutzfeldt-Jakob disease have durations of disease exceeding 2 years, most patients exhibit a subacute and progressive encephalopathy and succumb to their illness within 1 year from onset.

Differential diagnosis. While Creutzfeldt-Jakob disease can present as focal/asymmetric cortical degeneration syndromes, these atypical presentations usually evolve over several months, and therefore are more rapidly progressive than any of the degenerative disorders. The critical issue in subacute as well as chronic encephalopathies is to fully evaluate potentially reversible or treatable causes,[28,29] which include infectious (e.g., viral), metabolic (e.g., porphyria), paraneoplastic (e.g., paraneoplastic limbic encephalitis), and autoimmune/inflammatory disorders (e.g., "Hashimoto's encephalopathy," limbic encephalitis associated with voltage-gated potassium channel antibodies, primary central nervous system vasculitis, etc.).

Evaluation. All patients with a subacute encephalopathy should undergo a thorough evaluation, which would include blood and urine studies; magnetic resonance imaging using fluid attenuation inversion recovery, diffusion-weighted images, and contrast (looking for increased signal in the basal ganglia and/or cortical ribbon consistent with Creutzfeldt-Jakob disease, or contrast-enhancing findings suggesting a non-Creutzfeldt-Jakob disease disorder); CSF analysis (testing for oligoclonal bands, IgG synthesis rate and index [increased values for any of these would suggest a non-Creutzfeldt-Jakob disease disorder], neuron specific enolase and 14–3-3 protein [elevated levels would suggest, but not confirm, Creutzfeldt-Jakob disease]); and electroencephalography (quasiperiodic sharp wave complexes would suggest Creutzfeldt-Jakob disease; triphasic waves or diffuse generalized slowing would suggest a non-Creutzfeldt-Jakob disease disorder). Definitive diagnosis requires examination of tissue, and since most institutions do not offer brain biopsy if Creutzfeldt-Jakob disease is suspected, autopsy is typically necessary to establish the diagnosis of Creutzfeldt-Jakob disease.

Management. Recent experiments and small human clinical trials have suggested that certain compounds, particularly quinacrine and flupirtine, may affect prion protein pathophysiology.[30–32] There have been mixed results with quinacrine, and flupertine decreased the degree of cognitive impairment but did not affect survival. Management is otherwise directed toward target symptoms or behaviors, and referral to hospice care is appropriate for many patients.

## Other

***Huntington's disease.***

Overview. Huntington's disease, initially characterized by George Huntington in 1872, is an autosomal-dominant neurodegenerative disorder that begins insidiously in middle adulthood. Over 250,000 Americans currently have Huntington's disease or are genetically at risk. Huntington's disease is characterized by progressive chorea, neuropsychiatric symptoms, and cognitive impairment. An expansion of a trinucleotide repeat (CAG) increases polyglutamine, which in turn increases expression of the protein huntingtin that is encoded on chromosome 4. Additional information on Huntington's disease can be accessed on the Huntington's Disease Society of America Web site (http://www.hdsa.org/site/PageServer?pagename=homepage) and the OMIM Web site (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=143100).

Clinical features. Of particular importance to psychiatrists is to consider Huntington's disease in any patient with early-onset parkinsonism associated with abulia and akinesia, since such cases may represent Huntington's disease prior to the onset of chorea and more prominent neuropsychiatric features. Chorea is present at some point in the illness in almost every patient, but may be quite late in the course. Dysfunction in psychomotor speed, attention-concentration, and learning and memory are the primary cognitive features, while the neuropsychiatric features of Huntington's disease include depression, hallucinations, delusions, disinhibition, and behavioral dyscontrol.[33]

Neuropathologic features. Striatal degeneration is the consistent histopathologic change in Huntington's disease, with neocortical atrophy clearly also present

but more variable in the topographic distribution of degeneration.

Clinical course. Time from onset to death is generally around 10 to 20 years.

Differential diagnosis. In the absence of chorea, the combination of dementia and neuropsychiatric features in a middle-aged individual opens a wide differential, which includes primary psychiatric disorders (e.g., depression, schizophrenia), neurodegenerative diseases (e.g., frontotemporal dementia, dementia with Lewy bodies, Alzheimer's disease), and other medical disorders (e.g., hypothyroidism). Chorea with or without rigidity leads one to consider Parkinson's disease, corticobasal degeneration, progressive supranuclear palsy, Wilson's disease, and Sydenham's chorea.

Evaluation. The presence of cognitive and behavioral changes plus chorea, particularly with a similarly affected parent, strongly suggests Huntington's disease. While some relatively specific findings on MRI, SPECT, and PET imaging have been reported in Huntington's disease, definitive diagnosis requires genetic testing, which quantifies the number of CAG repeats. A listing of testing centers in the United States can be accessed at http://www.hdsa.org/site/PageServer?pagename=testing_centers.

Management. Numerous open-label studies and controlled clinical trials have been carried out over the past 30 years in patients with Huntington's disease (reviewed in detail in reference 34), but there is no consensus on the most appropriate agents for patients with Huntington's disease. The *N*-methyl-D-aspartate (NMDA) antagonists, minocycline, and creatine have shown the most promise.[35–39] Physical therapy, occupational therapy, and speech therapy are beneficial for many patients. Symptomatic therapy for target symptoms should be considered (see final section of this article), particularly those medications with serotonergic activity.

***Frontotemporal lobar degeneration with ubiquitin-positive inclusions.***

Overview. *Frontotemporal lobar degeneration with ubiquitin-positive inclusions* (*FTLD-U*) is the most frequently used term for this entity.[40] *Frontotemporal lobar degeneration with motor neuron disease–like inclusions*, *motor neuron disease inclusion dementia*, and *frontotemporal lobar degeneration with inclusions, tau- and synuclein-negative, ubiquitinated* are other labels for such cases. The specific protein (or proteins) that form the inclusions that ubiquitin immunocytochemistry stains has not been identified as yet, and it is possible that FTLD-U represents more than 1 pathophysiologic process. Importantly, approximately 50% of cases that present with frontotemporal dementia or progressive aphasia have underlying FTLD-U pathology.

Clinical features. Most patients present with frontotemporal dementia, progressive aphasia, or features of both. Rarely, the corticobasal syndrome can be exhibited, but no case of posterior cortical atrophy with FTLD-U pathology has been reported. Fasciculations, pyramidal tract findings, or full-blown motor neuron disease can co-occur, and in approximately half of cases, a positive family history of dementia, motor neuron disease, or both is present. FTLD-U pathology has been found in families demonstrating linkage to chromosomes 9 and 17 (see next section), but the causative gene on chromosome 9 has not been identified yet.[41] Additional information on frontotemporal dementia-motor neuron disease can be accessed on the Association for Frontotemporal Dementias Web site at http://www.ftd-picks.org/?p=diseases/ftdmnd and on the OMIM Web site at http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=105550.

Neuropathologic features. The neuropathologic features of FTLD-U are ubiquitin-positive, tau-negative and α-synuclein–negative, abnormal neurites and/or intraneuronal, cytoplasmic inclusions in either frontal or temporal cortex, or dentate granule cell layer.[41] Usually there is also gliosis and neuronal loss in a frontotemporal pattern. These same findings may be seen in a less severe manner in patients with amyotrophic lateral sclerosis with mild or no significant cognitive or behavioral features. Importantly, many cases originally characterized as dementia lacking distinctive histopathology (DLDH) (see later) have been reclassified as FTLD-U with refined ubiquitin immunocytochemistry.[42]

Clinical course. The duration of symptoms from onset to death in FTLD-U is short—usually 2 to 4 years—compared to most other neurodegenerative disorders.

Differential diagnosis. Because of the often rapid course, FTLD-U can be confused with Creutzfeldt-Jakob disease, as well as many of the other nondegenerative and nonprion disorder causes of progressive encephalopathy. The pyramidal tract findings plus fasciculations in the musculature referable to 2 or more sections of the spine and/or head are strongly suggestive of FTLD-U.

Evaluation. The clinical features and findings on CSF analysis, EEG, and MRI usually differentiate FTLD-U from Creutzfeldt-Jakob disease, and electromyography may show diffuse denervation changes typical of motor neuron disease. Some patients ultimately found to have FTLD-U pathology have clinical upper and lower motor neuron findings; yet electromyography fails to show widespread denervation changes.

Management. Management of target symptoms is reviewed in the sections on frontotemporal dementia and progressive aphasia.

***Frontotemporal dementia and parkinsonism linked to chromosome 17 due to a progranulin mutation.***

Overview. Frontotemporal dementia and parkinsonism linked to chromosome 17 due to a progranulin mutation (FTDP-17progranulin) was very recently characterized.[95,96] Over the past 10 years, several families had been linked to chromosome 17 in a region immediately adjacent to tau, but affected individuals never had tau-positive

  

pathology, nor did any have mutations in tau. As of August 2006, well over 50 independent families have been found to have progranulin mutations, and the frequency of frontotemporal dementia due to progranulin mutations appears to be similar to that due to tau mutations with both accounting for approximately 5% of all cases. This figure increases to approximately 20% if the analysis is restricted to familial cases (Mike Hutton, Ph.D., written communication, August 2006). All mutations thus far appear to represent null alleles such that there is a 50% reduction in the production of progranulin. Progranulin is involved in wound healing, and excess production of progranulin appears to promote tumorigenesis, but how a reduction in progranulin leads to neurodegeneration is not yet known. The finding of progranulin mutations causing frontotemporal dementia and parkinsonism has major implications for neurodegenerative disease research. The location of progranulin being very close to the location of tau on chromosome 17 also could be viewed as an amazing coincidence of nature, with mutations in 2 nearby genes causing the same clinical phenotypes.

Clinical features. The clinical phenotypes associated with FTDP-17progranulin include frontotemporal dementia, progressive aphasia, and corticobasal syndrome, while some individuals have features highly typical of Alzheimer's disease or Parkinson's disease. The phenotype of amyotrophic lateral sclerosis associated with FTDP-17progranulin appears to be very rare.

Neuropathologic features. All affected individuals studied thus far have had FTLD-U pathology. The unique finding of neuronal intranuclear inclusions, which only rarely is found in individuals without progranulin mutations, is almost universal in FTDP-17progranulin.[97] The protein that is ubiquitinated has not been identified yet.

Clinical course. The duration of symptoms varies from 2 to 15 years.

Differential diagnosis, evaluation, and management. These aspects are very similar to those described in FTLD-U.

***Dementia lacking distinctive histopathology.***

Overview. Dementia lacking distinctive histopathology refers to 1 (or more) disease process in which all immunostains directed toward tau, α-synuclein, ubiquitin, b-amyloid, prion protein, etc., fail to reveal any distinctive histopathologic abnormalities other than neuronal loss, gliosis, and spongiosus (spongiosus as described here is distinctly different from spongiform changes typical of Creutzfeldt-Jakob disease).[43,44] A large Danish family with DLDH pathology had been linked to chromosome 3. Mutations in the gene encoding for charged multivesicular body protein 2B (*CHMP2B*) on chromosome 3, which is a subunit of the endosomal sorting complexes required for transport-III, were very recently identified,[45] and it remains to be seen if other mutations in *CHMP2B* can explain DLDH in sporadic and familial cases. More information on chromosome 3–linked dementia lacking distinctive histopathology can be accessed on the OMIM Web site: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600795.

Clinical features. Patients with DLDH pathology typically present as would those with frontotemporal dementia or progressive aphasia, although the corticobasal syndrome and posterior cortical atrophy have been observed.[44,46,47] Motor neuron disease may also co-occur, similar to what is associated with FTLD-U pathology.

Neuropathologic features. Most older cases examined before more recent and refined immunostains were available have been reexamined and reclassified as FTLD-U.[42] Once any other causative gene(s) is identified, most or all DLDH cases will likely be reclassified after immunostains directed against the proteins are developed.

Clinical course. The duration of symptoms is quite variable, sometimes longer than 10 years, with motor findings (rigidity, gait impairment) typically being a late feature.

Differential diagnosis. DLDH pathology must be considered in the differential diagnosis of any dementia syndrome.

Evaluation. Diagnostic studies can provide insights as to the most appropriate syndromic label, but there are no antemortem features or findings that are diagnostic of DLDH. Furthermore, sampling error during brain biopsy may reveal only nonspecific features when specific histopathologic findings may be found with a more complete neuropathologic examination at autopsy.

Management. Treatment is directed at target symptoms.

## CLINICAL COGNITIVE IMPAIRMENT/ DEMENTIA SYNDROMES

An important and all-too-often unappreciated concept in dementia is that clinical symptomatology reflects the topographic distribution of pathology more so than the specific underlying histopathologic disorder. Therefore, each disorder can manifest as a spectrum of clinical syndromes, and each syndrome is associated with a spectrum of histopathologic disorders. This concept is the foundation of the focal and asymmetric cortical degeneration syndromes initially formulated by Caselli.[48–50]

The most common clinical syndromes in cognitive impairment and dementia are shown in Table 2, and the clinical criteria for each syndrome are presented in Tables 3 to 10. Because no currently available therapy targets any of the pathophysiologic processes of these disorders, up to this point errors in the diagnosis of specific diseases generally have not affected pharmacologic management. Symptomatic therapy involving drugs and nonpharmacologic strategies that target signs and symptoms can improve daily functioning, and this continues to be the mainstay of treatment for management of degenerative and

**Table 2. Clinical Cognitive Impairment/Dementia Syndromes**

| |
|---|
| Mild cognitive impairment |
| Dementia of the Alzheimer type |
| Frontotemporal dementia |
| Primary progressive aphasia/nonfluent aphasia/semantic dementia |
| Corticobasal syndrome |
| Posterior cortical atrophy |
| Dementia with Lewy bodies |
| Parkinson's disease with dementia |

**Table 3. Clinical Criteria for the Diagnosis of Amnestic Mild Cognitive Impairment[a]**

| |
|---|
| Memory complaint usually corroborated by an informant |
| Objective memory impairment for age |
| Essentially preserved general cognitive function |
| Largely intact functional activities |
| Not demented |

[a]Reprinted with permission from Petersen et al.[53]

prion disorders. As therapies are developed that target specific pathophysiologic processes, it will become increasingly important to establish the underlying disorder, particularly if these therapies have some degree of toxicity. Advancements in neuroimaging may allow identification of the dysfunctional proteins (e.g., tauopathy), which will very likely be more important than identifying the particular disorder (e.g., corticobasal degeneration vs. progressive supranuclear palsy).

Although most patients have features that fit into 1 of these syndromes, some have features that overlap with 2 or more syndromes, and many have additional features that evolve as their illness progresses. Parkinsonism or motor neuron disease (or both) can evolve in most of the syndromes. Readers are encouraged to review other resources for more comprehensive discussions on diagnosis and management in the non-Alzheimer dementias.[2,29]

## Amnestic Mild Cognitive Impairment

***Overview.*** Patients with anterograde memory impairment that has evolved insidiously and progressively worsened, but without sufficient impairment in social and occupational functioning and activities of daily living, likely have dysfunction in 1 or both mesial temporal lobes, which is consistent with the syndrome of amnestic mild cognitive impairment (MCI).[51–53] More recent work has expanded the concept of MCI to be further subtyped on the basis of which domains are impaired (i.e., single nonmemory domain MCI, multiple domain MCI with and without an amnestic component) and which etiology is underlying the impairment (e.g., degenerative, vascular, psychiatric).[54]

***Clinical features.*** The criteria for the clinical diagnosis of amnestic MCI are shown in Table 3.[51–54] Those with amnestic MCI tend to perform within the normal range of performance on screening and global mental status examinations (i.e., score 24 or greater on the Mini-Mental State Examination and 30 or greater on the Short Test of Mental Status), yet do poorly on neuropsychological measures of learning and particularly delayed recall.

***Neuropathologic features.*** The topographic distribution of pathology is degeneration of the mesial temporal lobes and/or basal forebrain, which explains why memory is impaired but other cognitive domains are preserved.[55,56]

***Clinical course.*** While some patients with amnestic MCI have a remarkably stable course of several years, approximately 80% of patients will develop dementia within 6 years from the onset of symptoms. Predictors of progression from MCI to dementia include the presence of at least 1 apolipoprotein ε4 allele, low hippocampal volumes on quantitative MRI, and poor performance on certain neuropsychological measures.[53]

***Differential diagnosis.*** While most individuals with amnestic MCI have evolving Alzheimer's disease, argyrophilic grains and neurofibrillary tangles restricted in the mesial temporal lobes have been identified in MCI patients who have undergone autopsy.[55,56] Pick's disease, frontotemporal lobar degeneration with ubiquitin-positive inclusions, dementia lacking distinctive histopathology, and corticobasal degeneration can rarely present with severe anterograde amnesia.[57]

***Evaluation.*** The clinical and neuropsychological features and absence of structural lesions on neuroimaging form the basis of the diagnosis in patients with memory concerns. One issue of debate is the degree of changes in activities of daily living allowable for the diagnosis to be applied (e.g., is forgetting to pay 2 bills over 6 months sufficient to label a patient as having dementia?)

***Management.*** Several therapeutic trials have either been recently completed or are currently in progress to test whether any agents improve cognition or delay or prevent progression to dementia. The largest and most publicized trial completed to date involved donepezil (10 mg/day), vitamin E (2000 IU/day), and placebo, in which donepezil was shown to delay the conversion from mild cognitive impairment to dementia by approximately 12 months.[58]

## Dementia of the Alzheimer Type

There are important differences between the syndrome of dementia of the Alzheimer type, which is sometimes termed Alzheimer-type dementia, and the disorder of Alzheimer's disease. The typical evolution of Alzheimer's disease evolves through the syndrome of amnestic mild cognitive impairment and subsequently develops into a cortical Alzheimer-type dementia with dysfunction in other cognitive domains (e.g., language, visuospatial, gnosis, and executive functioning). Yet, a variety of clinical syndromes can be manifested in Alzheimer's disease.

Alzheimer's disease is discussed in detail in the article by Caselli et al.[98]

## Frontotemporal Dementia

***Overview.*** Several terms have been applied to a progressive neurobehavioral syndrome reflecting frontotemporal-subcortical network dysfunction, with the term used most often being *frontotemporal dementia* (FTD). FTD is further subtyped as the behavioral-dysexecutive or frontal variant. A family history positive for dementia, parkinsonism, or motor neuron disease can often be elicited, and parkinsonism or motor neuron disease can develop in patients with FTD. Some excellent reviews on FTD can be found in references 41, 59, and 60. More information on FTD can be accessed on the Association for Frontotemporal Dementias Web site at http://www.ftd-picks.org.

***Clinical features.*** The consensus criteria for the diagnosis of frontotemporal dementia is shown in Table 4.[61] Patients with marked degeneration in the nondominant (usually right) frontotemporal cortex tend to exhibit more behavioral problems and neuropsychiatric features.[62,63]

***Neuropathologic features.*** The topographic distribution of pathology is uniformly degeneration of 1 (or more commonly both) frontal lobe, often with degeneration in 1 amygdala or both,[41] which explains why executive functioning and social behavior are impaired but other cognitive domains are typically preserved.

***Clinical course.*** Time from onset to death varies depending on the underlying disorder, with frontotemporal lobar degeneration with ubiquitin-positive inclusions and neurofilament inclusion body dementia typically evolving to death in 2 to 4 years, whereas most others evolve over 5 to 15 years.

***Differential diagnosis.*** Several disorders can present with features of frontotemporal dementia, including the tauopathies (e.g., Pick's disease, corticobasal degeneration, progressive supranuclear palsy, argyrophilic grain disease, multisystem tauopathy, and frontotemporal dementia and parkinsonism linked to chromosome 17 with a tau mutation) and the numerous nontauopathy disorders (e.g., frontotemporal lobar degeneration with ubiquitin-positive inclusions, dementia lacking distinctive histopathology, hippocampal sclerosis, FTDP-17 not linked to tau mutations, neurofilament inclusion body dementia, familial encephalopathy with neuroserpin inclusion bodies, and frontotemporal dementia, Paget's disease, and inclusion body myositis, and rarely Alzheimer's disease, Creutzfeldt-Jakob disease, and Huntington's disease. Lewy body disease can also present as frontotemporal dementia, but other features (e.g., REM sleep behavior disorder, visual hallucinations) are either coexisting or evolve later, allowing stronger suspicion of underlying Lewy body disease.

***Evaluation.*** The early onset of symptoms (often at 30–60 years of age), clinical features, neuropsychological findings, and frontotemporal pattern of atrophy on MRI, hypoperfusion on SPECT, or hypometabolism on PET usually allow easy diagnosis. Early in the course of symptoms, performance on screening tests such as the Mini-Mental State Examination and Short Test of Mental Status may be normal or even perfect. Yet many frontotemporal dementia patients have atypical features—normal performance on all neuropsychological tests including those sensitive to frontal lobe dysfunction, abnormal performance on memory and/or visuospatial tasks, normal findings or significant parietal lobe findings on neuroimaging, etc. Genetic testing may provide definitive diagnosis early in the disease course, even in patients without a family history suggesting an autosomal-dominant disorder.

***Management.*** Although numerous agents are being tested in the transgenic tau mice, no therapy has been developed that halts or delays the progression of neurodegeneration in the disorders that present with frontotemporal dementia. For symptomatic therapy, the results have been mixed with the selective serotonin reuptake inhibi-

**Table 4. Consensus (Neary) Criteria for Clinical Diagnosis of Frontotemporal Dementia[a]**

| |
|---|
| Core features |
| Insidious onset and gradual progression |
| Early decline in social interpersonal conduct |
| Early impairment in regulation of personal conduct |
| Early emotional blunting |
| Early loss of insight |
| Instrumental functions of perception, spatial skills, praxis, and memory are intact or relatively well preserved |
| Supportive features |
| Behavioral disorder |
| Decline in personal hygiene and grooming |
| Mental rigidity and inflexibility |
| Distractibility and impersistence |
| Hyperorality and dietary changes |
| Perseverative and stereotyped behavior |
| Utilization behavior |
| Speech and language |
| Altered speech output |
| Aspontaneity and economy of speech |
| Pressure of speech |
| Stereotype of speech |
| Echolalia |
| Perseveration |
| Mutism |
| Physical signs |
| Primitive reflexes |
| Incontinence |
| Akinesia, rigidity, and tremor |
| Low and labile blood pressure |
| Investigations |
| Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder |
| Electroencephalography: normal on conventional electroencephalogram despite clinically evident dementia |
| Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality |

[a]Reprinted with permission from Neary et al.[61]

**Table 5. Clinical Criteria for the Diagnosis of Primary Progressive Aphasia (core features)[a]**

| |
|---|
| Insidious onset and gradual progression of word finding, object-naming, or word-comprehension impairments as manifested during spontaneous conversation or as assessed through formal neuropsychological tests of language |
| All limitations of daily living activities are attributable to the language impairment, for at least 2 years after onset |
| Intact premorbid language function (except for developmental dyslexia) |
| Absence of significant apathy, disinhibition, forgetfulness for recent events, visuospatial impairment, visual recognition deficits or sensory-motor dysfunction within the initial 2 years of the illness |
| Acalculia and ideomotor apraxia may be present even in the first 2 years |
| Other domains possibly affected after the first 2 years but with language remaining the most impaired function throughout the course of the illness and deteriorating faster than other affected domains |
| Absence of "specific" causes such as stroke or tumor as ascertained by neuroimaging |

[a]Reprinted with permission from Mesulam.[70]

**Table 6. Clinical Criteria for the Diagnosis of Progressive Nonfluent Aphasia Syndrome[a]**

| |
|---|
| Core features |
| Insidious onset and gradual progression |
| Disorder of expressive language is the dominant feature initially and throughout the disease course |
| Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, anomia |
| Other aspects of cognition are intact or relatively well preserved |
| Supportive features |
| Speech and language |
| Stuttering or oral apraxia |
| Impaired repetition |
| Alexia, agraphia |
| Early preservation of word meaning |
| Late mutism |
| Behavior |
| Early preservation of social skills |
| Late behavioral changes similar to frontotemporal dementia |
| Physical signs |
| Late contralateral primitive reflexes, akinesia, rigidity, and tremor |
| Investigations |
| Neuropsychology: nonfluent aphasia in the absence of severe amnesia or perceptuospatial disorder |
| Electroencephalography: normal or minor asymmetric slowing |
| Brain imaging (structural and/or functional): asymmetric abnormality predominantly affecting dominant (usually left) hemisphere |

[a]Reprinted with permission from Neary et al.[61]

tors,[64] particularly paroxetine,[65,66] for managing problematic neuropsychiatric features. Trazodone has recently been shown to be efficacious in many and generally well tolerated.[67] In an open-label trial with rivastigmine, there was improvement in neuropsychiatric features and caregiver burden in patients with frontotemporal dementia.[68] The atypical neuroleptics, particularly quetiapine, are increasingly being used to manage problem behaviors in frontotemporal dementia.

## The Progressive Aphasia Syndromes: Primary Progressive Aphasia, Progressive Nonfluent Aphasia, and Semantic Dementia

***Overview.*** In 1982, Mesulam first described a series of patients who had aphasia without dementia and later termed this entity *primary progressive aphasia*.[69,70] The groups from Europe proposed somewhat different terms: *progressive nonfluent aphasia* and *semantic aphasia* and *associative agnosia*; the latter term has been changed to *semantic dementia*.[61] The clinical presentations fall into 2 main categories that are separable by fluency. Patients categorized as having progressive nonfluent aphasia and primary progressive aphasia typically have nonfluent aphasia, often have apraxia of speech and nonverbal oral apraxia, and have a striking tendency to say "yes" for "no" and vice versa. They may or may not be anomic for objects. Patients with fluent aphasia typically have marked dysnomia. Semantic dementia refers to those with fluent aphasia plus loss of word meaning (and hence agnosia) for words spoken aloud and given in writing, and imaging studies show prominent atrophy in the dominant temporal lobe (most evident in the anterior inferolateral temporal cortex). More information on primary progressive aphasia, progressive nonfluent aphasia, and semantic dementia can be accessed on the Association for Frontotemporal Dementias Web site at http://www.ftd-picks.org/?p=diseases/progressiveaphasia and on the Northwestern University's Web site for primary progressive aphasia at http://www.brain.northwestern.edu/ppa/.

***Clinical features.*** The criteria for the clinical diagnoses of primary progressive aphasia, progressive nonfluent aphasia, and semantic dementia are shown in Tables 5 through 7, respectively. Although not readily evident from these criteria, most or all cases of progressive nonfluent aphasia would also be considered consistent with primary progressive aphasia, whereas only some cases meeting criteria for semantic dementia would also be considered consistent with primary progressive aphasia. Some patients can develop features of frontotemporal dementia and corticobasal syndrome, atypical parkinsonism, motor neuron disease, or some combination of these.

***Neuropathologic features.*** The topographic distribution of pathology is degeneration of frontal and/or temporal cortex in the dominant hemisphere. In progressive nonfluent aphasia, degeneration tends to be maximal in the insula or frontal opercular region, and in semantic dementia, degeneration is maximal in the anterior inferolateral temporal cortex.

***Clinical course.*** The course is similar to frontotemporal dementia.

***Differential diagnosis.*** The same spectrum of disorders that underlie frontotemporal dementia can present as a progressive aphasia syndrome.

**Table 7. Clinical Criteria for the Diagnosis of Semantic Dementia[a]**

- Core features
  - Insidious onset and gradual progression
  - Language disorder characterized by
    - Progressive, fluent, empty spontaneous speech
    - Loss of word meaning, manifest by impaired naming and comprehension
    - Semantic paraphasias
    - and/or
  - Perceptual disorder characterized by
    - Prosopagnosia: impaired recognition of identity of familiar faces, and/or
    - Associative agnosia: impaired recognition of object identity
  - Preserved perceptual matching and drawing reproduction
  - Preserved single-word repetition
  - Preserved ability to read aloud and write to dictation orthographically regular words
  - Autobiographic memory is intact or relatively well preserved
- Supportive features
  - Speech and language
    - Pressure of speech
    - Idiosyncratic word usage
    - Absence of phonemic paraphasias
    - Surface dyslexia and dysgraphia
    - Preserved calculation
  - Behavior
    - Loss of sympathy and empathy
    - Narrowed preoccupations
    - Parsimony
  - Physical signs
    - Absent or late primitive reflexes
    - Akinesia, rigidity, and tremor
  - Investigations
    - Neuropsychology
      - Profound semantic loss, manifest in failure of word comprehension and naming and/or face and object recognition
      - Preserved phonology and syntax and elementary perceptual processing, spatial skills, and day-to-day memorizing
    - Electroencephalography
      - Normal
    - Brain imaging (structural and/or functional)
      - Predominant anterior temporal abnormality (symmetric or asymmetric)

[a]Reprinted with permission from Neary et al.[61]

***Evaluation.*** The clinical, neuropsychologic, and radiologic features usually allow easy recognition and diagnosis. While most patients with progressive aphasia complain of memory problems, anterograde memory functioning is typically preserved, whereas impairment in language functioning is more obvious. Performance on tests of confrontational naming is usually very poor in semantic dementia. Letter and/or semantic fluency are usually impaired in primary progressive aphasia and progressive nonfluent aphasia. The topography of atrophy and hypoperfusion/hypometabolism on neuroimaging studies mirrors that described in the distribution of histopathologic degeneration, although those with primary progressive aphasia and progressive nonfluent aphasia may have little or no focal cortical atrophy. Genetic testing may also be revealing in select patients.

**Table 8. Criteria for the Clinical Diagnosis of the Corticobasal Syndrome[a]**

- Core features
  - Insidious onset and progressive course
  - No identifiable cause (eg, tumor, infarct)
  - Cortical dysfunction as reflected by at least 1 of the following:
    - Focal or asymmetrical ideomotor apraxia
    - Alien limb phenomenon
    - Cortical sensory loss
    - Visual or sensory hemineglect
    - Constructional apraxia
    - Focal or asymmetric myoclonus
    - Apraxia of speech/nonfluent aphasia
  - Extrapyramidal dysfunction as reflected by at least 1 of the following:
    - Focal or asymmetrical appendicular rigidity lacking prominent and sustained L-dopa response
    - Focal or asymmetrical appendicular dystonia
- Supportive investigations
  - Variable degrees of focal or lateralized cognitive dysfunction, with relative preservation of learning and memory, on neuropsychometric testing
  - Focal or asymmetric atrophy on computed tomography or magnetic resonance imaging, typically maximal in parietofrontal cortex
  - Focal or asymmetric hypoperfusion on single photon emission-computed tomography and positron emission tomography, typically maximal in parietofrontal cortex/basal ganglia/thalamus

[a]Reprinted with permission from Boeve et al.[7]

***Management.*** There is no established treatment for patients with primary progressive aphasia, progressive nonfluent aphasia, or semantic dementia. Bromocriptine was modestly beneficial in a small number of patients with primary progressive aphasia.[71] Speech therapy is appropriate for most patients, but the benefits are variable. For those with moderate to severe nonfluent aphasia and preserved functioning in other cognitive domains, therapy with communication devices may be worthwhile. No drug treatment has been shown to improve agnosia in patients with semantic dementia.

## Corticobasal Syndrome

***Overview.*** Due to the pathologic heterogeneity of patients presenting with the core syndrome of progressive asymmetrical rigidity and apraxia, the term *corticobasal syndrome* is increasingly being used. Information on the phenotype of corticobasal syndrome and the disease of corticobasal degeneration can be accessed at these Web sites: http://www.ftd-picks.org/?p=diseases/corticobasal degeneration and http://www.tornadodesign.com/cbgd/.

***Clinical features.*** The clinical criteria for the diagnosis of the corticobasal syndrome are shown in Table 8.[7]

***Neuropathologic features.*** The topographic distribution of pathology is degeneration of parietofrontal cortex, often associated with degeneration in the striatum and substantia nigra.[8] The cerebral cortical atrophy can be symmetric but is often asymmetric.

***Clinical course.*** Duration of symptoms varies from 2 to 15 years, most often in the 5 to 8 year range. Rarely, motor neuron disease can develop, but more commonly

features of frontotemporal dementia, progressive aphasia, or posterior cortical atrophy evolve as the disorder progresses.

***Differential diagnosis.*** The same spectrum of disorders that underlie the frontotemporal dementia and progressive aphasia syndromes can present as corticobasal syndrome, with the exceptions of familial encephalopathy with neuroserpin inclusion bodies, frontotemporal dementia with Paget's disease and inclusion body myositis, and Huntington's disease not being observed to date.

***Evaluation.*** The clinical features are striking, and in the absence of any structural lesion on neuroimaging studies, diagnosis is straightforward to the trained eye. Many of the clinical findings are similar to those seen following a middle cerebral artery distribution infarct, but the slowly progressive course and absence of infarct on CT and MRI are the distinctive features. The typical neuropsychologic and radiologic findings are described in Table 8.

***Management.*** The only report to consider specifically the effect of various pharmacologic interventions in patients with corticobasal syndrome is that of Kompoliti et al., in which no agent was found to provide a consistent and prolonged benefit for any symptom or sign.[72] Yet, some patients may experience mild improvement in parkinsonism with carbidopa/levodopa, and improvement in myoclonus has been observed with valproic acid and clonazepam. Physical, occupational, and speech therapy are warranted, as are handicapped privileges. A motorized scooter or wheelchair can enhance independence and minimize falls but can be difficult to obtain through federal and private payors. A technique known as constraint-induced movement therapy has been beneficial for some patients.

## Posterior Cortical Atrophy

***Overview.*** Posterior cortical atrophy refers to the syndrome associated with dysfunction in the posterior cortical networks; dysfunction can occur in the ventral or "what" pathway and/or the dorsal or "where" pathway.[47,73] Involvement of the dorsal pathway is typically manifested as simultanagnosia (the inability to grasp the gestalt of a visual image) or Balint syndrome (simultanagnosia, optic ataxia, and ocular apraxia). Involvement of the ventral pathway is usually manifested as visual agnosia. Other features include micropsia (images appear smaller than they actually are), macropsia (images appear larger than they actually are), metamorphopsia (images appear to change shape or texture), illusions (objects appear to be images different from the actual objects, for example, perceiving a lamp as a person), and hallucinations. Several other terms have been used to describe these conditions, including *progressive visuoperceptual syndrome*, *progressive posterior cortical syndrome*, *progressive posterior cortical dysfunction*, *progressive simultanagnosia/Balint syndrome*, and *the visual variant of Alzheimer's disease*.[73]

**Table 9. Criteria for the Clinical Diagnosis of Posterior Cortical Atrophy[a]**

| |
|---|
| Core features |
| Insidious onset and gradual progression |
| Presentation of visual complaints in the absence of significant primary ocular disease explaining the symptoms |
| Relative preservation of anterograde memory and insight early in the disorder |
| Disabling visual impairment throughout the disorder |
| Absence of stroke or tumor |
| Absence of early parkinsonism and hallucinations |
| Any of the following findings: |
| Simultanagnosia with or without optic ataxia or ocular apraxia |
| Constructional dyspraxia |
| Visual field defect |
| Environmental disorientation |
| Any of the elements of Gerstmann syndrome |
| Supportive features |
| Alexia |
| Presenile onset |
| Ideomotor or dressing apraxia |
| Prosopagnosia |
| Investigations |
| Neuropsychological deficits referable to parietal and/or occipital regions |
| Focal or asymmetric atrophy in parietal and/or occipital regions on structural imaging |
| Focal or asymmetric hypoperfusion/hypometabolism in parietal and/or occipital regions on functional imaging |

[a]Reprinted with permission from Tang-Wai et al.[73]

These patients typically present to ophthalmologists, often undergoing repeated refraction yet symptoms persist.

***Clinical features.*** The clinical criteria for the diagnosis of posterior cortical atrophy are shown in Table 9.[73] Patients tend to be female, have onset prior to age 65, and the clinical course is usually very long—well over 10 years. Despite the prominent parieto-occipital pathology in cases with posterior cortical atrophy, visual hallucinations are rare.[73]

***Neuropathologic features.*** The topographic distribution of pathology is degeneration of parieto-occipital cortex, which can be symmetric but is often asymmetric.[73]

***Clinical course.*** Duration of symptoms varies from 3 to 20 years, most often in the 8 to 15 year range. Rarely, parkinsonism can develop, but motor neuron disease almost never evolves. Many patients with posterior cortical atrophy develop features of the corticobasal syndrome over time.

***Differential diagnosis.*** In typical Alzheimer's disease, the neuritic plaques and neurofibrillary tangles are rarely most dense in the posterior cerebrum, but in patients with posterior cortical atrophy, Alzheimer's disease has been the most frequently identified histopathologic process. Alzheimer's disease with Lewy body disease, nonspecific histopathology, progressive subcortical gliosis, corticobasal degeneration, fatal familial insomnia, and Creutzfeldt-Jakob disease have also been reported.[73]

***Evaluation.*** Since memory and insight are preserved early in the course, patients rarely seek evaluation with or

  

are referred to neurologists. Hence, recognition of posterior cortical atrophy often relies on the clinical acumen of a sharp optometrist or ophthalmologist, or the development of other symptoms referable to brain dysfunction leading to referral to a neurologist. The diagnosis depends on findings on clinical examination, neuropsychological testing, and neuroimaging studies. Table 9 shows the core and supportive features.

***Management.*** No therapy has been shown to improve any of the core posterior cortical atrophy features, but the atypical neuroleptics can be effective for managing hallucinations and delusions and antidepressant agents can be used for depression (which is common in this syndrome because insight is often preserved). Some have found that placement of colored marks on kitchen items can help them orient where to place their thumb and fingers so that they can hold and use objects correctly (e.g., coffee cup, telephone). Recognition is critical so that patients and their families can be counseled about the danger of patients walking in public alone, which is being struck by cars that they do not see, and about voluntarily discontinuing driving, also to avoid accidents.

## Dementia With Lewy Bodies

***Overview.*** The syndrome most often associated with limbic- and neocortical-predominant Lewy body disease is termed *dementia with Lewy bodies*. Other clinical terms include *Lewy body dementia*, *the Lewy body variant of Alzheimer's disease*, *diffuse Lewy body disease*, *cortical Lewy body disease*, and *senile dementia of the Lewy type*.

***Clinical features.*** The most recently modified criteria for the clinical diagnosis of dementia with Lewy bodies are shown in Table 10.[25,74] REM sleep behavior disorder is often present in dementia with Lewy bodies, typically preceding the cognitive and neuropsychiatric features by many years, and the presence of REM sleep behavior disorder may be a particularly specific feature of dementia with Lewy bodies in the setting of dementia.[75–78] Besides the cognitive, neuropsychiatric, and motor features of dementia with Lewy bodies, patients often have sleep disorders in addition to REM sleep behavior disorder, and autonomic dysfunction is common as well.[78,79] Additional information on dementia with Lewy bodies can be found at the excellent Lewy Body Dementia Association Web site at www.lewybodydementia.org.

***Neuropathologic features.*** Limbic- or neocortical-predominant Lewy body disease is the most common disorder underlying the syndrome of dementia with Lewy bodies.[24,25] The neurochemical alterations in Lewy body disease are more marked than in Alzheimer's disease, yet there is less hippocampal and whole brain atrophy in Lewy body disease, underscoring the potential impact of pharmacotherapies.[24,78,80]

***Clinical course.*** Early reports on dementia with Lewy bodies suggested that the disease course was more rapid than in Alzheimer's disease, but recent survival analyses indicate that the mean duration of symptoms between dementia with Lewy bodies and Alzheimer's disease are similar. Some have a remarkably slow course.

***Differential diagnosis.*** While Lewy body disease with or without Alzheimer's disease-type is by far the most common underlying substrate in dementia with Lewy bodies, pure Alzheimer's disease as well as progressive supranuclear palsy and slowly progressive Creutzfeldt-Jakob disease can present as dementia with Lewy bod-

**Table 10. Criteria for the Clinical Diagnosis of Dementia With Lewy Bodies (DLB): Third Report of the DLB Consortium or "McKeith" Criteria[a]**

| |
|---|
| Central feature |
| Progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent. |
| Core features (2 core features essential for a diagnosis of probable DLB, 1 for possible DLB) |
| Fluctuating cognition with pronounced variations in attention and alertness |
| Recurrent visual hallucinations that are typically well formed and detailed |
| Spontaneous features of parkinsonism |
| Suggestive features (1 or more present in addition to 1 or more core features is sufficient for a diagnosis of probable DLB, and in the absence of any core features is sufficient for possible DLB) |
| REM sleep behavior disorder (which may precede onset of dementia by several years) |
| Severe neuroleptic sensitivity |
| Abnormal (low uptake) in basal ganglia on SPECT or PET dopamine transporter scans |
| Supportive features (commonly present but not proven to have diagnostic specificity) |
| Repeated falls and syncope |
| Transient, unexplained loss of consciousness |
| Severe autonomic dysfunction, eg, orthostatic hypotension, urinary incontinence |
| Hallucinations in other modalities |
| Systematized delusions |
| Depression |
| Relative preservation of medial temporal lobe structures on CT/MRI scan |
| Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity |
| Abnormal (low uptake) MIBG myocardial scintigraphy |
| Prominent slow wave activity on EEG with temporal lobe transient sharp waves |
| A diagnosis of DLB is *less likely*: |
| In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging |
| In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture |
| If parkinsonism only appears for the first time at a stage of severe dementia |

[a]Reprinted with permission from McKeith et al.[74]
Abbreviations: CT = computed tomography, EEG = electroencephalogram, MIBG = metaiodobenzylguanidine, MRI = magnetic resonance imaging, PET = positron emission tomography, REM = rapid eye movement, SPECT = single photon emission-computed tomography.



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Table 11. Pharmacologic Management of Target Symptoms of Dementia

| Target Symptom | Preferred Class of Agents | Other Agents |
|---|---|---|
| Cognitive | | |
| Amnesia/forgetfulness | AChEI*, memantine | C/L, DA, PS |
| Aphasia | DA | |
| Apraxia | C/L, DA | |
| Executive dysfunction | AChEI* | C/L, DA, memantine, PS |
| Noncognitive | | |
| Agitation/aggression | AN*, SSRI* | AChEI*, BZD, MS |
| Anxiety | SSRI*, AN | BZD, AChEI |
| Apathy | AChEI*, SSRI (with stimulating properties) | PS, C/L, DA |
| Depression | SSRI* | AN, AChEI |
| Delusions | AN*, SSRI | AChEI |
| Disinhibition | AN, SSRI | AChEI, MS |
| Emotional lability | SSRI* | Dextromethorphan/quinidine* |
| Hallucinations | AN*, AChEI*, SSRI* | melatonin |
| Hyperphagia | AED (topiramate) | AN, AchEI |
| Hypersomnia | AChEI, SSRI (with stimulating properties) | PS |
| Insomnia | SSRI (with sedating properties), trazodone, S/H | melatonin, AN |
| Parasomnia | Melatonin*, clonazepam | AN |

*Efficacy has been demonstrated in open-label or randomized clinical trials.
Abbreviations: AChEI = acetylcholinesterase inhibitors, AED = antiepileptic drug, AN = atypical neuroleptic, BZD = benzodiazepine, C/L = carbidopa/levodopa, DA = dopamine agonist, MS = mood stabilizer, PS = psychostimulant, S/H = sedative/hypnotic, SSRI = selective serotonin reuptake inhibitor.

ies.[24,78] The autoimmune encephalopathies are an important group of potentially treatable disorders that can present as subacute or rapidly progressive dementia with Lewy bodies.[81]

***Evaluation.*** Neuropsychological testing in dementia with Lewy bodies typically shows maximal impairment in verbal fluency and visuospatial functioning with relative preservation in verbal memory and confrontation naming.[82–84] The hippocampi are usually minimally atrophic on MRI compared to Alzheimer's disease.[85,86] Electroencephalography tends to show moderate to severe diffuse slowing, and functional neuroimaging studies have tended to show maximal abnormalities in parieto-occipital cortices. The presence of REM sleep behavior disorder is a moderately sensitive but very specific feature for underlying Lewy body disease in the dementia with Lewy bodies syndrome, and thus polysomnography may provide diagnostic data in challenging cases.[76–78]

***Management.*** Cholinesterase inhibitors are the mainstay of management, with modest to marked improvement often seen in the cognitive and neuropsychiatric features and usually no impact on the motor features.[87,88] Other treatments depend on the severity of symptoms. The atypical neuroleptics, memantine, and/or anticonvulsants can be used to manage challenging neuropsychiatric problems.[78] Depression is very common and usually responds well to selective serotonin reuptake inhibitors. For parkinsonism, standard carbidopa/levodopa administered 3 to 4 times daily on an empty stomach is most effective and best tolerated; dopamine agonists are generally too cumbersome to use in dementia with Lewy bodies. Management of sleep disorders includes critical continuous positive airway pressure for obstructive sleep apnea, bilevel positive airway pressure with or without oxygen for central sleep apnea, clonazepam or melatonin for REM sleep behavior disorder, and psychostimulants for daytime hypersomnolence.[78] Autonomic dysfunction can be disabling in some patients, particularly orthostatic hypotension. Orthostatic hypotension can be managed by elevating the head of the bed 30 degrees, using thigh-high stockings or abdominal binders, increasing salt intake, and using midodrine and/or fludrocortisone.[78]

## Parkinson Disease With Dementia

***Overview.*** Some degree of cognitive impairment often exists in patients with Parkinson's disease, but this is usually not functionally disabling early in the course of the illness. However, approximately 80% of Parkinson's disease patients develop dementia within 8 years.[89] Other than the timing of when motor features evolve, almost every other aspect of Parkinson's disease with dementia is similar to dementia with Lewy bodies, including the cognitive/neuropsychiatric/sleep/autonomic features, neuropsychological profile of impairment, and radiologic features. The distribution of Lewy body and Lewy neurite pathology and neurochemical alterations in dementia with Lewy bodies are also very similar to those in Parkinson's disease with dementia, and management is similar regardless of the clinical diagnosis. Thus, many regard dementia with Lewy bodies and Parkinson's disease with dementia to be variants of a similar pathophysiologic process, but Parkinson's disease with dementia is being discussed as a separate entity in this article based on historical grounds.

***Clinical features.*** Despite the wide acceptance that dementia often evolves in Parkinson's disease, there are no published consensus criteria for the diagnosis of Parkinson's disease with dementia. Since the diagnosis of dementia with Lewy bodies has been considered appli-

  

cable to patients who develop dementia no more than 1 year after the onset of parkinsonism, one could view the diagnosis of Parkinson's disease with dementia as appropriate for those who develop dementia at least 1 year after the onset of parkinsonism.

***Neuropathologic features.*** The neuropathologic features have been described in detail elsewhere,[90] and are identical to those found underlying dementia with Lewy bodies.

***Clinical course.*** While rapidly progressive Parkinson's disease with dementia can occur, the duration of symptoms is often protracted, with some individuals having neurologic symptoms in excess of 20 years.

***Differential diagnosis and evaluation.*** Differential diagnosis and evaluation are similar to those of dementia with Lewy bodies (see previous section).

***Management.*** Management is also similar to dementia with Lewy bodies. Rivastigmine and perhaps other cholinesterase inhibitors are most important in the management of the cognitive and neuropsychiatric features of Parkinson's disease with dementia.

## MANAGEMENT OF TARGET SYMPTOMS IN DEMENTIA

No therapy is available that directly alters the pathophysiologic processes in the various degenerative and prion disorders that cause dementia. Thus, management is tailored toward target symptoms. Many of the studies involving pharmacotherapies have been focused on patients with clinically suspected Alzheimer's disease, yet these agents may be helpful in the management of non-Alzheimer disorders as well. A summary of the target symptoms and classes of agents clinicians should consider for each symptom is shown in Table 11. Readers are encouraged to review more detailed articles and texts on the management of problematic symptoms and behaviors in dementia.[2,91–93]

*Drug names:* bromocriptine (Parlodel and others), carbidopa/levodopa (Sinemet, Carbilev, and others), clonazepam (Klonopin and others), donepezil (Aricept), fludrocortisone (Florinef and others), memantine (Namenda), midodrine (Proamatine, Orvaten, and others), minocycline (Dynacin, Minocin, and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), rivastigmine (Exelon), topiramate (Topamax and others), valproic acid (Depakene, Myproic Acid, and others).

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*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Focus on Alzheimer's Disease and Related Disorders section. Please contact Eric M. Reiman, M.D., at Eric.Reiman@bannerhealth.com.