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considered independently. Interactions between cerebrovascular and neurodegenerative processes may also contribute to dementia. Such interactions might involve loss of blood-brain barrier integrity (pos sibly allowing brain penetration of neurotoxic or inflammatory agents) and impaired clearance of β-amyloid or other pathogenic molecules from the brain (postulated to occur along perivascular drainage path ways driven by physiologic vascular motion). APPROACH TO THE PATIENT Vascular Dementia Identifying vascular contributors to a patient's cognitive impair ment can clarify the etiologic diagnosis and point to specific interventions aimed at slowing progression. Clinical evaluation is focused on identifying vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, tobacco use, atrial fibrillation, coronary artery disease, or peripheral vascular disease), history of prior symptoms of stroke or transient ischemic attack, and family history of early stroke or vascular disease. Although stepwise progression and certain cognitive deficits such as loss of executive function are particularly suggestive, most individuals with VCID follow the more typical pattern of gradual progression of impaired episodic memory. The mainstay for detection and subtyping of cerebrovascular disease is brain MRI. The MRI should include FLAIR, diffusionweighed, and T2∗-weighted sequences to detect the range of lesions noted above: large and small chronic infarcts, acute microinfarcts, microbleeds, and white matter hyperintensities. Vessel imaging studies such as computed tomography or magnetic resonance angi ography are not required for initial evaluation of cognitive impair ment, though they may be useful for determining the cause of any macroscopic infarcts that are identified. Genetic testing for rare hereditary forms of VCID such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Chap. 438) or hereditary cerebral amyloid angiopathy can be considered for cases in which there is a particularly young onset, positive family history, or suggestive neuroimaging, but is otherwise unnecessary. TREATMENT Vascular Dementia Very few trials have addressed the optimal treatment for individuals with asymptomatic large- or small-vessel cerebrovascular disease, leaving uncertainty as to whether to follow primary or secondary stroke prevention guidelines. At a minimum, treatment should assiduously follow primary stroke prevention guidelines. The American Heart Association recommends the prudent approach for vascular health of managing blood pressure, controlling choles terol, reducing blood sugar, maintaining an active lifestyle, adhering to a heart-healthy diet, losing weight, discontinuing tobacco, and getting healthy sleep (Life's Essential 8, https://www.heart.org/en/ healthy-living/healthy-lifestyle/lifes-essential-8). Blood pressure tar gets are <140/90 mmHg for all individuals and <130/80 mmHg for those with estimated 10-year cardiovascular disease risk ≥10%,

which likely applies to many individuals with imaging evidence of asymptomatic brain infarcts or advanced small-vessel disease. The usefulness of other treatments for secondary stroke prevention such as antiplatelet or statin therapy has not been established for asymp tomatic infarcts. These agents are reasonable to consider, however, when the imaging appearance suggests embolic or large-vesselrelated strokes. All individuals with asymptomatic infarcts should be screened for atrial fibrillation, and those with embolic-appearing infarcts can be considered for prolonged cardiac monitoring. Simi larly, patients with infarcts in the territories of large arteries should be considered for vascular imaging. The few trials of symptomatic medications for cognitive impair ment due to vascular etiologies have suggested modest cognitive

benefits comparable to those found in Alzheimer's disease patients. Therefore, it may be reasonable in VCID to consider agents such as the cholinesterase inhibitors donepezil, rivastigmine, or galan tamine for mild to moderate cognitive impairment and high-dose donepezil or the N-methyl-d-aspartate receptor antagonist meman tine for moderate to severe impairment (Chap. 442). A shared decision-making approach in considering these medications is use ful, given their relatively small impact on daily function.

■ ■FURTHER READING Boyle PA et al: Person-specific contribution of neuropathologies to cognitive loss in old age. Ann Neurol 83:74, 2018. Corriveau RA et al: The science of vascular contributions to cogni tive impairment and dementia (VCID): A framework for advancing research priorities in the cerebrovascular biology of cognitive decline. Cell Mol Neurobiol 36:281, 2016. Dichgans M, Leys D: Vascular cognitive impairment. Circ Res CHAPTER 445 120:573, 2017. Düering M et al: Neuroimaging standards for research into small ves sel disease-advances since 2013. Lancet Neurol 22:602, 2023. Greenberg SM et al: Cerebral amyloid angiopathy and Alzheimer dis ease: One peptide, two pathways. Nat Rev Neurol 16:30, 2020. Levine DA et al: Trajectory of cognitive decline after incident stroke. Dementia with Lewy Bodies JAMA 314:41, 2015. Smith EE et al: Prevention of stroke in patients with silent cerebro vascular disease: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 48:e44, 2017. Snowdon DA et al: Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 277:813, 1997. Vermeer SE et al: Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 348:1215, 2003. Irene Litvan, William W. Seeley,

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Dementia with

Lewy Bodies Lewy body disease (LBD), manifesting as Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB), is the second most com mon cause of neurodegenerative dementia, after Alzheimer's disease (AD) (Chap. 442). Approximately 10% of patients with Parkinson's disease (PD) develop PDD per year, with the majority of PD patients developing PDD over time. The incidence of DLB is ~7 per 100,000 person-years. The prevalence of both PDD and DLB increases with aging, and both affect men more often than women. The development of increasingly useful biomarkers for PD and DLB is making possible new operational definitions, classifications, and staging for these disor ders, and these are likely to continue to evolve over time. CLINICAL MANIFESTATIONS Most investigators conceptualize PDD and DLB as points on a spec trum of LBD pathology. Cognitively, PDD and DLB usually manifest with severe executive,

attentional, and visuospatial deficits but pre served episodic memory. Cognitive decline in LBD affects performance of daily living activities beyond other PD symptoms. Early psychosis including well-formed visual hallucinations, fluctuating cognition, rapid eye movement sleep behavior disorder (RBD), and parkinson ism are the main diagnostic features in DLB. The sense of a presence behind the person may precede well-formed hallucinations. Delusions

are less frequent than hallucinations and are usually related to mis identification, infidelity, theft, or persecution. Fluctuating attention and concentration are other characteristic features. Minor day-to-day variation in cognitive functioning is common across dementias, but in DLB, these fluctuations can be marked, with short periods of confusion or severe lethargy that may rapidly resolve. Patients with PDD and DLB are highly sensitive to infectious or metabolic disturbances. The first manifestation of DLB in some patients is delirium, often precipitated by an infection, new medicine, or other systemic disturbance. Parkin sonism in DLB is usually associated with early postural instability and can present early or later in the course. RBD is a characteristic, often prodromal, feature. Normally, dreaming is accompanied by skeletal muscle paralysis, but patients with RBD enact dreams, often violently, leading to injuries to themselves or their bed partners. Both PDD and DLB may be accompanied or preceded by anosmia, constipation, RBD, depression, and anxiety.

The symptom profile in DLB and PDD can provide clues for the differential diagnosis at the clinic. Clinically, the time interval between parkinsonism and dementia differentiates PDD and DLB. PDD presents in patients with long-standing PD, who manifest dementia often with visual hallucinations, fluctuating attention or alertness, and RBD. On the other hand, when the dementia and the neuropsychiatric symptoms precede or co-emerge with the parkinsonism, the patient is diagnosed with DLB. Patients with DLB, more frequently than those with PDD, also have AD co-pathology, making the prediction of underlying pathol ogy challenging for clinicians. Episodic memory disturbance points to the diagnosis of comorbid AD. Orthostatic hypotension that can lead to syncopal events, erectile dysfunction, and constipation can be present early in DLB, at times making it challenging to differentiate DLB from multiple system atrophy (MSA). In MSA, the autonomic disturbances occur early and are usually more severe than in DLB, and cognition is relatively preserved. Anosmia is also more characteristic of LBD than MSA. Skin biopsy and serum with biomarkers for α-synuclein oligomers, a major component of Lewy bodies, have shown potential for differentiating PD from MSA, and if validated for clinical use, this type of test may also differentiate DLB or PDD from MSA in the future. PART 13 Neurologic Disorders ■ ■PRODROMAL PHASE Both DLB and PDD have a prodromal phase where patients have a mild cognitive impairment (MCI), with cognitive deficits that do not have a substantial impact on daily life. PD-MCI is characterized by def icits in executive, attention, and visuospatial disturbances, but can also present with an amnestic or multiple-domain MCI. Prodromal DLB is characterized by similar cognitive disturbances but is also associated with either hallucinations unrelated to medications, RBD, fluctuations in attention, or parkinsonism. It is at times challenging to differentiate prodromal MCI-DLB and PD-MCI when the major features are RBD and parkinsonism, for which the term prodromal MCI–Lewy body (MCI-LB) was recently proposed. RBD may precede the development of an LBD-related syndrome by many years, usually evolving into either PD or DLB. The clinical profile and several biomarkers can help differentiate MCI due to LBD versus AD pathology (Table 445-1). PATHOLOGY The key neuropathologic feature in LBD is the presence of Lewy bod ies and Lewy neurites throughout specific brainstem nuclei, substan tia nigra, amygdala, cingulate gyrus, and,

ultimately, the neocortex. Lewy bodies are intraneuronal cytoplasmic inclusions that stain with periodic acid–Schiff (PAS) and ubiquitin but are now identified with antibodies to the presynaptic protein α-synuclein. Lewy bodies are composed of straight neurofilaments 7–20 nm long with surrounding amorphous material and contain epitopes recognized by antibodies against phosphorylated and nonphosphorylated neurofilament pro teins, ubiquitin, and α-synuclein. The presence of α-synuclein aggre gates in neurons and glia in PDD and DLB molecularly classifies these diseases as synucleinopathies. In general, neuronal and synaptic loss, rather than Lewy pathology per se, best predicts the clinical deficits. Formal criteria identify three stages of progression: (1) brainstem predominant; (2) transitional limbic; and (3) diffuse neocortical.

TABLE 445-1 Distinguishing MCI Due to Lewy Body Disease or Alzheimer’s Disease CLINICAL FEATURES PRODROMAL MCI-LB PATHOLOGY PRODROMAL MCI-AD PATHOLOGY MCI MCI usually affecting executive, attention, and/or visuospatial functions MCI with impaired memory and semantic naming Fluctuating cognition with variations in attention Frequent and severe Rare or not severe Sleep REM sleep behavior disorder Insomnia, frequent awakenings Recurrent visual hallucinations Frequent Rare Biomarkers Polysomnogram REM sleep behavior disorder without atonia Normal CSF Decreased CSF α-synuclein by RT-QuIC Decreased CSF β-amyloid and increased phospho-tau. This can now be performed in blood. MRI Atrophy of the amygdala Atrophy of the parahippocampal/ hippocampal areas 18F-deoxyglucose PET scan Hypometabolism in occipital lobe and increased in posterior cingulate (cingulate island sign) Hypometabolism in parietotemporal lobes Amyloid PET scan Normal, unless associated with AD Abnormal parietotemporal areas MIBG myocardial scintigraphy Postganglionic sympathetic denervation Normal DAT scan or PET dopamine scan Reduced dopamine transporter in the basal ganglia, particularly putamen Normal Abbreviations: AD, Alzheimer’s disease; CSF, cerebrospinal fluid; DAT, dopamine transporter; LB, Lewy bodies; MCI, mild cognitive impairment; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography; REM, rapid eye movement; RT-QuIC, real-time quaking-induced conversion. Importantly, healthy older individuals may also show isolated scattered Lewy body pathology in the substantia nigra, amygdala, or olfactory bulb. Pathologic studies have shown that PD usually starts in the enteric nervous system and spreads through the vagus nerve to the heart, lower brainstem, substantia nigra, limbic system, and lastly the cerebral cortex. PD may also begin in the olfactory bulb and spread through olfactory system connections or start independently in enteric and olfactory bulb areas. Evidence from human anatomic pathology and animal models suggests that LBD may similarly propagate via a prionlike mechanism. Abnormally folded α-synuclein aggregates propagate transneuronally following connection pathways of the nervous system. This pathologic propagation from the periphery to the brain correlates with the evolution of clinical symptoms; PD usually manifests first with nonmotor features characterized by constipation and/or hypos mia, followed by anxiety, depression, RBD, parkinsonism, and lastly dementia. PDD is manifested clinically when limbic and cortical areas are involved. A profound cholinergic deficit, owing to basal forebrain and pedun culopontine nucleus involvement, is present in most patients with DLB and may be associated with the characteristic fluctuations, inattention, and visual hallucinations. Adrenergic deficits from locus coeruleus involvement further undermine arousal and alerting. PATHOGENESIS Both genes and environmental factors are thought to contribute to the development of LBD. The presence of α-synuclein aggregates in Lewy bodies led to the discovery of α-synuclein duplications and

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