Major or Mild Neurocognitive Disorders with Lewy Bodies

Poh Choo How, Pachida Lo, and Glen L. Xiong

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20.1 Background

20.1.1 Definition

Major or mild neurocognitive disorder with Lewy bodies (formerly termed dementia with Lewy bodies) is a leading cause of non-Alzheimer-related major or mild neurocognitive disorders (NCDs) [1]. Clinically, it is characterized by cognitive impairment accompanied by additional neuropsychiatric features, motor dysfunction, sleep, and autonomic disorders. At autopsy, NCD with Lewy bodies is characterized by the presence of Lewy bodies which are neuronal inclusions or aggregates of the protein alpha-synuclein. Neuropathological studies have demonstrated differential localization of Lewy bodies in major or mild NCD with Lewy bodies compared to other Lewy body diseases or alpha-synucleinopathies, which include major or mild NCD due to Parkinson disease and multiple system atrophy [2]. With histopathological evidence and efforts to clarify clinical diagnostic criteria over the years, NCD with Lewy bodies has been recognized as a distinct diagnostic entity since 1996 [3]. Yet, diagnostic challenges remain, and these criteria continue to be revised by the Lewy body NCD Consortium [4, 5] based on new clinical and histopathological information and have been incorporated in the *Diagnostic and Statistics Manual of Mental Disorders*, 5th edition (DSM-5), used in psychiatry. Table 20.1 clarifies the terms used in the Consortium criteria and the DSM-5 with regard to Lewy body NCD [6–8].

According to the DSM-5 [6], diagnosis of major or mild NCD with Lewy bodies requires that diagnostic criteria are met for major or mild NCD, with symptoms having an insidious onset and gradual progression. Given that definitive findings of Lewy body pathology can only be ascertained on autopsy, criteria have been developed to differentiate between probable versus possible NCD with Lewy bodies based on the number of core and suggestive diagnostic features that patients present with.

Core diagnostic features include fluctuating cognition, visual hallucinations, and parkinsonism. One or more core features are required for a diagnosis of probable NCD with Lewy bodies. Per the DSM-5, suggestive features include the presence of rapid eye movement (REM) sleep behavior disorder and demonstrated sensitivity to antipsychotics. The criteria proposed by the Lewy body NCD Consortium allow for the diagnostic weight of SPECT or PET studies of dopamine transporter uptake activity as a suggestive feature as well, which theoretically increases the sensitivity of the Consortium criteria [9]. However, these studies may not be accessible or practical in most clinical settings.

One or more suggestive features in the presence of one or more core features point to a diagnosis of probable NCD with Lewy bodies. If only one core feature is present without suggestive features, or if suggestive features are present without core features, then only a diagnosis of possible NCD with Lewy bodies is appropriate. This is summarized in Table 20.2 [4]. Table 20.3 compares the current key DSM-5 diagnostic criteria and the criteria put forward by the Consortium on Lewy body NCD [3, 4, 6]. The latter includes supportive features which are noted to be commonly present in Lewy body NCD but do not carry diagnostic weight. For a complete review of the DSM-5 diagnostic criteria for major or mild NCD with Lewy bodies, the reader is referred to the DSM-5 manual [6].

Features of NCD with Lewy bodies may overlap with those of other NCDs, notably Alzheimer disease and Parkinson disease-related NCD, at different time points in the course of the disease [10]. Hence, the time course of symptom presentation and progression is crucial in distinguishing

Table 20.1 Terminology of Lewy body diseases and related neurocognitive disorders (dementia) [6–8]

Lewy body dementias	An umbrella term that includes clinically diagnosed dementia with Lewy bodies and Parkinson disease dementia
Dementia with Lewy bodies	Dementia that occurs before or concurrently with parkinsonism or within 1 year of onset of motor symptoms. Not all patients develop parkinsonism [7]
Parkinson disease dementia	Dementia starting 1 year or more after well-established Parkinson disease [8]
Mild cognitive impairment in Parkinson disease	Cognitive impairment in patients with Parkinson disease not sufficient to interfere greatly with functional independence [7]
Lewy body disease	Pathological diagnosis. The distribution of Lewy body-type pathology and additional pathologies is often specified
Major or mild neurocognitive disorder with Lewy bodies or due to Parkinson disease	New terms proposed by DSM-5 corresponding to dementia with Lewy bodies and Parkinson disease dementia, respectively

Table 20.2 Diagnostic criteria for probable and possible major or mild NCD with Lewy bodies [4]

	Probable	Probable	Possible	Possible
Core features Fluctuating cognition Visual hallucinations Parkinsonism	≥ 2	≥ 1	1	0
Additional features	+	+	+	+
Suggestive features REM sleep behavior disorder Antipsychotic sensitivity	0	≥ 1	0	≥ 1

Table 20.3 Summary of the diagnostic criteria for neurocognitive disorder (dementia) with Lewy bodies (DLB) [3, 4, 6]

DSM-5 criteria	DLB Consortium criteria
The criteria are met for major or mild neurocognitive disorder There is insidious onset and gradual progression	Central feature (essential for a diagnosis of possible or probable DLB) 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 diagnostic features: (a) fluctuating cognition/variations in attention and alertness; (b) recurrent visual hallucinations, well-formed and detailed; (c) spontaneous parkinsonism (onset after development of cognitive decline) *Suggestive diagnostic features*: (a) meets criteria for REM sleep behavior disorder; (b) severe antipsychotic sensitivity *Probable*: 2 core features or 1 suggestive feature *with* 1 (or more) core feature *Possible*: 1 core feature or 1 (or more) suggestive feature	*Core features*: (a) fluctuating cognition/variations in attention and alertness; (b) recurrent visual hallucinations, well-formed and detailed; (c) spontaneous parkinsonism *Suggestive features*: (a) REM sleep behavior disorder; (b) severe antipsychotic sensitivity; (c) low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET *Probable*: 2 core features or 1 suggestive feature *with* 1 (or more) core feature *Possible*: 1 core feature or 1 (or more) suggestive feature
	Supportive features (commonly present but not proven to have diagnostic specificity): repeated falls and syncope; transient, unexplained loss of consciousness; severe autonomic dysfunction; hallucinations in other modalities; systematized delusions; depression; relative preservation of medial temporal lobe on CT/MRI; generalized low uptake on SPECT/PET with reduced occipital activity; low uptake MIBG myocardial scintigraphy; EEG slow wave activity with temporal lobe transient sharp waves
The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another psychiatric, neurological, or systemic disorder	A diagnosis is less likely: (i) if cerebrovascular disease is evident as focal neurologic signs or on neuroimaging; (ii) if any other physical illness or brain disorder is sufficient to account for the clinical picture; (iii) if parkinsonism only appears for the first time at a stage of severe dementia

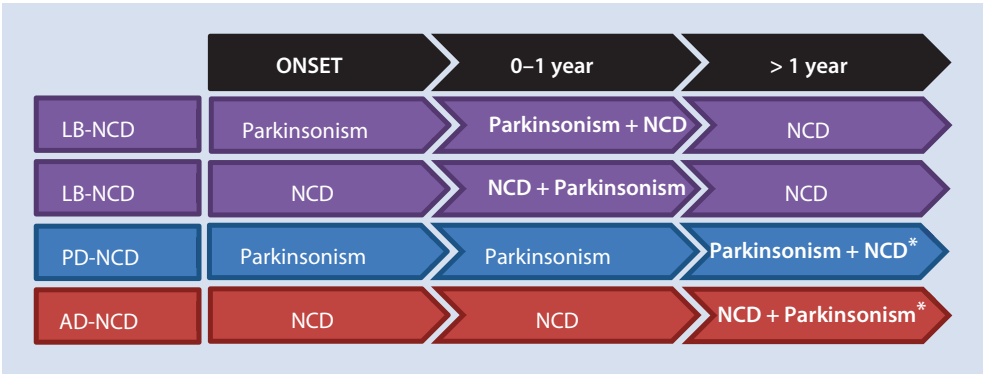

Fig. 20.1 Time course of LB-NCD versus PD-NCD versus AD-NCD [5]. *AD-NCD* neurocognitive disorder due to Alzheimer disease, *LB-NCD* neurocognitive disorder with Lewy bodies, *PD-NCD* neurocognitive disorder due to Parkinson disease. *Parkinsonism and NCD may co-occur in later stages of AD-NCD and PD-NCD due to generalization of the neuropathology to various brain regions but do not represent LB-NCD

among these entities. Predominance of parkinsonism during initial presentation may be a prelude to either Parkinson disease or NCD with Lewy bodies. Development of cognitive symptoms of major or mild NCD within the subsequent year would point to a diagnosis of NCD with Lewy bodies (see Fig. 20.1; purple arrows) [5]. If cognitive symptoms of NCD develop after the 1 year mark, the disease is defined as NCD due to Parkinson disease (see Fig. 20.1; blue arrow). Predominance of cognitive impairment early in the disease course may portend the development of Alzheimer disease (see Fig. 20.1; red arrow) (if parkinsonism does not occur or occurs very late (greater than 1 year) in the course of the disease) or NCD with Lewy bodies (see Fig. 20.1; purple arrows) (if parkinsonism develops within 1 year of presentation). Thus, in NCD with Lewy bodies, features of either cognitive impairment or parkinsonism may be initially present at disease onset and necessitate close observation and evaluation of other symptoms that may develop within the first year of disease for diagnostic clarity. Often times, these distinctions are difficult to parse out as they require meticulous gathering of history to determine the time course of specific symptoms, especially when patients present at a later stage of disease and are already experiencing concurrent symptoms of parkinsonism and cognitive impairment.

20.1.2 Epidemiology

Epidemiological studies of NCD with Lewy bodies are limited and have been confounded by overlapping diagnostic features with Parkinson disease-related NCD and other NCDs. The prevalence and incidence of NCD with Lewy bodies vary tremendously based on study type, age range, and location of the populations that are studied. Neuropathology at autopsy demonstrates NCD with Lewy bodies findings in 10–15% of autopsy cases [5]. In similar studies using the same clinical criteria, the prevalence of NCD with Lewy bodies ranged from 2.6% in rural Japan [11] to 10.9% outside London, England [12], whereas population studies of those aged 65 and older range show a population prevalence ranging from 0.1% in Sri Lanka [13] to 2% in London, England [12]. Prevalence of NCD with Lewy bodies is reported to be higher in studies conducted in Europe which parallels a higher reported rate of overall major NCD.

Since the most recent revision of the Lewy body NCD Consortium criteria in 2005 [5], which added diagnostic weight to suggestive features, the proportion of cases of probable major NCD has increased by 24% [14] with a 15.8% rate of probable major NCD with Lewy bodies and 4.1% of possible major NCD with Lewy bodies of all NCD cases. Studies incorporating dopamine transporter imaging [15] and screening for REM sleep behavior disorder [12] into the diagnostic criteria suggest a prevalence of 10–15% of NCD with Lewy bodies in those with major NCDs. Two studies looking at the incidence of NCD with Lewy bodies estimated an incidence rate of 0.1% of patients with Lewy body NCD older than 65 years of age in Cache County, UT [16], and an incidence of 3.5 per 100,000 person-years in Olmsted County, MN [17]. There is a slight male predominance [18, 19], although not as pronounced as in Parkinson disease-related NCD. The mean age at initial diagnosis is 75 years (range, 50–80 years of age) [20]. In a study on the projected prevalence of major NCDs, it is estimated that the prevalence of Lewy body NCD will increase by 131% by 2050 [21]. A recent study in Sweden suggests a 16–20% prevalence of major NCD with Lewy bodies in the nursing home population [22].

20.1.3 Etiology

NCD with Lewy bodies is characterized by the accumulation of alpha-synuclein inclusion bodies, also known as Lewy bodies, within neurons. Lewy neurites are also composed of alpha-synuclein aggregates but have a distinctive curvilinear shape or dot-like process [23]. Alpha-synuclein is a member of a family of presynaptic proteins thought to be involved in neurotransmitter release at the presynaptic terminals. It is coded by the alpha-synuclein gene (SNCA) on chromosome 4. Duplications [24] and point and missense mutations in the SNCA gene have been implicated in the pathogenesis of NCD with Lewy bodies [25] and are speculated to be involved in the regulation of dopamine transmission [26].

Other genes that have been implicated in NCD with Lewy bodies include the leucine-rich repeat kinase 2 (LRRK2) on chromosome 12 [27] and the glucocerebrosidase (GBA) gene on chromosome 1 [28]. A study of familial NCD with Lewy bodies in a Belgian family recently mapped Lewy body pathology to chromosome 2q35–36 [29], although a specific mutation of a gene or regulatory region at this locus has not yet been described. The mechanism of accumulation of alpha-synuclein inclusion bodies is not known. It is speculated that oxidative stress may upregulate both SNCA and LRRK2 [27]. Both mitochondrial dysfunction [30, 31] in the oxidative stress pathway and lysosomal dysfunction [32, 33] in the autophagy pathway have been implicated in the accumulation of alpha-synuclein inclusion bodies in Lewy body disease in general and NCD with Lewy bodies specifically [30, 31].

Lewy bodies occur in Lewy body disease broadly, encompassing neuropathology in NCD with Lewy bodies, Parkinson disease, Parkinson disease-related NCD, and multiple system atrophy [34]. The distinguishing factor that leads to the variable manifestations of Lewy body pathology in these different alpha-synucleinopathies lies in the primary location of these aggregates. In Parkinson disease, Lewy bodies primarily affect the midbrain substantia nigra and other brainstem nuclei leading to primary manifestations of a movement disorder [35]. Alpha-synuclein pathology may spread to other areas in the brain (e.g., neocortical areas) later in the course of Parkinson disease leading to Parkinson disease-related NCD, but the initial insult in Parkinson disease lies in the basal ganglia.

In NCD with Lewy bodies, Lewy bodies are seen additionally in the limbic (hippocampus, amygdala), paralimbic (anterior cingulate), and cortical areas (frontal, inferior temporal) and the peripheral nervous system [10, 36, 37]. Lewy neurites can also be seen in high densities in the limbic cortex, amygdala, and CA2/3 sectors of the hippocampus [28]. These explain the additional manifestations such as cognitive dysfunction, visual hallucinations, REM sleep behavior disorder, and autonomic dysfunction that are seen earlier in the course of the disease along with parkinsonism (by definition, within 1 year). The differential localization of Lewy body pathology has also been detected in SPECT studies in probable and possible cases of NCD with Lewy bodies [38].

20.1.4 Clinical Description

The early course of NCD with Lewy bodies is marked by complex and heterogeneous cognitive, other neuropsychiatric, motor, sleep, and autonomic symptoms. Initial manifestation of NCD with Lewy bodies may involve a combination of cognitive and/or motor symptoms and/or a core feature with or without parkinsonism or cognitive impairment [39]. For example, there are case reports of isolated initial symptoms such as autonomic dysfunction [40, 41], REM sleep behavior disorder [42, 43], or other symptoms without accompanying parkinsonism or cognitive impairment. On the other

hand, autopsies have revealed the presence of Lewy bodies in asymptomatic patients [44].

Cognitive Impairment

Cognitive impairment is a frequent initial symptom of NCD with Lewy bodies [45]. Around 15% of patients with major NCD are found to have Lewy body type [5]. As an initial symptom alone, cognitive impairment in NCD with Lewy bodies is most commonly misdiagnosed as Alzheimer disease [37]. However, while the hallmark of cognitive dysfunction in Alzheimer disease centers on anterograde memory loss and language loss, cognitive impairment in NCD with Lewy bodies more consistently involves the domains of attention and concentration, executive functioning, and visuospatial functioning [46]. Patients will have difficulty with sequential tasks, for example, using a microwave oven and finding their way in familiar surroundings. On cognitive screening test of Mini Mental State Examination (MMSE), patients will show difficulty with attention (serial 7s, spelling WORLD backward), following the three-step command, and difficulty with intersecting pentagons and/or clock drawing.

Some patients with initial NCDs that later overlap with developing psychotic and extrapyramidal symptoms may simultaneously meet criteria for both frontotemporal NCD and NCD with Lewy bodies [47]. However, the cognitive features of frontotemporal NCD are more prominent for behavior and personality changes than those of NCD with Lewy bodies. Patients presenting with major or mild NCDs need comprehensive initial evaluations to determine specific domains of cognitive dysfunction and co-occurring symptoms that may help categorize their NCD in order to direct appropriate treatment. Often serial assessments are necessary in 6–12 month intervals to follow the trajectories of various symptoms in order to make the most reliable clinical diagnosis. There, the initial finding of mild or major NCD alone warrants close follow-up to detect symptoms that may point to the development of a specific type of NCD.

Fluctuating Cognition

Fluctuating cognition refers to changes in cognition and arousal from baseline and reflects interruption in the flow of awareness and/or attention [39, 48]. It is a core diagnostic feature of NCD with Lewy bodies but remains ill-defined and circumscribed in clinical practice. The use of structured scales to more clearly describe this feature has been encouraged. More recent neuroimaging techniques suggest a link with thalamic damage and cholinergic imbalance as the etiology of this feature [49], while others propose that it is more likely a feature of an underlying sleep disorder [50]. Of note, fluctuating cognition may affect performance on cognitive testing and lead to higher variability in formal results.

Neuropsychiatric Features

Delusions and hallucinations are present in 50–75% of patients with NCD with Lewy bodies with visual hallucinations occurring in up to 60% of patients. The visual hallucinations are usually complex, recurrent, well-defined three-dimensional images of people or animals [39]. Auditory and tactile hallucinations are less frequently reported. Patients' responses vary from fear to amusement to anger if others do not believe their report of symptoms. These symptoms are presumably related to the involvement of the limbic system in the neuropathology of Lewy bodies. There may also be a link with the occipital (visual) cortex with studies showing increased excitability [51] and GABAergic involvement [52] associated with recurrent complex visual hallucinations in NCD with Lewy bodies. Delusions also occur in high frequency and can be complex. Themes vary widely and may be non-bizarre, bizarre, or, more commonly, paranoid (e.g., theft, conspiracy, infidelity). Patients may report the Capgras syndrome (i.e., that their loved ones have been replaced by impostors) [53, 54]. Depression is also common in NCD with Lewy bodies, as it is in other Lewy body disease, and is proposed to represent a pure psychiatric presentation of NCD with Lewy bodies [55].

Motor Dysfunction

The spontaneous development of parkinsonism is a hallmark of NCD with Lewy bodies. The word "spontaneous" clarifies the involvement of Lewy bodies in the basal ganglia in the etiology of these symptoms rather than secondary causation via exposure to dopamine antagonists. Patients may present with parkinsonism as an initial syndrome, with masked facies, stooped posture, shuffling gait, tremors (intention more commonly than resting), symmetrical rigidity, and bradykinesia, or these symptoms may develop soon after the onset of cognitive impairment. Patients presenting with initial parkinsonian symptoms need to be followed closely with serial cognitive testing as the timeline of the development of cognitive dysfunction (◘ Fig. 20.1) distinguishes between a diagnosis of NCD with Lewy bodies (within 1 year) or Parkinson disease-related NCD (greater than 1 year).

Sleep Dysfunction

REM sleep behavior disorder is the sleep disorder most closely linked with NCD with Lewy bodies. It is characterized by loss of atonia during REM sleep, and patients appear to "act out" their dreams. A patient may not be aware of the REM sleep behavior disorder unless he or she has a sleep partner who is able to witness and report this behavior. REM sleep behavior disorder may present as the sentinel symptom (without accompanying core or suggestive features) [39, 43], and there is momentum building to promote it to a core feature to increase the sensitivity of the Consortium criteria for Lewy body NCD [39, 56]. NCD with Lewy bodies is also associated, less commonly, with other sleep disorders such as obstructive sleep apnea, central sleep apnea, restless legs syndrome, and periodic limb movement disorder [57]. As a point of differentiation, daytime sleepiness occurs more commonly in NCD with Lewy bodies than in Alzheimer disease [50].

Autonomic Dysfunction

Lewy bodies and Lewy neurites have been found in the peripheral nervous system, more specifically, the autonomic plexus, and are thought to explain the autonomic dysfunction seen in NCD with Lewy bodies. These alpha-synuclein inclusions have been detected in the intermediolateral column of the spinal cord, thoracic sympathetic nerves (including those that surround the heart), and Auerbach's and Meissner's plexus in the abdomen. As a result, pathology involving these nerve groups can lead to significant autonomic dysfunction, causing orthostatic hypotension (50%), constipation (30%), urinary incontinence (30%), and impotence [58, 59]. The presence of persistent orthostatic hypotension with or without constipation and/or urinary incontinence is linked with a shorter survival period [58]. As mentioned before, autonomic dysfunction may be the only presenting symptom of NCD with Lewy bodies and may represent a prodrome to the full-spectrum disease [60].

20.1.5 Diagnostic Evaluation

Accurate diagnosis of NCD with Lewy bodies is challenging and may require multiple visits over time given the importance of the time course of progressing symptoms. The initial evaluation may only warrant a rule out of the diagnosis or possible NCD with Lewy bodies. Patients and their caregivers need education to remain vigilant on reporting the development of relevant symptoms as well as the time course associated with new symptoms. Identification of a prodromal period of NCD with Lewy bodies has been suggested [9, 61, 62], although a consensus on what symptoms the prodrome may include has not been reached.

Clinical History

A thorough personal history and review of systems should be obtained and can be very informative in the diagnostic process. This should include a history obtained from a partner or caregiver who may report symptoms unacknowledged by the patient. This is especially useful in the domains of cognitive dysfunction, REM sleep behavior disorder, delusions, and visual hallucinations where patients may not be aware of minor cognitive deficits, or that they are acting out their dreams, or if they believe that their delusions or visual hallucinations are real.

Family history is equally important. While NCD with Lewy bodies is a relatively newer diagnostic entity, it would be important to determine if there were family members with formal clinical diagnoses of major NCDs and/or a movement disorder or uncharacterized motor and/or cognitive symptoms without any formal diagnoses. It is also important to rule out other etiologies of major NCDs, previous exposure to antipsychotics (including antiemetics with antidopaminergic activity), and other secondary causes of major NCDs or parkinsonism (see ▶ Sect. 20.1.6). With regard to antipsychotics, it is noted that a test of sensitivity to antipsychotics should never be a part of a diagnostic workup for NCD with Lewy bodies given the increased risk of mortality associated with antipsychotic treatment. Given the heterogeneity of symptoms in Lewy body disease, a thorough review of all systems is important to detect the broad-ranging symptoms that will need to be addressed clinically (especially autonomic and neuropsychiatric symptoms).

Cognitive Assessment

Formal cognitive testing should be a routine part of the initial and follow-up evaluations. In the early stages of cognitive impairment, whenever possible, it is helpful to characterize specific domains of cognitive deficiencies that may help differentiate between cognitive domains seen more in NCD with Lewy bodies (e.g., diminished attention, visuospatial deficits, executive dysfunction) from those seen in Alzheimer disease (e.g., anterograde amnesia, language impairment). The Montreal Cognitive Assessment (MoCA) and Mini Mental State Examination (MMSE) are good starting points to screen for domains of dysfunction. More comprehensive testing may be pursued, as clinically indicated and if tolerated by the patient (see ◘ Table 20.4 for recommended formal cognitive

◘ **Table 20.4** Recommended cognitive tests in Lewy body disorders [5, 9]

Cognitive domain	Subcategory	Examples
Brief screening tools		Montreal Cognitive Assessment, Parkinson's Disease Cognitive Rating Scale, Parkinson Neuropsychometric Dementia Assessment Instrument, Scales for Outcomes in Parkinson's Disease—cognition
Visuospatial	Figure copy tests	Cube, clock, interlocking pentagons, or complex figures
	Spatial judgment tests that do not rely on motor functions	Visual Object and Space Perception Battery, Benton Judgement of Line Orientation
Executive or attention	Measures of working memory, selective attention, set shifting, planning, and verbal fluency	Wisconsin Card Sorting Test, NIH EXAMINER test battery, Trail-Making Test, Stroop Test
Memory	Word list, figure, or associative learning with delayed recall and recognition	Rey Auditory Verbal Learning Test, California Verbal Learning Test, Free and Cued Selective Reminding Test, Brief Visuospatial Memory Test-Revised (Note: visual memory might be poor for reasons of visual perceptual or memory deficit)

Table 20.5 Structured scales used in measuring fluctuating cognition [5]

Scales	Comments
Clinician Assessment of Fluctuation Scale	Structured; requires experienced clinician to administer and interpret
One Day Fluctuation Assessment Scale	Semistructured; can be administered by less experienced raters
Mayo Fluctuations Composite Scale	Uses caregiver answers to structured questions
Other	Recording variations in attentional performance using a computer-based test system

tests in Lewy body disorders) [5, 9]. The utility of formal testing at a given time point may be limited. However, repeat administrations over time help clinicians determine disease progression, development of new symptoms, and patient response to symptomatic treatment.

The core feature of fluctuating cognition may confound a patient's performance in cognitive testing over time. Specifically quantitating cognitive fluctuation remains a vague and somewhat arbitrary construct. Subjective caregiver- and observer-rated scales may be useful [63], although it has been found that caregiver ratings of fluctuations are less reliable predictors of NCD with Lewy bodies and less able to differentiate between Lewy body type and Alzheimer disease-related NCD compared to more formal questions [63]. Some formal psychometric measures exist that attempt to quantify the severity of this feature but have not been tested for their reliability or validity [64]. The Lewy body NCD Consortium, however, recommends the use of at least one formal measure of cognitive fluctuation in applying the diagnostic criteria [5] though their use is dependent on the clinical setting and availability of expert clinicians in administering and interpreting these scales. The names of the suggested scales and administration are summarized in Table 20.5 [5].

Physical Exam

A thorough physical exam including a complete neurological examination is required at each encounter. A detailed motor exam including specific attention to laterality can help differentiate between typical (resting tremor, limb rigidity, bradykinesia) and atypical (intention tremor, axial rigidity, bulbar or balance disturbances, vertical gaze paresis, myoclonus) parkinsonian symptoms. While motor dysfunction in Parkinson disease more distinctively presents with typical and asymmetrical motor signs, those of NCD with Lewy bodies can present with either typical or atypical parkinsonism and can be symmetrical or asymmetrical, reflecting the heterogeneity of the disease pathology [65].

Laboratory Studies and Electroencephalogram (EEG)

There are no specific blood or cerebrospinal fluid laboratory studies diagnostic of NCD with Lewy bodies. Patients should have routine laboratory tests and any abnormal results followed up, if only to rule out other etiologies of their symptoms (e.g., nutritional deficiencies and hypothyroidism presenting with neuropsychiatric and cognitive dysfunction). Cerebrospinal fluid studies of tau protein and alpha-synuclein levels may help differentiate between Alzheimer and Lewy body disease [66], although neither plasma nor cerebrospinal fluid studies have yielded a reliable biomarker for the diagnosis of NCD with Lewy bodies. Similarly, while slow wave activity on EEG is prominent in NCD with Lewy bodies [67], there has yet to be a distinctive pattern of neuroelectrical activity that is specific to NCD with Lewy bodies; hence EEG is not routinely recommended.

Neuroimaging

Structural neuroimaging such as routine CT and MRI studies should be part of an initial neuropsychiatric workup for patients presenting with signs and symptoms of NCD and Parkinson disease. MRI is preferred unless clinically unobtainable. MRI findings in NCD with Lewy bodies may show a more diffuse pattern of atrophy compared to other types of NCD and less medial temporal lobe atrophy compared to Alzheimer disease. Diffusion tensor imaging may show loss of parieto-occipital white matter [9]. Depending on the time course, and especially early in disease progression, routine neuroimaging results are often nonspecific or normal, yet it may remain useful in ruling out other secondary etiologies (e.g., vascular NCD, normal pressure hydrocephalus, corticobasal degeneration).

Functional neuroimaging can more precisely differentiate between Lewy body disease and other NCDs but may not be able to differentiate Lewy body NCD from Parkinson disease-related NCD and other parkinsonian syndromes. However, some studies have been determined to be specific enough to be given diagnostic weight as a suggestive feature of NCD with Lewy bodies. Hypometabolism of dopamine transporter markers or overall hypoperfusion of the occipital lobe may be seen on SPECT. The [123-I]-FP-CIT SPECT marker shows a 78% sensitivity and 90% specificity in differentiating between NCD with Lewy bodies and other NCDs [68]. Decreased glucose metabolism in the occipital lobe may also be detected on PET studies [69]. In addition, metaiodobenzylguanidine (MIBG) myocardial scintigraphy showing reduced activity at post-ganglionic sympathetic terminals as part of the manifestation of autonomic dysfunction in the disease has a sensitivity of 94% and specificity of 96% in predicting a diagnosis of NCD with Lewy bodies in subjects with mild cognitive impairment [70].

Polysomnography

The use of polysomnography can help clarify sleep disturbances in NCD with Lewy bodies. It can help differentiate between moderate-to-severe obstructive sleep apnea which may have dream enactment behavior similar to REM sleep behavior disorder, restless legs syndrome, periodic limb movement in sleep, and central sleep apnea, all of which require different approaches in treatment.

20.1.6 Differential Diagnosis

As mentioned earlier, given the core features of NCD and parkinsonism, the major differential diagnoses for NCD with Lewy bodies include Parkinson disease-related NCD and Alzheimer disease. The timeline of the development of cognitive and motor symptoms and functional neuroimaging can help to differentiate between Lewy body disease (Lewy body NCD and Parkinson disease-related NCD) and Alzheimer disease. The distinction between Parkinson disease-related NCD and Lewy body-related NCD is usually less clear cut particularly if the timeline of symptoms is unclear, leading to the diagnostic approach of classifying probable or possible diagnoses. Similarly, NCD with Lewy bodies may also be misdiagnosed as other forms of NCDs (e.g., frontotemporal NCD [47]).

On a broader scale, the differential diagnosis includes other sporadic degenerative parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration. Similarly, other forms of secondary parkinsonian syndromes with cognitive deficits including drug-induced parkinsonism, vascular parkinsonism, normal pressure hydrocephalus, Whipple disease, and dementia pugilistica are also on the differential diagnosis and can more easily be distinguished with routine evaluation, laboratory studies, and neuroimaging.

20.1.7 Treatment

Thus far, no disease-modifying therapy has been found for Lewy body disease or other alpha-synucleinopathies. Therefore, treatment remains symptomatic, targeting the various clinical manifestations of the disease. Treatments may improve symptoms but only rarely will eliminate them. A general approach is to determine, together with the patient, the degree of symptomatology that is acceptable or tolerable to ascertain whether it should be treated. Of note, aside from the evidence supporting the safety and efficacy of cholinesterase inhibitors in improving cognition in Lewy body disease [56], there is generally mixed or insufficient evidence (namely, lack of randomized controlled trials) for the use of pharmaceuticals in addressing other symptoms associated with NCD with Lewy bodies. Hence, prudent and cautious use of medications is advised, with low initial doses and slow and small increments of dose titration with close follow-up. There is great variability in treatment response from patient to patient and from none to minimal to robust. Hence, during the course of treatment, clinicians should discuss the risks and benefits of continuing with treatments that may not yield significant clinical improvement, more so if they carry significant risks of morbidity and/or mortality.

Treatment of Cognitive Impairment with Cholinesterase Inhibitors and Other Agents

Autopsy studies have found a greater degree of cholinergic deficit and less neuronal loss in Lewy body disease than in Alzheimer disease [71]. Thus, it is thought that patients with Lewy body pathology may be more responsive to cholinesterase inhibitor therapy. In a placebo-controlled, double-blind, multicentered study, patients with Lewy body NCD taking 6–12 mg of rivastigmine daily for 20 weeks showed significantly less apathy and anxiety and had fewer delusions and hallucinations than controls [72]. More recently, a randomized, double-blind, placebo-controlled phase 2 trial of donepezil in Japan yielded similar findings with Lewy body NCD patients showing significant improvement in cognitive, behavioral, and global domains at doses of 5 mg or 10 mg daily [73]. The NMDA-receptor antagonist, memantine, has recently been shown in a randomized double-blind, placebo-controlled multicenter trial to improve cognitive tests of attention and episodic recognition in subjects with either Lewy body NCD or Parkinson disease-related NCD at a dose of 20 mg daily [74]. Some uncontrolled trials, as well as clinical experience, report the efficacy (although unpredictable) of galantamine and wakefulness promoters (armodafinil and modafinil) in improving cognition or preventing cognitive deterioration in NCD with Lewy bodies, but there has yet to be efficacy or safety studies with these agents [39, 75].

Treatment of Visual Hallucinations with Antipsychotic Agents

The use of antipsychotics in treatment of visual hallucinations associated with NCD with Lewy bodies should be approached cautiously and judiciously, not least due to the hallmark of antipsychotic sensitivity which partially defines the disease. Visual hallucinations may improve with the use of cholinesterase inhibitors alone so these agents should be tried first [72]. A trial of lower-potency atypical antipsychotics (e.g., quetiapine) may be initiated if the hallucinations continue to be significantly distressing and impairing after the trial of a cholinesterase inhibitor. There is some evidence for the efficacy of quetiapine, olanzapine, and clozapine, as well as risperidone (which is of higher D_2 potency), in the treatment of visual hallucinations in patients with NCD with Lewy bodies [76–80]. However, a meta-analysis of various medications for NCD with Lewy bodies indicated that many patients are unable to tolerate the antipsychotic quetiapine (33% withdrew from small retrospective study of 9 patients), risperidone (65% withdrew in randomized

controlled study of 31 participants), and olanzapine (38% did not tolerate even small doses of 2.5 mg daily in retrospective study) [75]. As noted earlier, an adverse reaction or worsening of motor symptoms after antipsychotics is often used as a diagnostic feature for NCD with Lewy bodies. In our clinical experience, low-dose quetiapine does appear to be helpful for some patients and is a reasonable first-line antipsychotic if the sedation and other side effects are tolerated. Clozapine has the strongest evidence supporting its use [75]; however, due to monitoring of blood neutrophil count requirements and risk for seizure and delirium, clozapine is infrequently used. A newer agent, pimavanserin (a serotonin-2A receptor inverse agonist), has recently been approved by the FDA to treat hallucinations and delusions associated with psychosis in patients with Parkinson disease. This medication was studied in a 6-week clinical study with 199 participants [81]. It was found to be effective in reducing frequency and severity of psychosis without worsening the motor symptoms of Parkinson disease. Its application in NCD with Lewy bodies would be off-label. While this medication holds promise in NCD with Lewy bodies, given the similarities between Lewy body NCD and Parkinson disease, further prospective studies and post-marketing monitoring are needed to better understand the benefits versus risks in real-world settings.

It should be noted that somnolence, dizziness, and orthostatic hypotension are potential side effects of some atypical (second generation) antipsychotics and extra caution should be employed in their use in Lewy body patients with manifestations of autonomic dysfunction. Similarly, further caution is advised as these agents carry a "black box" warning due to the risk of increasing mortality in patients with major NCD [82]. Typical (first generation) antipsychotics should not be used as they have a higher relative risk of inducing antipsychotic sensitivity in this high-risk population.

Dopaminergic Therapy to Target Motor Dysfunction

There are some uncontrolled studies but overall insufficient evidence for broad use of L-dopa in the treatment of motor dysfunction in NCD with Lewy bodies [9, 75]. A small study of 14 patients with Lewy body NCD showed that low doses of L-dopa were generally well tolerated but produced a significant motor response in only 1/3 of patients, who tended to be of younger age [83]. In general, motor dysfunction in NCD with Lewy bodies appears to be less responsive to L-dopa than in Parkinson disease, although this might be an artifact of insufficient dosing due to the amount of caution exercised given the risks of worsening neuropsychiatric symptoms in NCD with Lewy bodies. These risks should be balanced against the benefits of improved functioning in patients who respond well to a trial of L-dopa therapy. There has yet to be any evidence for the use of other dopaminergic agents such as selegiline, pramipexole, bromocriptine, and ropinirole. Anticholinergic medications should be avoided in NCD with Lewy bodies due to the increased risk of further cognitive impairment and/or delirium with their use. Other treatment modalities for parkinsonism such as deep brain stimulation or pallidotomies are contraindicated in patients with NCDs, thus excluding Lewy body patients.

Treatment of Autonomic Dysfunction

Orthostatic hypotension, constipation, and urinary incontinence are common manifestations of autonomic dysfunction in NCD with Lewy bodies. Many non-pharmacologic strategies can be used to address these symptoms. Orthostatic hypotension can be addressed with increasing fluid and salt intake, use of compression stockings, and elevating the head of the bed during sleep to avoid "pressure natriuresis" [39]. Should these strategies fail, clinicians may start a trial of fludrocortisone and/or midodrine to address orthostatic dysfunction. Constipation may be minimized with increased fiber and water intake. Symptomatic over-the-counter treatments for constipation are generally safe on an as-needed basis. Patients with urinary incontinence may attempt behavioral modification with scheduled urination. Oxybutynin, a potent anticholinergic agent, should be avoided. An alternative treatment for urinary incontinence is trospium chloride, which was shown to be noninferior to oxybutynin in addressing urinary incontinence with fewer reports of dry mouth [84], although there have not been any specific studies in patients with NCD with Lewy bodies.

Treatment of Sleep Dysfunction

Treatment of sleep disorders associated with NCD with Lewy bodies can be complicated. Accurate diagnosis is essential for appropriate treatment, and clinicians should not hesitate to obtain formal polysomnography to delineate the etiology of sleep dysfunction in NCD with Lewy bodies which can be due to one or more primary sleep disorders, depressive disorders, medication, or circadian rhythm dysfunction. Clonazepam is considered the most effective treatment for REM sleep behavior disorder, but it should be avoided in obstructive sleep apnea due to risk of further depressing respiratory drive. There is increasing evidence for the use of melatonin in improving sleep and reducing dream enactment in REM sleep behavior disorder [85], although it has not been specifically studied in NCD with Lewy bodies. Patients with comorbid obstructive sleep apnea may benefit from a trial of continuous positive airway pressure. If already used to target neuropsychiatric symptoms, atypical antipsychotics with more sedating effects such as quetiapine (at a dose of 25 to 100 mg at nighttime) [57] may be used to target insomnia. Other classes of medications (e.g., trazodone, mirtazapine, zolpidem, zaleplon, chloral hydrate) may also be tried [39]. If depressive disorder is associated with the insomnia, antidepressants may be added to treat both. Gamma-hydroxybutyrate and eszopiclone are being considered in NCD with Lewy bodies and related insomnia. Modafinil and methylphenidate have shown some efficacy in addressing excessive daytime somnolence [57].

20.2 Case Studies

The following cases are intended to illustrate the variable initial presentation and disease course of major or mild NCD with Lewy bodies, as well as the diagnostic approach and treatment options for the disease.

20.2.1 Case 1

Case 1 History

Mr. A. was a 75-year-old man who presented to a geriatric psychiatric clinic with a chief complaint of "depression" and "thinking problems" for the previous 3 months. He reported increasing symptoms of insomnia, poor concentration, and anhedonia. He also reported a low appetite associated with abdominal pain from constipation. He used to look forward to watching the Wheel of Fortune program every day but had lost interest due to difficulty paying attention to the program. His wife reported that he started to fall asleep in the middle of the show which aired at 11:00 AM. He denied any items on review of systems. He was otherwise healthy and denied any medical problems, except dizziness. On mental status exam, he was an older male sitting hunched over on the chair. His gait was normal and no tremor was noted. His speech was soft, slow, and monotone. His mood was described as "depressed" and he had a flat affect. He scored 24 out of 30 points on the MoCA due to difficulty with serial 7 subtraction starting at 100 and being unable to copy the cube. He did not show impairment in anterograde memory.

Case 1 Questions and Answers

Case 1 Questions

Question 1. What is the differential diagnosis at this point in time?

Question 2. What further workup should be pursued?

Case 1 Answers

Case 1 Answer 1 (Question 1—What is the differential diagnosis at this point in time?)

The patient presents with a combination of depressive (depressed mood, flat affect, poor appetite, poor concentration, and insomnia) and cognitive symptoms (MoCA score less than 25, with poor attention and visuospatial functioning). The differential diagnosis will therefore include major depressive disorder or unspecified depression and mild NCD. Certainly Alzheimer disease is on the differential as well. However, the presence of symptoms of autonomic dysfunction (constipation, urinary incontinence, and dizziness) should alert the clinician to think about Lewy body disease as a category that needs to be ruled out.

As major or mild NCD with Lewy bodies is not a widely known entity, patients may report symptoms as fitting into specific categories they are more familiar with. In the case above, a low appetite may be seen as fitting into the paradigm of major depressive disorder. However, the source of the low appetite appears to be due to constipation, which points toward an element of autonomic dysfunction. At the same time, the loss of interest in his television program may represent anhedonia or, in this case, with the reasoning given by the patient, was due more to issues of attention and daytime somnolence, which may represent fluctuating cognition or effects from a sleep dysfunction which is common in Lewy body disease. In addition, a depressed mood and flat affect could herald development of parkinsonism (masked facies or hypomimia), and clinicians will need to be vigilant in monitoring for further development of other symptoms of Parkinson disease. In analyzing the results of the MoCA, an experienced clinician may be able to note the specific domains of dysfunction—in this case inattention and poor visuospatial functioning—which can help differentiate from the anterograde memory loss which is typically more prominent in Alzheimer disease.

Teaching Point

Symptoms of depression, cognitive decline, and/or autonomic dysfunction can be initial presenting symptoms of Lewy body disease.

Case 1 Answer 2 (Question 2—What further workup should be pursued?)

Before the patient leaves the office, the psychiatrist can perform orthostatic vital signs to determine if there is orthostatic hypotension. The psychiatrist should perform a preliminary neurological exam. In either case, the patient should be encouraged to follow up with their primary care physician for a full medical workup including routine laboratory tests and, if indicated, referral for a full neurological workup. To facilitate continuity of care, the patient should be provided with a summary of the initial psychiatric visit, noting the suspicion for Lewy body disease, so that it can be provided to the primary care physician.

Teaching Point

A simple intervention psychiatrists can do in their office when suspecting Lewy body disease is to obtain orthostatic vital signs.

Teaching Point

Communication and collaboration with the patient's primary care physician and/or neurologist are key to accurate diagnosis when Lewy body disease is suspected.

Case 1 Analysis Patients with early stage of NCD with Lewy bodies may initially present for evaluation in a psychiatric setting. Major or mild NCD with Lewy bodies should be

considered in the differential when older patients present with new-onset depression and cognitive impairment. The initial interview should include careful exploration of the sources of reported symptoms that may be attributed to a depressive disorder. A full review of systems and formal cognitive testing is also essential. While a full physical examination is not feasible in a psychiatric clinic, a psychiatrist can obtain orthostatic vital signs to rule out autonomic dysfunction, and, if not already done, patients should be referred for a full medical workup with their primary care physician. Coordination of care among general medical, psychiatric, and neurology clinicians is essential to facilitate accurate diagnosis and treatment of major or mild NCD with Lewy bodies.

20.2.2 Case 2

Case 2 History

Mr. B., a 70-year-old man, was diagnosed with major depression and started on citalopram 20 mg daily. Six months later, he presented to the emergency department for distressing visual hallucinations and paranoia. He told his wife that he saw zoo animals in their living room, including tigers, zebras, and monkeys. He became angry when his wife did not believe him. He was evaluated by a psychiatrist in the emergency department and treated for a diagnosis of major depressive disorder with psychotic features. The psychiatrist increased citalopram to 40 mg daily and added risperidone 1 mg daily. Three months after that, Mr. A. moved into a residential home, and his risperidone dose was discontinued, and paliperidone 6 mg daily was started. After a single dose, the patient became more confused, rigid, and ataxic. He was taken back to the emergency department for further evaluation.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What may explain the patient's extreme response to paliperidone?

Question 2. What is the patient's diagnosis? What should be done next?

Question 3. What is a reasonable treatment approach for this patient?

Case 2 Answers

Case 2 Answer 1 (Question 1—What may explain the patient's extreme response to paliperidone?)

Mr. B. appeared to have suffered a side effect from paliperidone, the principal active metabolite of risperidone, which is roughly equipotent to risperidone. It appears that he was given a dose that is about six times the risperidone equivalent by mistake. Although it is possible that his rigidity likely reflected extrapyramidal side effects from a potent atypical antipsychotic, the symptoms could in fact have been secondary to antipsychotic sensitivity.

Teaching Point
In older adult patients with extrapyramidal symptoms after antipsychotic administration, consider that the patient may be exhibiting the suggestive feature of antipsychotic sensitivity related to NCD with Lewy bodies.

Case 2 Answer 2 (Question 2—What is the patient's diagnosis? What should be done next?)

By definition, patients with major or mild NCD with Lewy bodies develop cognitive symptoms around the same time or within 1 year of the onset of parkinsonism. Cognitive symptoms that occur 1 year or more after the diagnosis of Parkinson disease had been called Parkinson disease with dementia or, now in the DSM-5, NCD due to Parkinson disease (see Fig. 20.1). In this case, mild or major NCD due with Lewy bodies should be considered. This patient meets criteria for probable NCD with Lewy bodies as he has at least one core feature (visual hallucinations) and at least one suggestive feature (antipsychotic sensitivity) (see Table 20.2). A full neurological and cognitive workup should be performed. Examination of this patient may reveal Parkinson disease symptoms such as bradykinesia, asymmetric rigidity, shuffling gait, hypomimia or masked facies (reduced facial expression), and/or hypophonia. Patients with NCD with Lewy bodies and Parkinson disease are highly sensitive to antipsychotic side effects because of the neurodegeneration of the nigrostriatal pathway. Antipsychotics may precipitate or worsen confusion and may paradoxically even increase hallucinations. Catatonia and mutism in patients with major NCD with Lewy bodies have also been reported. The patient's previously undiagnosed NCD with Lewy bodies predisposed him to acute extrapyramidal symptoms when an antipsychotic medication with a relatively high extrapyramidal side effect profile was increased by up to sixfold.

Teaching Point
Symptoms of cognitive impairment and parkinsonism occurring within 1 year of each other are suggestive of major or mild NCD with Lewy bodies, and further workup should be pursued.

Teaching Point
Antipsychotic sensitivity can occur in patients with NCD with Lewy bodies at lower doses during initial administration. It can also be unmasked when there is a large increase in the dosing of antipsychotics. It is a suggestive feature of major or mild NCD with Lewy bodies.

Case 2 Answer 3 (Question 3—What is a reasonable treatment approach for this patient?)

First, the highly potent antipsychotic paliperidone should be discontinued. Next, a cholinesterase inhibitor should be considered as this class of medication appears to have the strongest evidence base and may be helpful for cognition and possibly even for hallucinations [72, 74]. Sleep should be monitored carefully, and melatonin and other medications may be considered to help with insomnia, if present. Finally, quetiapine with gradual dose titration or pimavanserin may be considered.

Teaching Point

Visual hallucinations in patients with major or mild NCD due to Lewy bodies can be addressed with low-potency atypical antipsychotics. Typical antipsychotics should be avoided. Cognitive symptoms and possibly hallucinations can improve with treatment with a cholinesterase inhibitor. Pimavanserin may be considered in patients with NCD with Lewy bodies given its efficacy in treating psychosis in Parkinson disease.

Case 2 Analysis In this case, a patient with NCD with Lewy bodies was initially misdiagnosed with major depressive disorder with psychotic features. Thus, NCD with Lewy bodies should be on the differential when older adults present with symptoms of depression and psychosis. If the patient indeed meets criteria for NCD with Lewy bodies, cholinesterase inhibitors should be considered and treatment with antipsychotics reconsidered. Patients vary in terms of sensitivities to antipsychotics. Some patients with NCD with Lewy bodies may not exhibit sensitivity to antipsychotics at lower doses but may experience severe extrapyramidal symptoms at higher doses or during dose titrations. Antipsychotics should be used judiciously in the older adults given the increased risk for mortality and morbidity. Risks and benefits should be discussed with the patient. (See ▶ Chap. 22.) In this case, the visual hallucinations appeared to be impairing Mr. B.'s functioning and relationships. Low-potency atypical antipsychotics should be considered first to avoid extrapyramidal symptoms.

20.3 Key Points: Major or Mild Neurocognitive Disorder with Lewy Bodies

- Major or mild NCD with Lewy bodies is a leading cause of non-Alzheimer-related NCDs and should be considered in the differential of new-onset cognitive impairment or parkinsonian symptoms in the older adults.
- Time course of symptoms is important for diagnosis of NCD with Lewy bodies. The development of cognitive impairment and parkinsonian symptoms within 1 year of each other strongly suggests a diagnosis of NCD with Lewy bodies.
- Core (fluctuating cognition, visual hallucinations, parkinsonism) and suggestive (REM sleep behavior disorder, antipsychotic sensitivity) features are used in the diagnosis of NCD with Lewy bodies.
- The early course of the disease is marked by heterogeneity, and patients may present with a range of symptoms at onset including autonomic, sleep, and motor dysfunctions and neurocognitive and neuropsychiatric symptoms (e.g., depression, hallucinations, delusions).
- Unlike NCD due to Alzheimer disease with early impairment in language and memory, cognitive symptoms in NCD with Lewy bodies are marked by impairment in executive function.
- When NCD with Lewy bodies is suspected, complete psychiatric, medical, and neurological examinations should be performed. Coordination of care among clinicians helps with the diagnosis and treatment of NCD with Lewy bodies.
- Treatment with cholinesterase inhibitors may help slow the progression of cognitive symptoms.
- Antipsychotics should be used judiciously and cautiously in patients with NCD with Lewy bodies. Carefully weigh the risks and benefits to the patient. Consider low-potency antipsychotics to begin with slow titration if needed.

20.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. A 72-year-old man has mild cognitive impairment and presents with parkinsonism and orthostatic hypotension. What is his diagnosis?

A. Probable major NCD with Lewy bodies
B. Probable mild NCD with Lewy bodies
C. Possible major NCD with Lewy bodies
D. Possible mild NCD with Lewy bodies

Answer: D

Diagnosis of NCD with Lewy bodies requires that patient meet criteria for major or mild NCD. Diagnosis of probably NCD with Lewy bodies requires two or more core features (fluctuating cognition, visual hallucinations, parkinsonism) or one or more core features plus one or more suggestive features (REM sleep behavior disorder, antipsychotic sensitivity). If only one core feature or one suggestive feature is present, criteria are only met for possible NCD with Lewy bodies. In addition, given his mild cognitive impairment, the patient likely has mild NCD. Therefore this patient's diagnosis is possible mild NCD with Lewy bodies. Therefore the correct answer is D.

MCQ 2. A 78-year-old patient presents with complaints of forgetfulness. What is his likely diagnosis if he were to develop Parkinson-like symptoms in (1) 8 months versus (2) 3 years?[1]

A. (1) AD-NCD, (2) LB-NCD
B. (1) LB-NCD, (2) PD-NCD
C. (1) LB-NCD, (2) AD-NCD
D. (1) LB-NCD, (2) LB-NCD

Answer: C

Occurrence of cognitive impairment and parkinsonism within 1 year of each other warrants a diagnosis of probable or possible major or mild NCD with Lewy bodies. If these symptoms are not linked temporally within 1 year of each other, another diagnosis should be considered. In this case, if the patient with cognitive impairments develops parkinsonism in 8 months, it is likely that he has LB-NCD. If the patient developed parkinsonism greater than 1 year after cognitive impairment, one would consider a diagnosis of AD-NCD as symptoms of parkinsonism may develop late in the evolution of Alzheimer tauopathy as the pathology generalizes to various neurological domains. Therefore, the correct answer is C.

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1 AD-NCD, neurocognitive disorder due to Alzheimer disease; LB-NCD, neurocognitive disorder with Lewy bodies; PD-NCD, neurocognitive disorder due to Parkinson disease.

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