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Lewy body dementia and Parkinson's disease with dementia

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Abstract Parkinson's disease (PD) is characterized by its motor impairment. However, non-motor symptoms such as psychiatric disorders, autonomic disturbances and sleep disorders frequently complicate the course of the disease. In particular, psychiatric disturbances including cognitive impairment, depression and psychosis impact these patients considerably. Approximately 31 % of PD patients suffer from cognitive impairment and dementia. Currently, two different clinical presentations are distinguished in PD patients, who present with dementia: Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB), which are two different presentations of a single underlying disease process leading to the deposition of α-synuclein. Clinically, PDD is distinguished from DLB alone by the different temporal manifestations of extrapyramidal motor symptoms. Dementia is characterized by a subtle onset and progressive cognitive decline with a predominant dysexecutive syndrome, which can be accompanied by different behavioral symptoms such as hallucinations, depression, anxiety and sleep disorders. Dysregulation of different neurotransmitters has been associated with cognitive decline, but reduced cholinergic transmission is currently thought to be the pivotal mechanism in the development of cognitive dysfunction. Therefore, cholinesterase inhibitors are used in the treatment of dementia and accompanying behavioral symptoms in PDD and DLB. The occurrence of dementia impacts not only the patients themselves but also their caregivers and family.

This article focuses on the clinical issues related to both disorders and is based on a meeting of experts which took place in April 2008 in Dresden.

Key words Parkinson's disease · dementia with Lewy bodies · dementia · α-synuclein · cholinesterase inhibitors

Introduction

Parkinson's disease (PD), one of the most common neurodegenerative disorders, is clinically characterized by rigidity, tremor, bradykinesia and impaired postural reflexes. Over the last 15 years we have learned that nonmotor symptoms also occur and have a considerable impact on the patient. Especially psychiatric symptoms such as depression, psychosis and cognitive impairment have been recognized as common comorbidities in PD, affecting the patient in a multimodal manner and resulting in a significant reduction in quality of life. Cognitive impairment can occur as a consequence of the longstanding disorder or may occur early in conjunction with parkinsonism [3, 8]. The latter constellation of symptoms is coined Dementia with Lewy bodies (DLB) while dementia occurring during longstanding Parkinson's disease is called Parkinson's disease with dementia (PDD). In this review we will focus on the clinical issues of Parkinson's disease and dementia and Dementia with Lewy bodies and compile current knowledge based on an expert meeting which took place in April 2008 in Dresden.

Etiology

There is a large debate whether PDD and DLB are two distinguishable disorders or whether they have a common etiology [20, 25]. The current available knowledge does not allow for a definite decision [20]. Therefore we will maintain throughout the article the concept of two distinct clinically defined disorders, representing two manifestations of the same disease etiology.

Currently, PDD and DLB are recognized as a subgroup of disorders characterized by pathological α-synuclein processing and deposition, termed synucleinopathies [15]. The neuropathology of DLB displays a wide spectrum of Lewy bodies (e.g. from classical limbic LB containing a core and a halo in HE stain to nearly invisible cortical LB), a broad distribution from the brainstem to the cortex and in many cases is associated with concurrent Alzheimer's disease pathology [29]. Based on recent clinicopathological studies three different dementia types can be distinguished:) PDD, DLB, and a Lewy body variant of Alzheimer's disease. The latter type distinguishes patients with clinical dementia where both cortical Lewy bodies and Alzheimer-typical neuropathological changes are found [29] but where there is a prevalence of the neurofibrillary AD pathology. The combination of AD associated pathology and LB pathology is common in patients with DLB (occurring in up to 70 %).

In neuropathological sections, PDD patients show a greater nigral neuronal loss compared with DLB patients, which probably reflects disease severity and duration, while DLB patients always show more cortical β-amyloid depositions and a severe involvement of the hippocampal CA2 sector in α-synuclein pathology [17]. However, concerning the histopathology, there is still no definite distinction criteria to discriminate between PDD and DLB [20].

Epidemiology

Only a few studies are available which evaluate the prevalence or incidence of cognitive impairment in patients with DLB or PDD [41]. In most studies, the currently available criteria for clinical diagnosis were not applied. Therefore, a wide range of estimates are communicated in the different studies. Based on neuropathological data, approximately 15 to 30 % of all dementias are caused by DLB (Table 2). In recent epidemiological clinical studies prevalence estimates for DLB range from 0–5 % for the general population and from 0–30.5 % of all dementia cases [41]. Annual incidence is 0.1 % for the general population and 3.2 % for all new dementia cases.

In a recent review the prevalence of PDD was stated to be 0.5 % in subjects > 65 years for the general population and 3.6 % of all dementia cases [3]. In addition, there is a duration-dependent increase of the prevalence of dementia in PD with 26 % at baseline (at baseline disease duration was 9 years in this sample), 52 % at 4 years, and 78 % at 8 years (corresponding to approximately 17 years of disease duration), indicating an increasing prevalence of dementia in relation to disease duration [1]. Approximately 24 to 31 % of PD patients suffer from dementia [1].

Risk factors associated with increased risk of dementia are older age at onset of PD, longer duration of PD symptoms, akinetic-rigid type of PD, axial impairment, presence of hallucinations, occurrence of psychosis, lower MMSE at baseline, and neuropsychological impairment on tests of verbal fluency (lexical and semantic), executive, visospatial, or memory functions.

Table 1 Differences between DLB and PDD (adapted from [14])

Neuropsychological deficits are almost identical
Psychiatric symptoms are the same
Clinical motor features are more symmetrical and tremor is less in DLB
REM sleep behavior disorder is observable in both disorders
Neuroleptic sensitivity is similar or less in PDD
Levodopa response is less in DLB
There is a similar response to cholinergic treatment

Table 2 A Prevalence and incidence of DLB in population-based studies [40]

Study	Numbers screened	Age	Dementia/population	DLB/population	DLB/dementia
Prevalence					
De Silva (2003)	703	> 65	4.0 % (28/703)	0.1 % (1/703)	3.6 % (1/28)
Herrera (2002)	1656	> 65	7.1 % (118/1656)	0.1 % (2/1656)	1.7 % (2/118)
Rahkonen (2003)	601	> 75	22.8 % (137/601)	5.0 % (30/601)	21.9 % (30/137)
Stevens (2002)	1085	> 65	6.6 % (72/1085)	2.0 % (22/1085)	30.5 % (22/72)
Yamada (2001)	3715	> 65	3.8 % (142/3715)	0.1 % (4/3715)	2.8 % (4/142)
Yamada (2002)	157	> 70	12.1 % (19/157)	0.0 % (0)	0.0 % (0)
Incidence					
Miech (2002)	5092	> 65	3.6 % a year (185/5092)	0.1 % a year (6/5092)	3.2 % a year (6/185)

Table 2 B Frequency from histopathological studies

Study	Number of cases	Pathological Diagnosis			
		AD	FTD	DLB	VaD
Barker (2002)	382	77 %	5 %	26 %	18 %
Parkkenen (2001)	774	69 %	6 %	14–27 %	14 %
Perry (1990)	345	70 %	8 %	22 %	–
Lindboe (1998)	284	71 %	–	7.8 %	33.8 %

Table 3 Cognitive domains and their impairment related to the underlying disease

Cognitive domain	
Memory	
Working	AD > DLB
Episodic	AD > DLB
Semantic	DLB = AD
Recall	AD > DLB
Perception	
Visuoperception	DLB > AD
Spatiovisual	DLB > AD
Visuoconstruction	DLB >> AD
Attention	DLB = AD
Executive functions	DLB = AD

Clinical presentation

Current criteria for the diagnosis of DLB and PDD have been published and are outlined in Tables 4–6 [11, 29]. PDD is distinguished from DLB alone by the different temporal manifestations of extrapyramidal motor symptoms: by definition, in patients with PDD motor symptoms should precede dementia by at least one year, whereas in patients with DLB parkinsonian symptoms may set in synchronously with dementia or shortly afterwards. This "one year rule" is an "arbitrary" one and takes a back seat in the recent consensus criteria [29].

There is no major divergence between the clinical presentation of patients with DLB and patients with PDD. Striking differences have been described for age of onset (PDD>DLB), levodopa responsiveness (PDD>> DLB) and the temporal course. No major differences (Table 1) have been found in the following signs and symptoms: cognitive profile, attention performance, neuropsychiatric features, sleep disorder, autonomic dysfunction, type and severity of parkinsonism, neuroleptic sensitivity and responsiveness to cholinesterase inhibitors [28].

Progression in motor symptoms is faster than in PDD patients, with a decline in the UPDRS motor score of approximately 9 % in DLB per year compared with 6.5 % in AD patients. In young onset DLB patients, however, the decline can be up to 49 % per year [22].

Sleep

Rapid –eye movement (REM) sleep behavior disorder is a parasomnia manifested by vivid and frightening dreams associated with simple or complex motor behavior during REM sleep [12]. The disorder is frequently associated with DLB, PDD, and multiple system atrophy, but it rarely occurs in other dementing disorders. Sleep disorders could contribute to hallucinations and behavioural disorders typical of DLB, and their treatment can improve fluctuations and quality of life.

Autonomic failure

Autonomic abnormalities including orthostatic hypotension and carotid-sinus hypersensitivity are more common in patients with DLB than in those with AD or in age-matched controls [35]. The clinical presentation of DLB is commonly characterized by "dizziness," presyncope, syncope, and falls. Urinary incontinence has been reported early in the course of DLB compared with AD [9].

Table 4 Features of dementia associated with Parkinson's disease according to Emre et al. [11]

I. Core features
   1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
   2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
      - Impairment in more than one cognitive domain
      - Representing a decline from premorbid level
      - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features
   1. Cognitive features:
      - Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
      - Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
      - Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
      - Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
      - Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
   2. Behavioral features:
      - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
      - Changes in personality and mood including depressive features and anxiety
      - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
      - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
      - Excessive daytime sleepiness

III. Features which do not exclude PD-D, but make the diagnosis uncertain
   - Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
   - Time interval between the development of motor and cognitive symptoms not known

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D
   - Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
     Acute confusion due to
     a. Systemic diseases or abnormalities
     b. Drug intoxication
     Major Depression according to DSM IV
   - Features compatible with "Probable Vascular Dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Table 5 Criteria for the diagnosis of probable and possible PD-D according to Emre et al. [11]

Probable PD-D
   A. Core features: Both must be present
   B. Associated clinical features:
      - Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
      - The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis
   C. None of the group III features present
   D. None of the group IV features present

Possible PD-D
   A. Core features: Both must be present
   B. Associated clinical features:
      - Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
      - Behavioral symptoms may or may not be present

   OR

   C. One or more of the group III features present
   D. None of the group IV features present

Table 6 Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB) according to McKeith et al. [29]

1. Central feature (essential for a diagnosis of possible or probable DLB)
   Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or 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.
2. Core features (two core features are sufficient for a diagnosis of probable DLB, one 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
3. Suggestive features (If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLIi should not be diagnosed on the basis of suggestive features alone.)
   REM sleep behavior disorder
   Severe neuroleptic sensitivity
   Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging
4. Supportive features (commonly present but not proven to have diagnostic specificity)
   Repeated falls and syncope
   Transient, unexplained loss of consciousness
   Severe autonomic dysfunction, e.g., 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
5. 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
6. Temporal sequence of symptoms
   DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinicopathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or alpha-synucleinopathy.

Neuropsychology

In patients with PDD and DLB, the most consistent neuropsychological deficit is frontal/executive dysfunction. Patients show poor attention, planning and inhibition, as well as slowed information processing. Patients have difficulty multitasking and take longer to complete simple or familiar tasks.

The detailed neuropsychological evaluation of patients with PDD and DLB may disclose disturbances of memory, attentiveness, speech, psychomotor performance as well as striking deficits in their visuospatial and visuoconstructive abilities [8, 14]. However, patients with PDD and DLB matched for dementia severity display similarly impaired visual perception relative to control subjects and non-demented PD patients [32]. When compared with AD patients matched for severity of dementia, PDD patients show qualitative and quantitative differences: the visuospatial or visuoconstructive disabilities are found to be significantly more prominent than in patients with AD while memory impairment is considerably less marked than in patients with AD (Table 3). DLB and PDD patients also performed significantly worse on attention functions. Language tends to be relatively well preserved in patients with PDD and DLB, however, patients usually have difficulties with prosody.

Decline in cognitive function is more pronounced in DLB than in PDD and compared with AD with a reduction in annual MMSE of -5.8 ± -4.5 points/y in DLB compared with -4.1 ± 3.0 points/y in AD patients [33].

Neuropsychological testing is the pivotal component in the diagnosis of dementia. As the MMSE is not sensitive enough for the deficits seen in Lewy body disorders, a specific screening instrument to assess cognitive impairment in PD has been developed. The Parkinson Neuropsychometric Dementia Assessment (PANDA) [18] takes approximately 15 minutes and allows for rapid screening. It does not aim for an exact diagnosis and the neuropsychological deficits must be detected using more sophisticated approaches. For this purpose we rec-

ommend the CERAD plus in addition to the Wechsler memory scale revised to evaluate memory function, as well as a brief test of attention. A depression scale, such as the BDI (or BDI-II) or the MADRS should also be implemented.

Laboratory examinations

Currently, no blood or CSF markers are available which can be used for the diagnosis, the disease development or as an outcome parameter in DLB or PDD [34]. Alpha-synuclein is an essential intracellular component of Lewy bodies and may be a candidate as a more specific CSF-surrogate or CSF-biomarker; however it has not yet been established in the clinical setting [38]. Changes of $A\beta_{1-42}$, tau, phospho-tau, 14-3-3 in the cerebrospinal fluid of patients with AD and DLB can be used for the diagnosis (Table 7) but do not specifically contribute to the differential diagnosis between the two entities [30].

With respect to EEG no major differences have been found between DLB and PD but more temporal slow transients were described compared with AD [7]. EEG or other neurophysiological testing, however, is not required in the diagnostic process in patients with PDD or DLB.

No alterations in imaging including MRI or cCT have been found to date that would permit a clear demarcation between PDD and DLB. Structural imaging, however, is a required tool to rule out other diseases which can be accompanied by dementia such as AD, vascular dementia or normal pressure hydrocephalus. Recently FP-CIT-SPECT has been used as a differential diagnosis to AD because a reduced uptake of the tracer has been found in AD patients (Fig. 1). In addition, ^{99mc}Tc-HM-PAO-SPECT as well as ^{18}F-deoxyglucose PET have demonstrated reduced uptake in the occipital areas of DLB patients compared to AD [16, 21]. More recently, experimental amyloid imaging using PIB-PET has shown differences in patients with DLB compared with PD and PDD with a higher amyloid burden in the DLB patients. Further research is necessary to establish amyloid burden as a clinical marker [23].

Table 7 Changes of $A\beta_{1-42}$, tau, phospho-tau (181P), 14-3-3 in the CSF of patients with AD and DLB [30]

	$A\beta_{1-42}$	tau	*p*tau (181P)	14-3-3
AD	↓	↑	↑	4/28
DLB	↓	n	n	0/5

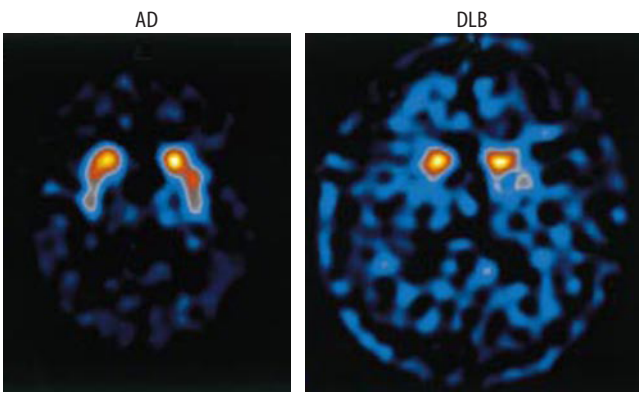

Fig. 1 FP-CIT SPECT in patients with Alzheimer's disease (AD) and Dementia with Lewy bodies (DLB). Tracer uptake is considerably reduced in DLB [39]

Therapeutics

There are different target signs and symptoms which have to be addressed in the treatment of PDD and DLB including treatment of the following: cognitive impairment, parkinsonian symptoms, depression and hallucinosis/psychosis.

Treatment of cognitive impairment

The treatment of DLB and PDD generally parallels that of Alzheimer's disease. At present there are only two multicenter double-blind and placebo-controlled studies available on the effect of cholinesterase inhibitors in DLB and PDD. The action of rivastigmine (3–12 mg) in PDD was assessed in a trial with 541 patients [10]. Minor albeit significant improvement of cognitive symptoms was documented. The patients treated with rivastigmine for 24 weeks scored a 2.1 point improvement versus an average deterioration by 0.7 points shown for the group receiving placebo.

In the study on DLB, 120 patients were treated with 6–12 mg rivastigmine over 20 weeks [26]. The defined target criterion was an improvement by 30 % versus the baseline constellation. This was met in 63 % of the patients treated with rivastigmine, compared to 30 % of the placebo group. Furthermore, the incidence of hallucinations and delusions was also reduced.

The effect of other cholinesterase inhibitors has so far only been studied in smaller patient populations. No aggravating effects on motor symptoms were demonstrated for either galantamine or donepezil; however an antidementive action was found based on the scales employed in the measurement of cognitive functions.

Since 2006, rivastigmine has been approved for the treatment of Parkinson's dementia. Despite limited data, the Cochrane Collaboration considers rivastigmine to be a drug with clinically relevant – albeit moderate – effects in 15 % of the patients [24]. The side effects observed under treatment with cholinesterase inhibitors must not be ignored. Close surveillance is recommended

for parkinsonian patients during the first 4 weeks of dosage adaption of their cholinesterase inhibiting medication. No data on the long-term action of rivastigmine and other cholinesterase inhibitors exist.

There are two commonly discussed issues that have not yet been resolved in clinical dementia research: (i) As a responder how can we define the response of patients treated with anti-dementia drugs? and (ii) When should a treatment be discontinued?

Currently, there are no evidence-based guidelines available. The expert group consented to the following procedure: neuropsychological testing should be repeated after three to six months and at least no deterioration of cognitive function should be found within this time period. Otherwise withdrawal of antidementive medication should be considered. The drug should be discontinued if there is considerable deterioration of the cognitive function after three years of treatment.

Treatment of parkinsonian symptoms

The treatment of parkinsonism parallels the treatment of PD. No controlled clinical trials have evaluated the treatment of parkinsonism in DLB or PDD. Responsiveness to levodopa is less pronounced than in patients with PD; however, there are reports of small series of DLB patients with improvement of motor symptoms following dopaminergic treatment. In DLB, one should only treat the movement disorder if the symptoms interfere with function. Anti-Parkinson drugs should be started at the lowest possible dosage and be increased cautiously, as visual hallucinations and delusions may be exacerbated or precipitated by the use of dopaminergic agents, especially with dopamine agonists and selegiline, antiglutamatergic and of course anticholinergic agents.

Treatment of depression

Depression is the most common psychiatric disturbance seen in PD, but also overlaps in patients with PDD and DLB [36]. Depressive episodes frequently aggravate the course of the disease, impacting gravely on the patients' quality of life [4]. According to prevalence estimates in the literature for comorbid depressive episodes, these vary between 7 and 76 % and occur notably more often in patients with parkinsonism than in patients with other non-neurological disorders. In contrast to other illnesses, establishing the diagnosis of depression as a concomitant interference can become difficult because of the overlapping symptoms of both Parkinson's disease and depression; it may thus be difficult to delimit one from the other. Depressive patients seldom spontaneously indicate typical depressive cardinal symptoms. Active exploration of additional symptoms of a depressive disorder in a clinical setting are therefore required. In diagnostic workup on depression, we follow a graded procedure consisting of four steps pursuant to the therapeutic suggestions of both the German Society for Psychiatry, Psychotherapy and Neurology and the Drug Safety Commission: (a) screening; (b) diagnostics in accordance with ICD-10; (c) defining the degree of depression; and (d) evaluating suicidal tendencies.

With respect to treatment, only a few controlled studies on the effectiveness of antidepressant agents in depression with IPS have been conducted, although a wide range of medication is available in Germany. From the current state of research, the meta-analyses at hand do not permit any evidence-based statement concerning the efficacy of antidepressants [37, 40]. Parkinsonian patients seem to respond to antidepressant medication considerably less than elderly patients without Parkinson's disease. The recommendations for their application are thus grounded on empirical insights. For a detailed description of the current treatment guidelines and drugs used we refer to recent published reviews [6, 19, 40].

Treatment of hallucinosis/psychosis

The treatment of psychiatric syndromes such as delirious states, hallucinations, delusion, and behavioral disorders often requires the application of neuroleptic agents. In DLB, this must be handled with caution in view of the severe reactions noticed under neuroleptic management. (Some authors regard this side effect "as an additional diagnostic criterion.") In addition, recent studies suggest a higher mortality in older subjects who are treated with neuroleptics. The application of neuroleptic agents can result in a serious parkinsonoid state, reduced consciousness and autonomic disturbances up to a malignant neuroleptic syndrome. Such adverse effects occur in 80 % of the DLB patients on administration of the classical neuroleptics. In about 54 % of cases, these were classified as severe [27]. With the newer atypical neuroleptics, these untoward effects are less frequently encountered; they have nonetheless been described for risperdal, olanazapine, clozapine and quetiapine. Thus, on the basis of current data clozapine or quetiapine should be given priority in treating psychosis, especially as the anticholinergic effect of quetiapine is considerably lower than in clozapine.

Although large clinical trials are missing, a comparative trial of quetiapine vs. clozapine suggested that quetiapine may have a beneficial effect without worsening parkinsonism [31]. Placebo-controlled data have shown that cholinesterase inhibitors may improve hallucinations in PDD and DLB. Further trials will be needed to investigate the indication of cholinesterase inhibitors in those afflictions.

Care of PD patients with cognitive impairment

Only one small study specifically assessed health status in patients with dementia with Lewy bodies. This study compared the health status of patients with dementia with Lewy bodies to that of patients with Alzheimer's disease [5]. In both conditions, health status as assessed by the QoL-Alzheimer's disease (an AD-specific health status scale) and the EuroQuol was markedly impaired. However, in DLB patients the reduction was considerably higher despite matching cognitive score, age and gender, and correlated with degree of independence, whether the patient lived with a caregiver and neuropsychiatric symptoms (in particular apathy and delusions). It was also found that almost a quarter of patients had negative scores on the EQ-5D utility index, which in population-based ratings equates to a condition considered worse than death. To the best of our knowledge, no study to date has addressed the impact of treatment with cholinesterase inhibitors on health status scores.

Dementia and associated psychosis has a major impact also on the caregivers and family. Associated illnesses and the likelihood of them staying in employment is considerably lower in caregivers, where PD patients suffer from cognitive complaints compared to PD patients without cognitive impairment. The odds for nursing home placement in PD patients with dementia is 2–2.5 but increases with accompanying psychosis to an OR of 17 [2, 13].

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