Chapter 2
Epidemiological Study on Dementia with Lewy Bodies

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Abstract Lewy bodies are the hallmark of the brainstem pathology of Parkinson's disease. Dementia with Lewy bodies (DLB) is a common degenerative dementing illness characterized by visual hallucination, fluctuation of cognitive function and consciousness, and REM-related behavior disorder. With the spread of the disease entity of DLB, the reported prevalence has been increasing; however, its accurate prevalence and incidence remains uncertain. In this chapter, we review the previous studies which reported the prevalence and incidence for DLB using the data from community and secondary care setting. As a result, DLB accounts for more than 4 % of all dementia cases, and the incidence of DLB is around 4 % of new dementia cases. However, with more widespread recognition of the clinicopathological entity of DLB, the values of its prevalence and incidence have recently been increasing. Although the consensus clinical criteria for DLB have been revised, its sensitivity remains lower. On the other hand, the results of pathological examination from a cohort study showed much higher prevalence of DLB. In the future, effort should be indispensable to dissipate the discrepancy between clinical and pathological diagnosis of DLB.

Keywords Prevalence • Incidence • Epidemiology • Dementia with Lewy bodies

2.1 Introduction

Lewy bodies, which are the hallmark of the brainstem pathology of Parkinson's disease, were found relatively recently to occur diffusely in the cerebral cortex and to be accompanied by a dementia syndrome with characteristic clinical features. Dementia with Lewy bodies (DLB) is now used as a preferred term for a variety of clinical diagnoses including diffuse LB disease (DLBD) [1], LB dementia (LBD) [2], and senile dementia of LB type (SDLT) [3].

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Although DLB was initially thought to be uncommon, with the spread of the disease entity of DLB, the reported prevalence has been increasing recently. Nevertheless, it is said that DLB remains underdiagnosed, with more than half cases missed [4]. Accurate diagnosis of DLB is particularly important, because it facilitates management of common associated symptoms such as hallucination, increased risk of falls, loss of consciousness, and REM-related behavior disorder. These symptoms of DLB are very burdensome for caregivers compared to those presented in other dementing illnesses. To determine the population prevalence and incidence of DLB, we review the previous studies which reported the prevalence and incidence for DLB using the data from community and secondary care setting.

2.2 Summarized Results of the Previous Studies

Thus far, two previous systematic reviews of epidemiological studies [5, 6] are available. Besides the data from studies reviewed in the reviews, we used three additional studies on the epidemiology of DLB. Hereafter, we describe the summarized results of the two reviews and show the main results of the additional studies.

2.2.1 Description of the Studies Examined

First we show the description of population-based studies reporting the prevalence or incidence of DLB listed in the above-noted systematic review 6) (Tables 2.1 and 2.2).

2.2.2 Zaccai's Review 2005 [5]

This is the first systematic review of epidemiological studies of DLB, which identified just six population prevalence studies and one incidence study [7–13]. All studies used the DSM-III-R or DSM-IV criteria to diagnose dementia. Five prevalence studies used the McKeith 1996 criteria [14] (Table 2.3), while one did a modified McKeith 1995 criteria [15]. with no restriction on duration of Parkinson's disease.

Study results are as follows. Prevalence estimates for clinical DLB ranged from 0 to 5 % (median 0.1 %) with regard to the general population and from 0 to 30.5 % (median 6.6 %) of all dementia cases. The Cache County study provides the only incidence report, estimated at 0.1 % a year for the general population and 3.2 % a year for all new dementia cases. Six studies did not report on the sex of those diagnosed, while one reported that they were all men. The authors noted that the

Table 2.1 Population-based prevalence studies

Study	No. in study	Age (years)	No. with dementia	No. of DLB	DLB/over 65 years, % (95 %CI)	DLB/all dementia, % (95 %CI)
Yamada (2001)	3715	65	142	4	0.11 (0.03–0.28)	0.28 (0.08–0.71)
Ikeda (2001)	1145	>65	60	1	0.09 (0.00–0.49)	1.67 (0.04–8.94)
Yamada (2002)	157	>70	19	0	0.00 (0.00–2.32)	0.00 (0.00–17.7)
Stevens (2002)	1085	>65	72	7	0.65 (0.26–1.32)	9.72 (4.0–19.0)
Herrera (2002)	1656	>65	118	2	0.12 (0.01–0.44)	1.69 (0.21–5.99)
de Silva (2003)	703	>65	28	1	0.14 (0.00–0.79)	3.57 (0.09–18.35)
Rahkonen (2003)	601	>75	137	30	4.99 (3.39–7.05)	21.9 (15.29–29.76)
Tognoni (2005)	1600	>65	99	3	0.19 (0.04–0.55)	3.03 (0.63–8.60)
Galasko (2007)	1984	>65	243	1	0.05 (0.00–0.28)	0.41 (0.01–2.27)
Molero (2007)	2438	>65	196	4	0.16 (0.04–0.42)	2.04 (0.56–5.14)
Fernandez Martinez (2008)	1931	>65	108	10	0.52 (0.25–0.95)	9.23 (4.53–16.37)
Gascon-Bayarri (2007)[a]	1754	>65	165	15	0.86 (0.48–1.41)	9.09 (5.18–14.55)
Jhoo (2008)	714	>65	37	2	0.28 (0.03–1.01)	5.41 (0.66–18.2)
Gurvit (2008)	1019	>65	93	9	0.88 (0.04–1.67)	9.68 (4.52–17.58)
Arslantas (2009)	3100	>55	262	0	0.00 (0.00–0.12)	0.00 (0.00–1.4)
Kim (2011)	1673	>65	351	2	0.12 (0.01–0.43)	0.57 (0.07–2.04)
Yusuf (2011)	322	>65	9	0	0.00 (0.00–1.14)	0.00 (0.00–33.63)
Dimitrov (2012)[a]	540	>65	39	2	0.37 (0.05–1.33)	5.13 (0.63–17.32)
Total	26137		2178	93	0.36 (0.29–0.44)	4.24 (3.44–5.17)

Van Jones et al. [6]
DLB dementia with Lewy bodies, *CI* confidence interval
[a]Used the revised 2005 criteria

number of available studies was too small to hypothesize on the potential effect of age, sex, and genetic background on the results.

It is of note the authors referred to the issue of the nosological relationship between DLB and Parkinson's disease dementia (PDD) which remains not yet clear. Theoretically, 1-year rule is the key to differentiate DLB from PDD;

Table 2.2 Population-based incidence studies

Study	No. in study	Age (years)	Dementia incidence (case/1000 person-years)	DLB incidence in whole population (cases/1000 person-years)	DLB incidence per dementia diagnosis (%)
Miech (2002)	5092	>65	36.3	0.57	3.2 (6/185)
Matsui (2009)[a]	887	>65	32.3	1.40	4.4 (12/275)
Perez (2010)[a]	3777	>65	26.9	1.12	4.5 (28/644)
Total				0.87	3.8 (3.39–4.15)

Van Jones et al. [6]
DLB dementia with Lewy bodies
[a]Used the revised 2005 criteria

Table 2.3 The 1996 original criteria for probable and possible DLB

1. The central feature required for a diagnosis of DLB is 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 and of fronto-subcortical skills and visuospatial ability may be especially prominent
2. Two of the following core features are essential for a diagnosis of probable DLB; one is essential for possible DlB:
(a) Fluctuating cognition with pronounced variations in attention and alertness
(b) Recurrent visual hallucinations which are typically well formed and detailed
(c) Spontaneous motor features of Parkinsonism
3. Features supportive of the diagnosis are:
(a) Repeated falls
(b) Syncope
(c) Transient loss of consciousness
(d) Neuroleptic sensitivity
(e) Systematized delusions
(f) Hallucinations in other modalities
4. A diagnosis of DLB is less likely in the presence of:
(a) Stroke disease, evident as focal neurological signs or on brain imaging
(b) Evidence on physical examination and investigation of any physical illness, or other brain disorder, sufficient to account for the clinical picture

Consensus guidelines for the c1inical and pathological diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop (McKeith et al. [15])

however, the differential diagnosis is difficult in general and community survey in particular.

2.2.3 *Vann Jone's Review 2014 [6]*

This is the second review on the epidemiological studies of DLB, which identified 18 population-based prevalence study [7–12, 16–27] and two [28, 29] population-based incidence studies. Of the 18 prevalence studies, seven had been included in the review by Zaccai et al. All of the studies reviewed used the DSM-III-R or DSM-IV criteria to diagnose dementia. As to the prevalence studies of DLB, two studies used the revised 2005 criteria and the remaining 16 did the original 1996 criteria. For the incidence studies, two did the revised 2005 criteria [30] (Table 2.4) and one the 1996 one.

Table 2.4 The 2005 revised criteria for DLB

Diagnostic criteria for Dementia with Lewy Bodies 2005
Central feature:
Progressive dementia – deficits in attention and executive function are typical. Prominent memory impairment may not be evident in the early stages
Core features:
Fluctuating cognition with pronounced variations in attention and alertness
Recurrent complex visual hallucinations
Spontaneous features of Parkinsonism
Suggestive features:
REM sleep behavior disorder (RBD), which can appear years before the onset of dementia and Parkinsonism
Severe sensitivity to neuroleptics occurs in up to 50 % of LBD patients who take them
Low dopamine transporter uptake in the brain's basal ganglia as seen on SPECT and PET imaging scans
Supportive features:
Repeated falls and syncope (fainting)
Transient, unexplained loss of consciousness
Autonomic dysfunction
Hallucinations of other modalities
Visuospatial abnormalities like depth perception, object orientation, directional sense, and illusions
Other psychiatric disturbances like systematized delusions, aggression, and depression
A probable LBD diagnosis requires either:
Dementia plus two or more core features
Dementia plus one core feature and one or more suggestive features
A possible LBD diagnosis requires:
Dementia plus one core feature
Dementia plus one or more suggestive features

Synucleinopathies, with and without dementia, encompass a wide range of diseases including Parkinson's disease, multiple system atrophy, rapid eye movement (REM) sleep behavior disorder, and dementia with Lewy bodies (DLB). DLB is a neurodegenerative disorder resulting in slowly progressive and unrelenting dementia until death

Regarding population prevalence of DLB, the mean value in the whole population over 65 years old was 0.36 % or one in 270 people, with a wide range from zero to 21.9 %. Among those with dementia, 4.2 % were found to have DLB. This equates to one in 24 cases. There was a wide variation in prevalence rates across studies. Among the more recent (after 2005) studies, the prevalence of DLB in the over-65 population ranged from zero to 1.2 % and from zero to 9.7 % of those with dementia. This is a narrower range than the results from previous report by Zaccai et al. [5]. According to the 1996 consensus criteria, probable DLB can be diagnosed if any two of the three key symptoms are present, namely, fluctuation, visual hallucinations, or spontaneous motor features of Parkinsonism, and possible DLB if only one is present. Above-described mean prevalence for all included studies is a reflection of probable DLB cases only. Two studies included possible and also probable DLB cases: these reported an increase in DLB diagnoses from 9.7 to 30.5 % and from 9.1 to 12.7 % of all dementias, respectively, once possible cases were added to probable ones.

Population prevalence studies that used the 2005 criteria reported a mean prevalence of 8.2 % compared to 3.7 % among those who used the 1996 criteria, a finding that indicated statistically significant difference. Consistent with these findings, the only study [24] that directly compared and contrasted the 1996 and 2005 criteria on the same sample found a 25 % increase in probable DLB cases identified.

As to population incidence of DLB, annual incidence rates for DLB were found to be 3.8 % (range 3.2–4.5 %) of new dementia diagnoses and 0.87 (range 0.57–1.4) cases/1000 person-years. The two most recent incident studies both used the 2005 criteria [28, 29] and found a 35–40 % increase in DLB compared to the only previous incidence study (1996 criteria), although this was not statistically significant.

Of the 11 population samples that included an average age of participants, there was a positive correlation between age and the proportion of DLB compared to all dementia, although this was not found to be significant. Regarding the gender difference of DLB, the authors showed controversial results.

2.2.4 Additional Recent Reports

An additional study that has not been examined in the review by Van Jones et al. [6] came from Japan. The study [31] was conducted in a rural island of Japan using door-to-door 2-phase design. As a result, the prevalence (cases/100 persons aged 65 years and older) was 11.0 for all types of dementia and 0.53 for DLB. Thus DLB accounted 4.8 % of all diagnosed dementia in this survey. This result appears to be similar with that reported in the review by Van Jones et al. A recent Spanish study [32] showed similar result. This study was conducted in an urban region of Valladolid, Spain. The authors showed that DLB accounted 7.7 % of all diagnosed dementia.

On the other hand, an incidence study has recently been reported from the USA [33]. This study was conducted among residents of Olmsted County, Minnesota, from 1991 through 2005. The report showed that the incidence rate of DLB was 3.5 per 100,000 person-years overall, and it increased steeply with age and is markedly higher in men.

Recognition of DLB has recently become more widespread since the discovery of α-synuclein as the major constituent of Lewy bodies in 1997. Particularly, immunostaining of α-synuclein makes it easy to identify neocortical-type Lewy bodies. Consequently, with the liberal definition of the pathological criteria of DLB in 1996, no less than 60 % of Alzheimer's disease cases may be considered to meet pathological criteria for DLB. Fujimi et al. [34] first reported a community-based clinicopathological study of DLB. Using the 2005 criteria, they examined community-based consecutive autopsy cases. As a result, 10.3 % of the non-demented subjects and 31.2 % of the demented subjects showed the Lewy body pathology. Applying the revised pathological criteria to the 205 demented subjects, they determined the types of Lewy body pathology. The results are as follows: 11 cases (5.4 %) were brainstem predominant, 24 (11.7 %) were limbic type, and 24 (11.7 %) were diffuse neocortical type. Thus, 28.8 % of the demented subjects were diagnosed as having Lewy body pathology in terms of the revised pathological criteria.

2.3 Issues for the Future Studies

When we discuss the epidemiological issues of DLB, we must refer to the predictive accuracy of consensus clinical criteria for DLB. Litvan et al. [35] showed that sensitivity of case detection was variable and unacceptably low in several others but one prospective study. In contrast, specificity was generally found to be high, suggesting that the clinical criteria for probable DLB are best used for confirmation of diagnosis (few false positives), whereas those for possible DLB may be more valuable in screening but have a relatively high false-negative rate. Improved methods of identifying the core feature "fluctuation" have potential to increase diagnostic accuracy [36].

2.4 Summary

Reviewing the previous epidemiological studies, DLB accounts for more than 4 % of all dementia cases, and the incidence of DLB is around 4 % of new dementia cases. However, with more widespread recognition of the clinicopathological entity of DLB, the values of its prevalence and incidence have recently increased. Although the consensus clinical criteria for DLB have been revised, its sensitivity remains lower. On the other hand, the results of pathological examination from a

cohort study showed much higher prevalence of DLB. In the future, effort should be indispensable to dissipate the discrepancy between clinical and pathological diagnosis of DLB.

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