Dementia With Lewy Bodies
A Clinicopathologic Series of False-positive Cases

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Abstract: Diagnosing dementia with Lewy bodies (DLB) is challenging as symptoms are heterogenous and not specific to the disease. Here we present a clinicopathologic series of false-positive DLB cases. Patients were enrolled retrospectively from the Netherlands Brain Bank when they met the clinical criteria of probable DLB, but with a pathologic diagnosis other than DLB or Parkinson's disease dementia. Twenty-two false-positive cases were selected. Alzheimer disease with or without copathology was the most common (64%) pathologic diagnosis. Other pathologic diagnoses, such as frontotemporal dementia, multiple-system atrophy, Creutzfeldt-Jakob disease, and autoimmune encephalitis, were also encountered. Atypical clinical signs for DLB were present in almost half of the cases and could be a trigger to consider other diagnoses than DLB. Additional diagnostic examinations, feedback of pathologic diagnosis, and the creation of a set of clinical features that are indicative of other conditions, could reduce the amount of false-positive DLB cases.

Key Words: dementia with Lewy bodies, false-positive cases, pathology, atypical clinical signs

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Dementia with Lewy bodies (DLB) is one of the most common types of dementia in the elderly[1] and is pathologically characterized by cortical Lewy bodies and Lewy neurites.[2] Clinical symptoms include progressive cognitive decline, parkinsonism, visual hallucinations, fluctuating cognition, and REM sleep behavior disorders (RBD).[2] Often, there is a large heterogeneity among DLB patients in their clinical presentation, making it rather difficult to determine a correct diagnosis. Furthermore, symptoms are not specific to the disease, which leads to many DLB cases being missed or misdiagnosed.[2] As DLB has a serious impact on quality of life and disease management is complex, an early and correct diagnosis is very important.[2]

The clinical criteria of DLB have been updated several times to improve diagnostic accuracy. A recent review by Rizzo et al,[3] shows an increased sensitivity of the 2005 clinical criteria in comparison with the 1996 clinical criteria, despite a decreased specificity. This means that false-positive cases may be encountered more frequently when using the clinical criteria of 2005. The diagnostic accuracy of the clinical criteria of 2017 is not yet known.

In this study, we focused on false-positive DLB cases (DLB mimics) to increase our understanding of their occurrence and causes thereof.

METHODS AND RESULTS

We collected all clinical and pathologic records in which the word "Lewy" was mentioned of patients who donated their brains to the Netherlands Brain Bank (NBB; www.brainbank.nl) between 1987 and 2016. Two medical doctors (L.P.M. and L.J.M.V.) reviewed the data and included all patients who met the clinical criteria of probable DLB[2] retrospectively. Symptoms were only considered present if literally mentioned or clearly described. Symptoms in all stages of the disease were considered. Mimics were selected on the basis of a pathologic diagnosis other than DLB or Parkinson's disease dementia (low probability that the clinical syndrome was related to Lewy pathology[2]). All patients or their representatives signed informed consents for brain autopsy and the use of their brain tissue and medical records for research purposes. All procedures of the NBB were approved by the medical ethical committee of VU University Medical Center (Amsterdam UMC, Amsterdam).

Of the 80 patients who met the clinical criteria, 58 patients had a high or intermediate probability that the clinical syndrome was related to Lewy pathology, leaving 22 DLB mimics. The mimics had a mean age of onset of 67.1 ± 11.8 years, a mean disease duration of 6.2 ± 3.2 years, and 55% were male individuals. Overall, 82% of the mimics presented with cognitive decline. Parkinsonism, visual hallucinations, and fluctuations were present in 73%, 86%, and 77% of the mimics, respectively. Magnetic resonance imaging (MRI) scan was performed in 59% (no conclusive results), cerebrospinal fluid (CSF) analysis in 14%, dopamine transporter imaging in 9% (no abnormal findings), and polysomnography in none of the mimics. Atypical signs were present during life in 45% of the mimics (Table 1).

A pathologic diagnosis of pure Alzheimer disease (AD) (n = 7) or AD with copathology (n = 7) was observed most often, followed by frontotemporal dementia (FTD) (n = 2) and other neurodegenerative diseases [multiple-system atrophy (MSA), Creutzfeldt-Jakob disease (CJD), and neurofilament inclusion body disease, n = 1 each] and non-neurodegenerative diseases [autoimmune encephalitis (AIE), glioblastoma, and old contusion, n = 1 each] (Table 1).

Pure AD

Severe AD pathology [Braak neurofibrillary tangles (NFT) > 4; CERAD C][4] without copathology was seen in

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TABLE 1. Patients' Characteristics According to Pathologic Diagnosis

	Pure AD							AD and Other Pathology			
	Patient I	**Patient II**	**Patient III**	**Patient IV**	**Patient V**	**Patient VI**	**Patient VII**	**Patient VIII**	**Patient IX**	**Patient X**	**Patient XI**
Pathologic diagnosis	Pure AD (5C*)	Pure AD (6C*)	Pure AD (5C*)	Pure AD (5C*)	Pure AD (6C*)	Pure AD (6C*)	Pure AD (5C*)	AD (3C*) +vascular damage	AD†+vascular damage	AD (6B*)+Lewy bodies in the amygdala	AD (3C*) +vascular damage
Age of onset (y)	77	65	85	66	54	79	83	80	75	55	73
Sex	F	M	M	F	M	F	F	M	F	F	F
Disease duration from first symptom (y)	4	6	2	4	10	12	8	3	4	7	10
Symptom of onset	Cognitive decline	Cognitive decline	Cognitive decline	Cognitive decline	Cognitive decline	Cognitive decline	Cognitive decline	Cognitive decline	Cognitive decline	Cognitive decline	Cognitive decline
Parkinsonism (years after onset)	Yes (3)	No	No	Yes (2)	No	Yes (2)	Yes (1)	Yes (1)	Yes (3)	Yes (2)	Yes (5)
Visual hallucinations (years after onset)	Yes (2)	Yes (3)	Yes (1)	No	Yes (9)	Yes (2)	Yes (0)	Yes (0)	Yes (3)	Yes (1)	Yes (4)
Fluctuations (years after onset)	No	Yes (5)	Yes (1)	Yes (2)	Yes (5)	Yes (2)	No	Yes (1)	Yes (3)	No	Yes (6)
CSF	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes, AD profile	NA
Positive DAT imaging	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Atypical signs	Early and prominent memory deficits	Early and prominent memory deficits	Early and prominent memory deficits	—	—	—	—	—	Early and prominent memory deficits	—	—

*Braak staging for neurofibrillary tangles and CERAD protocol for neuritic plaques.[4]

†No additional scoring available.

AD indicates Alzheimer disease; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; CT, computed tomography; DAT, dopamine transporter; F, female; FTD, frontotemporal dementia; M, male; MSA, multiple-system atrophy; NA, not available; PSP, progressive supranuclear palsy.

TABLE 1. *(Continued)*

AD and Other Pathology			FTD		MSA	CJD	Neurofilament inclusion body disease	Autoimmune encephalitis	Glioblastoma	Old Contusion
Patient XII	**Patient XIII**	**Patient XIV**	**Patient XV**	**Patient XVI**	**Patient XVII**	**Patient XVIII**	**Patient XIX**	**Patient XX**	**Patient XXI**	**Patient XXII**
AD (5C*) +vascular damage	AD (4B*) +PSP pathology	AD (6C*) +atypical Lewy bodies	Progressive subcortical gliosis	FTLD-TDP type A	MSA	Sporadic variant CJD	Neurofilament inclusion body disease	Autoimmune encephalitis	Glioblastoma	Contusion frontal and temporal lobe
84	65	51	55	60	56	79	56	55	57	41
F	M	M	F	M	M	M	M	M	F	M
6	8	6	5	3	10	1	7	5	12	25
Cognitive decline	Cognitive decline	Cognitive decline	Cognitive decline	Parkinsonism	Cognitive decline	Parkinsonism	Cognitive decline	Cognitive decline	Cognitive decline	Hallucinations
No	Yes (7)	No	Yes (1)	Yes (0)	Yes (7)	Yes (0)	Yes (5)	Yes (2/3)	No	Yes (25)
Yes (2)	Yes (5)	Yes (2)	Yes (2)	No	Yes (4)	Yes (0)	No	Yes (3/4)	Yes (0)	Yes (0)
Yes (3)	No	Yes (2)	No	Yes (2)	Yes (7)	Yes (0)	Yes (5)	Yes (2/3)	Yes (0)	Yes (25)
NA	NA	NA	NA	Yes, amyloid and tau not tested	NA	NA	NA	Yes with lymphocytic reaction	NA	NA
NA	NA	NA	NA	NA	NA	No	NA	No	NA	NA
—	—	—	Early and prominent behavioral changes; hypoperfusion in frontal lobes on SPECT imaging	—	Early and prominent autonomic nervous system complaints	Short disease duration	Positive family history; frontal hypoperfusion on SPECT imaging	Early and prominent psychiatric and behavioral problems; lymphocytic reaction in CSF	—	Early and prominent behavioral changes; long disease duration

7 patients. Clinical signs that were atypical for DLB were early and prominent memory deficits in patients I to III.

AD and Other Pathology

Intermediate or severe AD pathology (Braak NFT ≥ 3; CERAD ≥ B) with other pathology, for example, Lewy bodies or vascular damage, was seen in 7 patients. Atypical signs were early and prominent memory deficits in patient IX.

FTD

In patient XV, slight frontal atrophy, ballooned neurons, and subcortical gliosis were present, but no Pick bodies were found. Atypical signs were behavioral changes early in the disease course and hypoperfusion of the frontal lobes on SPECT imaging. In patient XVI, striatal atrophy and TDP-43-positive inclusions and no NFT were found.

MSA

Severe neuronal loss in the substantia nigra, the putamen and pallidum, and glial cytoplasmic α-synuclein-positive inclusions were observed in patient XVII. Signs that were atypical for DLB were severe autonomic dysfunction early in the disease course and dementia after 7 years of symptom onset.

CJD

The brain of patient XVIII showed severe spongiform degeneration with vacuolation, PrP depositions, Kuru plaques, and prion plaques. A sign that was atypical for DLB was a disease course of 1 year.

Neurofilament Inclusion Body Disease

Large, sometimes target-like neuronal inclusions localized in the cortical gray matter and the spinal cord were seen in patient XIX. In addition, this patient had a glioblastoma at autopsy, not seen on an MRI scan 1 year earlier. Atypical signs in this patient were a family history of neurofilament inclusion body disease and frontal hypoperfusion on SPECT imaging.

AIE

Lymphocytic infiltrates and extensive loss and gliosis of, among others, the hippocampi, amygdala, and basal ganglia, were observed in patient XX. Clinical signs that were atypical for DLB were severe depression, catatonia and behavioral problems, and a lymphocytic reaction in the CSF.

Glioblastoma

In patient XXI tumorous tissue was observed in the left temporal lobe composed of atypical glial cells, with considerable polymorphia, including multinucleated glial cells and necrosis.

Old Contusion

In patient XXII, 2 cortical defects with gliosis and ferruginous pigment were seen in the frontal and temporal lobe. Atypical signs for DLB were prominent behavioral changes at the age of 41 and a disease duration of 25 years.

DISCUSSION

We found 22 mimics in a population of 80 patients who retrospectively met the clinical criteria of DLB. The majority (87%) of the mimics had another neurodegenerative disease, which was most often AD or AD with copathology (64%). Atypical clinical signs for DLB were observed in 10 mimics and included atypical symptoms, atypical results of additional examinations, an atypical family history, and an atypical disease duration. These atypical signs could be a trigger to consider other diagnoses than DLB.

The amount of mimics in our population (28%) is slightly higher than has been shown in a recent study on the accuracy of the 2005 clinical criteria for the diagnosis of DLB.[5] This study reported a mimic frequency of 21% in 14 clinically diagnosed probable DLB patients. Differences between this study and our study include study design (prospective study vs. retrospective study), clinical criteria (2005 vs. 2017), and sample size (3 mimics vs. 22 mimics). Similar to our study, a pathologic diagnosis of AD was most often observed.

In our study, approximately half of the mimics had atypical signs during life. Atypical symptoms included prominent memory and behavioral, psychiatric, or autonomic nervous system complaints early in the disease course. When these symptoms are present, other diagnoses such as AD, FTD, AIE, or MSA should be considered. Dopamine transporter imaging is one of the best examinations to differentiate between DLB and AD.[6] An MRI scan or FDG-PET scan are often used to differentiate between DLB and FTD.[7] Measuring autoantibodies in serum and/or CSF and an MRI scan are important to differentiate between DLB and AIE.[8] The diagnosis of MSA is based on clinical symptoms, but an MRI scan might be useful to differentiate between DLB and MSA.[9] Atypical results of additional examinations included frontal hypoperfusion on SPECT imaging. When frontal hypoperfusion is present, FTD should especially be considered.[7] Furthermore, an atypical family history with multiple family members with proven neurofilament inclusion body disease was observed. If a patient has a similar clinical presentation as his family members, it deserves preference to consider this diagnosis until it can be excluded. At last, a disease duration of 1 year and > 25 years were seen, which is atypical for DLB (mean survival time in DLB: 6.1 ± 4.2 y).[10] The mean survival time of CJD is 5 months[11] and should be considered when the patient presents with a very rapidly progressive disease.

The main limitation of this study is its retrospective nature. Specific clinical information, such as the presence of fluctuations or RBD, were sometimes missing, and additional examinations were scarcely performed. Probable DLB patients may, therefore, be missed, and the total amount of probable DLB patients may be higher. This could have led to a slightly different DLB population in this study in comparison with the DLB population seen today, in which clinical signs are often better recognized and where additional examinations are increasingly performed. Furthermore, selection bias may have been introduced by the preference of patients to register as brain donors when the diagnosis during life was not clear. This may have led to a higher percentage of DLB mimics in this study.

This study shows that DLB mimics occur relatively often, especially those with a pathologic diagnosis of AD. Additional diagnostic examinations and feedback of pathologic diagnosis to clinicians is very important to reduce the amount of DLB mimics. Furthermore, the specificity of the clinical criteria of DLB could be improved by including a set of clinical features that are indicative of other conditions and justify further investigation.

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