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Twin Pairs Discordant For Neuropathologically Confirmed Lewy Body Dementia

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Abstract

Aim—Little is known about the concordance rate in twins for dementia with Lewy bodies (DLB). The rate of agreement between clinical and pathological diagnoses for DLB is typically low, necessitating confirmation of the diagnosis neuropathologically.

Methods—Participants were 17 twin pairs enrolled in the Duke Twins Study of Memory in Aging in which at least one member of the pair had an autopsy confirmed diagnosis of DLB, Alzheimer's disease (AD) with Lewy bodies, or fronto-temporal dementia with Lewy bodies. We assessed characteristics of those with dementia and examined rates of concordance for pathological confirmed dementia.

Results—Four monozygotic twin pairs had a proband with neuropathologically confirmed pure DLB; all remained discordant for dementia for periods up to 16 years or more. Five of 13 pairs in which the proband had AD plus DLB were concordant for dementia, but only one pair was concordant for AD plus DLB, while the cotwins in the other four pairs had other types of dementia.

Conclusions—The present study indicates that even among twins, a diagnosis of DLB in one twin does not predict the same diagnosis in the other twin. Neuropathological discordance in type of dementia among monozygotic pairs hints at environmental or epigenetic factors playing a role in Lewy body pathology.

Keywords

Twin Studies; Dementia with Lewy Bodies; Autopsy; Neuropathology

Introduction

Dementia with Lewy bodies (DLB) is reportedly the second most common neurodegenerative dementing disorder.[1] Pathologically Lewy bodies are distributed throughout the limbic system and neocortex and often co-occur with pathological signs of Alzheimer's Disease (AD). These

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"Lewy body variant" patients may not display the classic clinical phenotype of DLB, making pathologic verification necessary for accurate diagnosis.

Genetic factors are important determinants in neurodegenerative diseases, such as AD and Parkinson's disease (PD), but little is known about genetic predisposition to DLB. Mutations in alpha-synuclein, beta synuclein and presenilin 1 can cause dementia with Lewy body pathology. [2-4] Twenty three percent of individuals with DLB have also been found to have mutations in the lysosomal glucocerebrosidase gene.[5] Despite these reports, most DLB appears to be sporadic. We present a case series of twin pairs in which at least one twin had pathologic evidence of DLB.

Methods

Sample

Participants were 11 monozygotic (MZ) and 6 dizygotic (DZ) twin pairs enrolled in the Duke Twins Study of Memory in Aging in which at least one member of the pair had an autopsy confirmed diagnosis of Lewy body dementia, Alzheimer's disease with Lewy bodies, or fronto-temporal dementia with Lewy bodies. To be included in the sample, the co-twins with dementia must have had an autopsy for neuropathological diagnosis. Eleven of the twin pairs were members of the National Academy of Sciences-National Research Council (NAS-NRC) Registry of World War II veteran male twins and 6 pairs were elderly volunteers who had responded to recruitment advertisements for the Duke Twin Studies. Zygosity was determined by blood or buccal DNA samples for nine pairs and in eight pairs from the best available information from questionnaire responses, fingerprint analysis, and anthropometric data from military records. APOE genotype was determined from blood or buccal DNA samples.

Dementia Assessment and Diagnosis

The diagnosis of dementia was determined based on the outcome of a multi-step telephone screening and in-person assessment protocol that has been described previously.[6] Members of the NAS-NRC Twin Registry were screened for possible cognitive impairment using a two stage telephone screening protocol. Individuals whose telephone screening indicated possible dementia received a comprehensive in-person dementia evaluation. The diagnostic criteria for DLB have evolved during the 17 years of this study, so information on the currently accepted clinical symptoms associated with DLB[7] were not systematically obtained. We sought to obtain medical records for neuroimaging and laboratory results relevant to the diagnosis.

Members of the volunteer twin sample were screened for cognitive impairment using a telephone interview. Those with suspected dementia were either evaluated in-person (N = 17) or by medical record review to confirm the diagnosis of dementia (N = 5). For both study samples the cognitively intact co-twins were followed using the telephone screening instruments (n = 7) or in-person assessments (N = 5).

Consensus conferences of specialists in neurology, neuropsychology, and geriatric psychiatry assigned final clinical diagnoses based on review of available data. Diagnoses were based on published criteria[8, 9, 10, 7] from the time of their publication forward. We assigned a diagnosis of "Dementia, Undetermined Etiology" when the clinical presentation was too complex or atypical to permit a diagnosis of Possible AD, but there was no other apparent cause for dementia.

Neuropathologic diagnosis

The autopsy evaluations for fourteen individuals were done by co-investigators at Oregon Health and Science University (M.J. Ball) and Duke University Medical Center(C.M. Hulette).

For the remaining 8 individuals, the neuropathologic evaluation was conducted by neuropathologists with expertise in the diagnosis of neurodegenerative diseases throughout the U.S. The autopsies spanned from 1992 through 2007, a time period during which the neuropathological criteria for AD and other types of dementia have changed. The diagnostic criteria and the histochemistry procedures reflected the standards at the time the autopsies were done. Either the CERAD[11] or the NIA and Reagan Institute Working Group[12] criteria were used to diagnose AD. According to the protocols which were currently accepted at the center devoted to AD research, various methods were used to enhance the visibility of neurofibrillary tangles and neuritic diffuse plaques, including tau IHC, Abeta IHC, Bielschowsky or microwave King silver, congo red, Gallyas, Campbell-Switzer or Thioflavine-S.

Sections from the brainstem and cortex were stained for Lewy bodies using ubiquitin or alpha-synuclein immunohistochemistry. A diagnosis of Lewy Body Dementia was made if cortical Lewy Bodies (four or more per 250× field in several fields) were present.[7] In all cases where no Lewy bodies were found, the absence of Lewy bodies was confirmed by immunohistochemical staining for alpha-synuclein. The diagnosis of Pick's disease was made using IHC tau to identify tau positive intraneuronal inclusions (Pick bodies) in the cerebral cortex and basal ganglia. Frontotemporal dementia (FTD)was diagnosed according to Working Group Criteria.[13] Both cases diagnosed herein with FTD had tau positive inclusions. [14]

Results

Table 1 shows the characteristics of the 17 twin pairs. Only one of the twin pairs was concordant for a diagnosis of DLB and this was a MZ pair in which both twins had AD plus DLB. An additional four pairs were concordant for dementia, but in these pairs the proband had AD plus DLB while the cotwin had dementia attributable to non-DLB neuropathology. All four MZ pairs in which the proband had neuropathologically confirmed pure DLB remained discordant for dementia. Among the twin pairs discordant for dementia, there were numerous MZ and DZ pairs in which the cotwin remained cognitively intact for 13 - 22 years after the onset of the proband.

The average age of dementia onset was 72 years (s.d. = 4.0) for the subjects with pure DLB and 68.4 years (s.d. = 8.7) for subjects with AD+DLB. Spontaneous motor features of parkinsonism were noted in 14 of the 15 individuals who completed an in-person assessment and had Lewy bodies at neuropathology. Ten of 18 individuals with Lewy bodies at neuropathology were reported to have visual hallucinations; three of these individuals had pure DLB. Our methodology did not allow us to determine the time when the parkinsonism symptoms and hallucinations first presented. Review of the history of cognitive decline showed that seven of the individuals with AD plus DLB (but none of those with pure DLB) had a rapid decline from mild to severe impairment over a one year period. Two of the four twins with pure DLB and 9 of the 13 pairs with mixed DLB pathology had a family history of dementia in a first degree relative other than the cotwin. The APOE e4 allele frequency among the four cases with pure DLB was 12.5%, while the e4 allele frequency among those with mixed DLB pathology was 42.3%.

Discussion

We found that concordance for DLB is uncommon in twin pairs when one twin has DLB or mixed DLB-AD pathology. This low rate of concordance was present despite our finding that 59% of the twin pairs had a family history of dementia, which is in agreement with other research.[15] Consistent with another study [16], we also found that the APOE e4 allele frequency was higher among those with AD + DLB pathology compared to those with pure DLB. However, this may reflect the role of the e4 allele in AD, not in DLB. An inadequate follow-

up period due to mortality or other reasons is unlikely to explain our findings given the long period of survival and follow-up for many of these twin pairs. The duration of follow-up of the unaffected cotwins in the present study exceeded the average period of discordance for dementia (ie. about 4 years in MZ pairs and 4-8 years in DZ pairs) reported in the Duke Twins study overall and another large twin sample.[17]

Twin studies of AD suggest a multifactorial mode of inheritance with estimates of heritability ranging between 21 and 83%.[17-19] Twin studies in the early 1980's suggested little to no role of genes in the etiology of PD, [20] but by 1990, two large kindreds with an autosomal dominant inheritance pattern of PD were identified.[21] Subsequently, data on the NAS-NRC Twin Registry suggested genes play a role in early onset PD (<50 years of age), but not late onset disease[22] while the Swedish twin study reported no evidence for heritability of PD.[23] Although the sample size is small, our results support a limited role for genetic susceptibility in sporadic DLB. But the point should be emphasized that discordance does not exclude a significant genetic contribution to pathogenesis, because environmental or epigenetic changes may modify risk. With this in mind, it was interesting that in the present study, four pairs were concordant for dementia but were discordant for Lewy body pathology. One other study on three MZ twin pairs concordant for dementia also found the presence of Lewy body pathology differed within the pairs.[24]

There are several limitations to our study that should be noted. First, despite the unique nature of this twin study, our sample size is small, which diminishes our ability to examine environmental factors related to DLB. Clinically, we did not have consistent information on key features, such as onset of hallucinations, behavioral problems, and gait disturbance in relation to cognitive disturbance. Such information may have improved our ability to provide antemortem DLB diagnoses and to make clinico-pathological correlations. However, we note that clinico-pathological agreement has previously been found to be low.[25] We also did not obtain autopsy on the non-demented cotwins. We can confidently state that they did not have dementia, but we can not rule out the possibility that they had some Lewy body pathology.

Post-mortem twin studies are informative, but also highlight the complexity and heterogeneity of pathology in dementia. The present study indicates that even among twins, a diagnosis of DLB in one twin does not predict the same diagnosis in the other twin.

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References

1. Graeber MB, Muller U. Dementia with Lewy bodies: disease concept and genetics. Neurogenetics 2003;4(4):157–62. [PubMed: 12898286]
2. Ohtake H, Limprasert P, Fan Y, et al. Beta-synuclein gene alterations in dementia with Lewy bodies. Neurology 2004;63(5):805–11. [PubMed: 15365127]
3. Ishikawa A, Piao YS, Miyashita A, et al. A mutant PSEN1 causes dementia with Lewy bodies and variant Alzheimer's disease. Ann Neurol 2005;57(3):429–34. [PubMed: 15732120]
4. Ohara K, Takauchi S, Kokai M, Morimura Y, Nakajima T, Morita Y. Familial dementia with Lewy bodies (DLB). Clin Neuropathol 1999;18(5):232–9. [PubMed: 10505432]
5. Goker-Alpan O, Giasson BI, Eblan MJ, et al. Glucocerebrosidase mutations are an important risk factor for Lewy body disorders. Neurology 2006;67(5):908–10. [PubMed: 16790605]
6. Plassman BL, Steffens DC, Burke JR, et al. Duke Twins Study of Memory in Aging in the NAS-NRC Twin Registry. Twin Research and Human Genetics 2006;9:950–957. [PubMed: 17254435]

7. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. Neurology 1996;47:1113–1124. [PubMed: 8909416]
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Vol. Third Edition-Revised. Washington, D.C.: American Psychiatric Association; 1987.
9. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task force on Alzheimer's disease. Neurology 1984;34:939–944. [PubMed: 6610841]
10. Brun A, Englund B, Gustafson L, et al. Clinical and neuropathological criteria for frontotemporal dementia. Journal of Neurology, Neurosurgery, and Psychiatry 1994;57:416–418.
11. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41:479–486. [PubMed: 2011243]
12. National Institute on Aging Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. Neurobiology of Aging 1997;18(S4):S1–S2. [PubMed: 9330978]
13. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001;58(11):1803–9. [PubMed: 11708987]
14. Bigio EH. Update on recent molecular and genetic advances in frontotemporal lobar degeneration. J Neuropathol Exp Neurol. 2008
15. Woodruff BK, Graff-Radford NR, Ferman TJ, et al. Family history of dementia is a risk factor for Lewy body disease. Neurology 2006;66(12):1949–50. [PubMed: 16801670]
16. Galasko D, Saitoh T, Xia Y, et al. The apolipoprotein E allele E4 is overrepresented in patients with the Lewy body variant of Alzheimer's disease. Neurology 1994;44:1950–1951. [PubMed: 7936253]
17. Gatz M, Fratiglioni L, Johansson B, et al. Complete ascertainment of dementia in the Swedish Twin Registry: the HARMONY study. Neurobiology of Aging 2005;26:439–447. [PubMed: 15653172]
18. Breitner JCS, Welsh KA, Gau BA, et al. Alzheimer's disease in the National Academy of Sciences-National Research Council Registry of aging twin veterans. III. Detection of cases, longitudinal results, and observations on twin concordance. Archives of Neurology 1995;52:763–771. [PubMed: 7639628]
19. Bergem ALM, Engedal K, Kringlen E. The role of heredity in late-onset Alzheimer disease and vascular dementia. Archives of General Psychiatry 1997;54:264–270. [PubMed: 9075467]
20. Ward CD, Duvoisin RC, Ince SE, Nutt JD, Eldridge R, Calne DB. Parkinson's disease in 65 pairs of twins and in a set of quadruplets. Neurology 1983;33(7):815–24. [PubMed: 6683366]
21. Golbe LI, Di Iorio G, Bonavita V, Miller DC, Duvoisin RC. A large kindred with autosomal dominant Parkinson's disease. Ann Neurol 1990;27(3):276–82. [PubMed: 2158268]
22. Tanner CM, Ottman R, Goldman SM, et al. Parkinson's disease in twins: an etiologic study. Journal of the American Medical Association 1999;281:341–346. [PubMed: 9929087]
23. Wirdefeldt K, Gatz M, Schalling M, Pedersen NL. No evidence for heritability of Parkinson disease in Swedish twins. Neurology 2004;63(2):305–11. [PubMed: 15277625]
24. Brickell KL, Leverenz JB, Steinbart EJ, et al. Clinicopathological concordance and discordance in three monozygotic twin pairs with familial Alzheimer's disease. Journal of Neurology, Neurosurgery and Psychiatry 2007;78:1050–1055.
25. Weisman D, Cho M, Taylor C, Adame A, Thal LJ, Hansen LA. In dementia with Lewy bodies, Braak stage determines phenotype, not Lewy body distribution. Neurology 2007;69(4):356–9. [PubMed: 17646627]

Table 1

Characteristics of Twin Pairs

Twin	Zygosity	Sex	Education	Clinical diagnosis	Pathological diagnosis	Age of dementia onset	Current age	Age at death	Family history of dementia	APOE
1a	MZ	M	15	Probable AD	DLB	74		83	No	3/4
1b	MZ	M	13	Cognitively normal			87		No	3/4
2a	MZ	M	12	Possible AD	DLB	74		85	No	3/3
2b	MZ	M		Cognitively normal				78+	No	3/3
3a	MZ	M	16	Possible AD	DLB	74		76	Yes	3/3
3b	MZ	M	16	Cognitively normal			80		Yes	3/3
4a	MZ	M	20	PSP	DLB	66		78	Yes	3/3
4b	MZ	M	12	Cognitively normal				82+	Yes	3/3
5a	MZ	M	16	Possible AD	AD+DLB	75		83	Yes	4/4
5b	MZ	M	18	Dementia, undetermined etiology	AD+DLB	66		71	Yes	4/4
6a	MZ	M	19	Probable AD	AD+DLB	72		78	Yes	2/4
6b	MZ	M	18	Probable AD	FTD+AD	80		89	Yes	2/4
7a	MZ	F	13	Probable AD	AD+DLB	80		84	Yes	3/3
7b	MZ	F	17	Probable AD	Pick's disease	75		81	Yes	3/3
8a	DZ	M	12	Dementia, undetermined etiology	AD+DLB	75		77	Yes	DK
8b	DZ	M	11	Probable AD	AD	73		83	Yes	3/4
9a	MZ	F	16	None –deceased prior to assessment	AD+DLB	77		84	No	3/4
9b	MZ	F		Cognitively normal				85+	No	3/4
10a	DZ	M	14	Possible AD	AD+DLB	73		77	Yes	3/4
10b	DZ	M	15	Mild cognitive impairment due to neuropsychiatric disorder				79+	Yes	3/3
11a	DZ	M	16	Possible AD	AD+DLB	72		78	No	4/4
11b	DZ	M	16	Cognitively normal			88		No	DK
12a	MZ	M	11	Probable AD	AD+DLB	70		78	No	2/2
12b	MZ	M	12	Cognitively normal			83		No	2/2
13a	DZ	M	14	Possible AD	AD+DLB	61		66	No	3/3
13b	DZ	M	10	Cognitively normal			82		No	3/3
14a	MZ	F	12	Possible AD	AD+DLB	54		74	Yes	3/3

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Twin	Zygosity	Sex	Education	Clinical diagnosis	Pathological diagnosis	Age of dementia onset	Current age	Age at death	Family history of dementia	APOE
14b	MZ	F	13	Cognitively normal			76		Yes	3/3
15a	MZ	F	15	Probable AD	AD+DLB	61		73	Yes	3/4
15b	MZ	F	16	Mild cognitive impairment due to medical illness			83		Yes	3/4
16a	DZ	F	13	Probable AD	AD+DLB	53		70	Yes	3/4
16b	DZ	F	17	Cognitively normal			75		Yes	3/4
17a	DZ	M	11	Probable AD	FTD+DLB	77		84	Yes	3/3
17b	DZ	M	12	Possible AD	Modest vascular and AD neuropatholog y*	72		86	Yes	3/4

MZ –monozygotic, DZ – dizygotic. AD – Alzheimer's disease. DLB – dementia with Lewy bodies. FTD – frontotemporal dementia. PSP – Progressive supranuclear palsy. Education in years. APOE – apolipoprotein E genotype. DK – Do not know.

+No autopsy performed.

*Although there was only modest vascular and AD neuropathology present in this individual with clear clinical symptoms of advanced dementia, the key point is that there were no LBs present.