Distinguishing Dementia With Lewy Bodies From Alzheimer Disease

What is the Influence of the GBA Genotype in Ashkenazi Jews?

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Abstract: Cognitive deficits beyond memory impairment, such as those affecting language production or executive functioning, can be useful in clinically distinguishing between dementia syndromes. We tested the hypothesis that Ashkenazi Jewish (AJ) patients who have dementia with Lewy bodies (DLB) and carry glucocerebrosidase (*GBA*) mutations will have verbal fluency deficits different from those found in Alzheimer disease (AD), whereas AJ patients with DLB who have no *GBA* mutations will have similar deficits in verbal fluency to those found in AD. We compared performance in phonemic and semantic verbal fluency tasks in 44 AJ patients with DLB and 20 patients with AD, matched for age, education, and age of immigration. All groups were found to have a deficit in semantic verbal fluency. On conducting the phonemic task, patients with DLB who carried *GBA* mutations scored more poorly than patients with AD, whereas DLB-noncarriers performed similarly to patients with AD. We suggest that verbal fluency tasks could serve as a possible clinical marker to subtype patients with DLB, with phonemic fluency being a marker for *GBA*-associated DLB.

Key Words: dementia with Lewy bodies, glucocerobrosidase mutations, verbal fluency, Alzheimer disease, cognitive evaluation

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Cognitive deficits beyond memory impairment, such as those affecting language production or executive functioning, can be useful in clinically distinguishing between dementia syndromes. In Alzheimer disease (AD), patients tend to show greater impairments in semantic (category) fluency compared with phonemic (letter) fluency.[1]

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Mutations in the Glucocerebrosidase (*GBA*) gene are a risk factor for the development of dementia with Lewy bodies (DLB) and have an effect on the disease phenotype.[2] Studies examining verbal fluency in DLB have reported conflicting results[3] but generally suggest that patients with DLB show equal impairments in both phonemic and semantic fluency.[4] However, these studies explored DLB as a uniform disease, regardless of its genetic background.

We have previously shown that Ashkenazi Jewish (AJ) patients with DLB who are carriers of mutations in the *GBA* gene have a more significant deficit in phonemic verbal fluency than do patients with DLB who do not carry these mutations.[2] This led us to hypothesize that patients with DLB who carry one of the AJ-associated mutations in the *GBA* gene would have a different pattern of verbal fluency deficits from the one that characterizes patients with AD. In order to establish this hypothesis, the current study compared verbal fluency patterns in patients with DLB with one of the 7 known AJ mutations in the *GBA* gene, patients with DLB without any of the AJ *GBA* mutations, and patients with AD.

METHODS

Participants

The sample included 44 AJ patients who fulfilled the McKeith criteria[5] for probable or possible DLB, and 20 patients diagnosed with probable AD according to the revised NINCDS-ADRDA criteria.[6] Forty patients fulfilled the criteria for probable DLB; 1 patient in the carrier group and 3 from the noncarrier group met the criteria for possible DLB. Of the patients with DLB, 13 have been reported in our previous analysis.[2] Patients with DLB underwent genotyping for *GBA* mutations. Genotyping of founder *GBA* mutations was performed, as previously described.[2] Briefly, patients underwent testing for the 84GG, IVS2+IG > A, p.N370S, p.L444P, p.V394L, p.R496H, and RecTL *GBA* mutations, using an electronic microarray (Nano-Chip 400; Savyon Diagnostics Ltd). Patients who carry mutations in the *LRRK2* gene were not included in the cohort. There were 14 patients who carried the *GBA* mutation, and 30 patients were noncarriers. Participants were either born in Israel or immigrated to Israel by age 18, having used Hebrew as their main language throughout their life. Patients were tested on the Montreal Cognitive Assessment (MoCA) or the Mini-Mental State Examination (MMSE). MoCA scores were equated to MMSE scores using the equipercentile method. This statistical method allows for the determination of comparable test scores from 2 different measures on

the basis of their corresponding percentile ranks. This method can lead to an irregular distribution of scores, and thus a log-linear transformation is used to smooth the raw scores into a regular distribution. Equipercentile equating and log-linear smoothing were performed using the "equate" library in the R statistical package.[7] The study was approved by the Helsinki committee and ethical board of the Tel Aviv Medical Center. Patients with DLB provided informed written consent before participation, whereas data from patients with AD were collected retrospectively from medical records.

Fluency Tasks

Participants were asked to provide as many different words as possible within 60 seconds on each of 3 Hebrew letters (phonemic task) as well as on the category of animals (semantic task). The total number of correct responses was transformed into a z-score for each person on each task according to age-appropriate norms.[8]

Statistical Analyses

A 1-way analysis of variance (ANOVA) was used to compare groups on demographic variables. A 2-way ANOVA was conducted to compare fluency z-scores across groups, with fluency task as a within-subject variable and group as a between-subject variable. Planned comparisons were used to compare each DLB group to the AD group on each fluency task. Analyses were performed with SPSS.

RESULTS

Patient characteristics are presented in Table 1. A 1-way ANOVA that compared the 3 groups found no significant differences in age, $F_{2,63}=1.067$, $P=0.350$, MoCA scores, $F_{2,58}=2.835$, $P=0.067$, years of education, $F_{2,63}=1.809$, $P=0.173$, or age of immigration, $F_{2,61}=0.582$, $P=0.562$.

Table 1 also presents the mean number of words provided on each task, and Figure 1 presents z-scores on the 2 fluency tasks. A 2-way ANOVA found a significant difference between the 2 fluency tasks, so that across the 3 groups, patients were more impaired on the semantic fluency task than on the phonemic fluency task, $F_{1,58}=30.335$, $P<0.001$. The group difference was not significant, $F_{2,57}=2.344$, $P=0.105$. However, the task-group interaction was significant, $F_{258}=6.962$, $P=0.002$. Planned comparisons showed that on the semantic task, neither the DLB-*GBA* group ($t_{32}=1.582$, $P=0.123$), nor the DLB non-*GBA* group ($t_{48}=-0.099$, $P=0.922$) differed from the AD group. On the phonemic task, the DLB-*GBA* group scored significantly more poorly than did the AD group, $t_{29}=2.838$, $P=0.008$, whereas the DLB noncarriers did not differ from the AD group, $t_{45}=0.675$, $P=0.503$.

TABLE 1. Demographic Characteristics and Mean Number of Words (and SDs) on the Phonemic and Semantic Fluency Tasks, by Group

	DLB-*GBA* (N = 14)	DLB Non-*GBA* (N = 30)	AD (N = 20)
Age [mean (SD) (range)] (y)	70.86 (7.48) (57-83)	72.50 (6.31) (64-86)	74.15 (6.12) (63-85)
Women [n (%)]	3 (21)	7 (23)	10 (50)
MoCA [mean (SD) (range)]	18.23 (6.88) (6-27)	21.03 (4.02) (13-28)	18.41 (1.65) (16-21)
Years of education [mean (SD) (range)]	13.14 (2.18) (10-17)	14.70 (2.97) (10-24)	13.90 (2.22) (10-18)
No. immigrants from group [n (%)]	3 (21)	6 (20)	8 (40)
Age at immigration [mean (SD) (range)] (y)	11.67 (9.29) (1-18)	6.00 (6.16) (1-18)	6.71 (5.09) (2-16)
Phonemic [mean (SD)]	21.07 (8.00)	27.27 (11.09)	28.12 (7.77)
Semantic [mean (SD)]	8.57 (5.02)	10.37 (4.93)	10.45 (2.89)

The mean age at immigration is presented only for immigrants, without Israeli-born patients.

AD indicates Alzheimer disease; DLB, dementia with Lewy bodies; GBA, glucocerebrosidase; MoCA, Montreal Cognitive Assessment.

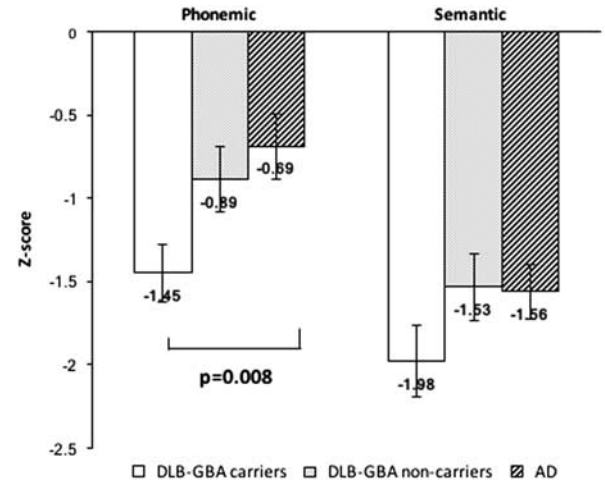

FIGURE 1. Mean z-scores (and SE) on both fluency tasks, by group. AD indicates Alzheimer disease; DLB, dementia with Lewy bodies; GBA, glucocerebrosidase.

DISCUSSION

We found that patients with DLB who carry one of the 7 Ashkenazi mutations in the *GBA* gene had a different pattern of verbal fluency deficits from patients with AD, with poor performance on both semantic and phonemic verbal fluency tasks. In contrast, patients with DLB who did not carry *GBA* mutations performed like patients with AD, and showed a selective deficit in semantic verbal fluency. That is, patients with DLB who were carriers of *GBA* mutations performed outside the normal distribution on both fluency tests, whereas patients with DLB who were noncarriers performed outside the normal distribution only on the semantic fluency task, as did patients with AD. The pattern seen in the *GBA* carriers is more representative of the pattern reported previously in patients with DLB.[6]

The ability to generate a list of words in a certain category (semantic verbal fluency) is dependent upon the integrity of the dominant temporal lobe and is therefore, commonly impaired in patients with AD and in focal temporal lesions.[9] However, this ability also relies on frontal lobe integrity and therefore semantic fluency deficits are also observed in patients with frontal lobe damage and in advanced Parkinson's disease dementia (PDD). In these non-AD dementia groups, the verbal fluency impairment might reflect difficulties in executive functions rather than specific retrieval deficits.

DLB is often misdiagnosed, as it lies on the clinical-pathologic spectrum between PDD and AD.[5] In fact, most patients with DLB have a mixed pathology with abnormal accumulation of both Lewy bodies and Lewy neurites as well as Alzheimer neuropathology. Recently, it has been

found that, although the amyloid load is elevated in the majority of patients with DLB, those who carry mutations in the *GBA* gene show lower levels of Alzheimer neuropathology at postmortem compared with those who do not carry the gene.[10] Thus, in terms of the disease pathology, it appears that carriers of the *GBA* mutation may be less similar to patients with AD than are noncarriers.

Previous studies that examined verbal fluency deficits in DLB without separating patients on the basis of the *GBA* genotype have provided conflicting results.[3] Most studies point to deficits that are more similar to those seen in non-AD dementia, with equal impairments of both semantic and phonemic fluency.[4] Of note, a study that compared PDD patients with and without *GBA* mutations, found no significant differences in verbal fluency between these groups.[11] This finding might be explained by the differing distribution of alpha-synuclein in patients with PDD compared with patients with DLB in whom high alpha-synuclein burden in the dorsal striatum, a main projection site of the dorsolateral prefrontal cortex, is more common.[12] Our results suggest that the presence or absence of the *GBA* gene mutation may have an effect on the pattern of verbal fluency, possibly attesting to differences in pathologic involvement, which will need to be corroborated in further studies. This interpretation is in keeping with some pathologic studies, which support the notion that patients with DLB who are carriers of *GBA* mutations represent a "purer" form of DLB, more similar to PDD, whereas the noncarriers represent a DLB/AD overlap group.[13] It should be noted, however, that the increasing amyloid deposition observed across the PDD, DLB, and AD spectrum is not always consistent, and, indeed, there is a subtype of PDD with a high deposition of amyloid as well.[14]

The strengths of our study lie in the use of a simple, clinically useful, easy to administer, and well-validated task, and in the use of well-matched populations of patients. We examined a homogeneous group of DLB patients, all of AJ origin, who were matched on a multitude of demographic characteristics to the AD group. Both DLB groups had fewer women, whereas the AD group consisted of equal numbers of men and women. Given that sex has not been shown to have a direct effect on verbal fluency,[15] and that both DLB groups had similar percentages of men, we believe that the sex differences are unlikely to explain our results. The main limitations of our study are the lack of corroborative neuropathology and the fact that diagnoses were made on the basis of clinical guidelines. There is also the possibility that our results are less generalizable to populations with a lower number of AJ patients.

In conclusion, our findings show that the pattern of verbal fluency deficits in patients with DLB who carry one of the 7 AJ *GBA* mutations is different from the pattern commonly found in AD, whereas patients with DLB who do not carry *GBA* mutations show a pattern of verbal fluency deficits typical of AD. We suggest that verbal fluency could serve as a clinical marker to subtype patients with DLB, with phonemic fluency potentially being a useful marker for *GBA*-associated DLB, which would then need to be corroborated with genetic testing. These findings could have implications for treatment decisions as well as for future research.

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