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Performance on MMSE sub-items and education level in *presenilin-1* mutation carriers without dementia

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Abstract

Background—Spanish-language screening tests that are sensitive to the early cognitive changes of Alzheimer's disease (AD) are needed. Persons known to be at 50% risk for young-onset AD due to *presenilin-1* (*PSEN1*) mutations provide the opportunity to assess which measures on the Mini-mental State Examination (MMSE) are most sensitive to these early changes.

Methods—We performed genetic and Spanish-language cognitive testing on 50 Mexican persons without dementia at risk for inheriting *PSEN1* mutations. We then compared the performance on sub-items of the MMSE between *PSEN1* mutation carriers (MCs) and non-carriers (NCs) using *t*-tests and Fisher's exact tests. Exploratory multiple logistic regression analyses were also performed.

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Conflict of interest
None.

Description of authors' roles
J. M. Ringman acquired funding for this study, interviewed all subjects, edited the paper and assisted in data analysis; Y. Rodriguez performed psychometric assessments and collected data; C. Diaz-Olavarrieta supervised data collection, assisted in identifying and recruiting subjects and edited the paper; M. Chavez performed psychometric assessments, collected data and assisted in identifying and recruiting subjects; M. Thompson wrote the initial draft of the paper and assisted in data analysis; L. Fairbanks assisted in data analysis; F. Paz collected data and assisted in identifying and recruiting subjects; A. Varpetian, H. Chaparro and M. A. Macias-Islas edited the paper and assisted in identifying and recruiting subjects; J. Murrell edited the paper and performed genetic analyses; and B. Ghetti and C. Kawas edited the paper and provided guidance in study design.

Results—Twenty-nine persons were MCs and 21 NCs. NCs tended to achieve higher levels of education ($p = 0.039$) than did MCs. MCs tended to perform more poorly when spelling "MUNDO" backwards and on Orientation, particularly regarding the date. In multiple regression analyses the ability of backwards spelling to predict *PSEN1* mutation status was reduced when education was included as an independent variable.

Conclusion—Subjects in the earliest stage of *PSEN1*-related AD showed deficits on orientation to date and in divided attention when spelling backwards. It is unclear if educational level should be considered an associated feature or a confounding variable in this population although it should be taken into account when considering performance on the MMSE task of divided attention. The relative lack of deficits on delayed recall of three words probably represents the insensitivity of this measure in early AD. This study supports the utility of autosomal dominant AD as a model of the more common sporadic form of the disorder.

Keywords

Alzheimer's disease; presenilin; cognition; preclinical; Mini-mental State Examination; screening test; Spanish; education

Introduction

Because of the incipient onset and gradually progressive nature of Alzheimer's disease (AD), it can be difficult to diagnose definitively in its earliest stages. Quick screening tests are needed, particularly in primary care settings, that help to differentiate persons in the earliest stage of the disorder from others whose cognitive complaints are due to other causes. The Mini-mental State Examination (MMSE) is a frequently used screening tool (Folstein *et al.*, 1975) that covers multiple domains of cognitive functioning, including orientation to time and place, recent memory, attention, language and visuospatial skills. Individual items on the MMSE that have been demonstrated to be affected in early AD include the ability to recall three words after a delay (Small *et al.*, 1997b), difficulties with orientation to time (Galasko *et al.*, 1990; Small *et al.*, 1997b) and attention as measured with serial subtraction of 7s from 100 (Meyer *et al.*, 2002).

Although accounting for only 2–5% of cases of AD, familial AD, which is inherited as an autosomal dominant trait, provides a unique opportunity to study the earliest cognitive manifestations of the disorder. There are three well-characterized genes coding for the proteins presenilin-1 (*PSEN1*), presenilin-2 (*PSEN2*) and amyloid precursor protein (*APP*), alteration of which causes an essentially fully penetrant autosomal dominant form of AD. Mutations in the gene coding for *PSEN1* generally have the youngest age of onset (44–46 years of age) (Lippa *et al.*, 2000) and account for the majority of such cases (Tanzi and Bertram, 2001). Familial AD due to mutations of *APP* are second most common, having an intermediate age of onset (49 years), with *PSEN2* mutations having the oldest and most variable age of onset (58–59 years) and being quite rare (Lippa *et al.*, 2000). Within families that harbor mutations in the *PSEN1* gene, the age of disease onset is fairly consistent (Fox *et al.*, 1997), and thus if and when a person will develop the disease can be reliably predicted. Therefore, by comparing the performance of *PSEN1* mutation carriers who are in the preclinical stage of AD with that of their non-mutation carrying kin, we can ascertain what the earliest changes are that are detectable on tests such as the MMSE.

We performed genetic and Spanish-language neuropsychological testing on Mexican persons without dementia known to be at 50% risk of inheriting one of two *PSEN1* mutations. In a previous paper we described early declines in performance on the Trail Making Test, delayed recall of a 10-word list, the Wechsler Adult Intelligence Scale Block Design Test, and total MMSE score in these subjects (Ringman *et al.*, 2005). In the current

paper we explore the sub-items on the MMSE that best differentiate *PSEN1* mutation carriers (MCs) and non-carriers (NCs) and explore the relationship of age and education to these scores.

Methods

Cases

Seventy-seven persons from 10 Mexican families affected by or known to be at risk for inheriting characterized *PSEN1* mutations were examined. The *PSEN1* gene was sequenced in a commercial laboratory for symptomatic members of three families and a *PSEN1* mutation was confirmed in each. In the remaining seven families, at-risk persons with a first-degree relative suspected of carrying a *PSEN1* mutation gave their consent for genetic testing in a research laboratory (see below). *PSEN1* mutation screening was performed using DNA amplification followed by restriction fragment length polymorphism (RFLP) analysis. This testing confirmed a *PSEN1* mutation in at least one member of each of the 10 families. Nine of the 10 families had the same missense mutation in exon 13 of the *PSEN1* gene causing an alanine to glutamic acid substitution at amino acid 431 (A431E) (Cochran *et al.*, 2001) in the presenilin-1 protein. The remaining family had a cytosine to guanine transversion at nucleotide 703 resulting in a leucine to valine missense substitution (L235V).

Subjects were informed in advance that they would not be told the results of the genetic testing and all subjects provided written informed consent. The protocol was approved by the Institutional Review Boards at the National Institute of Neurology and Neurosurgery in Mexico City and at the University of California at Irvine. Commercial testing for mutations in the *PSEN1* gene is available through a commercial laboratory but no subject in the current study had undergone this testing. To restrict our study population to those in the preclinical stage of the illness, subjects were excluded if they had dementia according to DSM-IV criteria ($n = 7$), were older than the median age of dementia diagnosis in their family ($n = 10$), or had a total MMSE score less than 25 ($n = 1$). Seven additional subjects who had incomplete cognitive data were excluded, as were two in whom mutation status was not ascertained.

Cognitive testing

Subjects underwent a clinical interview, blood draw for genetic testing, computerized cognitive testing and a neuropsychological battery including a Spanish version of the MMSE. All cognitive testing was performed in Mexico by persons for whom Spanish was their first language. In the version of the MMSE used in this study (Ostrosky-Solis *et al.*, 2000):

1. "Region" was used for "state"
2. "Provincia" was used for "county"
3. No serial 7s task was administered
4. "MUNDO" was used for "WORLD" backwards in the test of divided attention
5. "Ni sies ni noes ni peros" was used for "no ifs, ands, or buts"
6. In the three-step command task, subjects were asked to place the paper on their knees after they had folded it.

All data were acquired by investigators blind to the subjects' mutation status.

Statistical analyses

Subscale scores for the MMSE were calculated as follows:

1. Orientation to time and place (10 points)
2. Immediate registration (3 points)
3. Divided attention (5 points)
4. Delayed recall (3 points)
5. Language (4 points total)

    Confrontation naming (2 points)

    Repeat a short phrase (1 point)

    Reading and following instructions (1 point)
6. Following a three-step command (3 points)
7. Writing a sentence (1 point)
8. Copying a figure (1 point)

Demographic variables were compared using *t*-tests (age and education) and a χ^2-test (gender). Total MMSE scores were compared between groups by *t*-tests. *t*-tests were also performed comparing MMSE subscale scores between MCs and NCs (Orientation, Immediate Registration, Delayed Recall, Divided Attention, Language, Following a three-step command). For those items that were scored categorically (correct *vs.* incorrect, i.e. Writing a sentence and copying a figure), Fisher's exact tests were performed. In exploratory analyses, additional Fisher's exact tests were performed to determine which individual items were missed most frequently in *PSEN1* mutation carriers. Multiple forward stepwise regression analyses were then performed with MMSE sub-items as predictor variables and *PSEN1* mutation status as the outcome variable controlling for age. This was done both with and without years of education as a covariate (see below). Corrections were not made for multiple comparisons in any analysis. All analyses were performed using the Statistical Package for Social Sciences version 11.0.2 (SPSS, Chicago, IL, U.S.A.).

Results

Fifty subjects were included in these analyses, of which 39 were at risk for inheriting the A431E mutation and 11 for the L235V mutation. Twenty-nine subjects were found to be MCs and 21 NCs. Years of education differed between the groups with MCs tending to obtain less formal schooling (11 *vs.* 12.7 years, $p = 0.032$). Mean age (28.7 *vs.* 29.2 years) and gender distribution did not differ between MCs and NCs although the majority of subjects in both groups were female (Table 1). MCs had lower total MMSE scores than NCs (28.1 *vs.* 29.2, $p = 0.003$, Table 1). The observation that MCs, on average, achieved fewer years of education has multiple possible interpretations, discussed below.

NCs performed better, on average, than MCs on the Orientation (9.90 *vs.* 9.66, $p = 0.046$), Attention (4.95 *vs.* 4.52, $p = 0.019$) and Language (4.00 *vs* .3.86, $p = 0.043$) sub-items (Table 1). The individual orientation item most frequently missed by MCs was the date (5/29 incorrect *vs.* 0/21 in NCs, $p = 0.066$). Repetition was the language sub-item missed most frequently by MCs, with four of 29 (14%) making errors. Differences in performance on the Delayed recall test (2.42 *vs.* 2.20) was not significant at the 0.05 level.

As it is unclear whether years of education should be viewed as an associated feature or a confounding variable in this population, multiple regression analyses on the MMSE sub-

items were performed both with and without education in the model. No variables in these analyses significantly predicted mutation status although the following trends were seen. In the model in which age but not education was included as a covariate, score on the Divided Attention portion of the MMSE (spelling "MUNDO" backwards) was the best predictor of *PSEN1* mutation status ($\beta = -.2.11$, $p = 0.055$) with Orientation being the second strongest predictor of mutation status ($\beta = -1.525$, $p = 0.068$). In the model in which education was included as a covariate, Orientation subscore ($\beta = -1.615$, $p = 0.060$), years of education ($\beta = -0.257$, $p = 0.068$) and Divided Attention subscore ($\beta = -2.025$, $p = 0.091$) were the best predictors of *PSEN1* mutation status.

Discussion

Consistent with longitudinal studies of elderly persons at risk for AD, we found that difficulties with orientation and attention occur early in the course of *PSEN1*-related AD (Meyer *et al.*, 2002; Small *et al.*, 1997a). Contrary to at least one such population-based study (Small *et al.*, 1997b) we did not find significant early impairment in the delayed recall of three words in persons destined to develop AD. The lack of a difference between *PSEN1* MCs and NCs on the delayed recall portion of the MMSE might reflect relative sparing of memory early in *PSEN1*-related AD. However, delayed recall of a 10-word list is impaired early in this group (Ringman *et al.*, 2005), suggesting that memory deficits are present early and the three-item recall test on the MMSE lacks sensitivity to this change. We also found that, in this population, persons with *PSEN1* mutations achieved fewer years of formal education. When this is controlled for in the multiple logistic regression analysis, the effect of the ability of subjects to spell "MUNDO" backwards in predicting *PSEN1* mutation status was diminished.

There are several possible interpretations of the fact that *PSEN1* MCs tended to achieve fewer years of education. It is possible that this reflects other differences between the MCs and NCs in our study. However, the groups were matched for age and gender and there were no significant differences in the distribution of MCs and NCs among families with the two distinct mutations (data not shown due to confidentiality). Indeed, nine of the families harbored the same mutation, which probably reflects a founder effect (Murrell *et al.*, 2003), and thus these subjects may share other regions of the genome as well, making them highly comparable. Chance occurrence is also a possibility. If this is the case, or if it reflects differences between the study groups, then it would be appropriate to treat it as a confounder by including it as a covariate in the model.

It is also possible, however, that the fewer years of formal education obtained by *PSEN1* MCs relative to NCs reflects an effect of the mutation on their ability or motivation to undergo advanced education. As persons with the A431E mutation may start to develop symptoms as early as their late thirties, it is conceivable that AD could begin to manifest subtly in the late teens, when life circumstances influence the ultimate education level achieved. We have previously reported in this same population that female MCs tended to score higher on the Beck Depression Inventory than their non-mutation carrying female kin (Ringman *et al.*, 2004). Such depressive symptoms might negatively influence whether or not the person continues in school. Alternatively, there is evidence that *PSEN1* plays a role in development (Selkoe and Kopan, 2003) and therefore the presence of a pathogenic *PSEN1* mutation from birth might induce a learning disadvantage that also would militate against achieving higher levels of education. If such an effect exists, it is likely to be very subtle as no gross neuropsychological differences between *PSEN1* MCs and NCs were evident in the youngest two tertiles in our previous study (Ringman *et al.*, 2005). The deficits in executive function, verbal memory and visuospatial functions seen in *PSEN1* MCs without dementia were only seen in the oldest tertile that had an average age of 5 to 6

years prior to the typical age of AD diagnosis in their family. Furthermore, self-reported average grades in school did not differ between MCs and NCs in the current population (data not shown). Nonetheless, these findings do not completely rule out the presence of more subtle cognitive deficits or psychiatric differences (e.g. reduced motivation) that might adversely impact academic achievement.

Multiple studies have shown an association between lower levels of education and a higher risk for the subsequent development of sporadic AD (Stern *et al.*, 1994). This has been attributed to a protective effect of education and cognitive stimulation or that lower degrees of education are associated with a covariate that represents the true risk factor (Albert, 1995). One possibility is that there are unknown genetic influences that predispose both to lower levels of education and AD, as may be the case for *PSEN1* mutations. If educational level is directly influenced by the presence or absence of *PSEN1* mutations, it might then be appropriate to study the influences of *PSEN1* mutation status on cognitive performance independently of this factor.

Our study was not adequately powered to calculate meaningfully positive and negative predictive values of MMSE sub-items for the diagnosis of AD. Although multiple logistic regression was the most appropriate statistical analysis for the current study, the lack of significant findings using this technique was also probably due to inadequate statistical power. Nonetheless, exploratory logistic regression did reveal some insights. When such analyses did not include educational level as a covariate, orientation to time (particularly orientation to the exact date) and spelling “MUNDO” backwards best distinguished MCs from NCs. The inability to perform this test of divided attention is consistent with our previous findings of early problems with executive dysfunction/working memory in this population, as indexed by significant slowing on the Trail Making Test, Part B. *PSEN1*-related AD can present with clinical features suggesting frontal lobe dysfunction (Raux *et al.*, 2000), which would explain this observation. Early deficits in the serial 7s task, which shares some similarities with spelling a word backwards, have also been reported in persons who went on to develop late-onset AD, providing further support for this item’s sensitivity to early AD (Meyer *et al.*, 2002).

It is generally accepted that educational level affects MMSE performance and it has been argued that the MMSE has no utility in persons with the lowest levels of formal education (Ostrosky-Solis *et al.*, 2000). Additionally, it has been demonstrated that Spanish-speaking Hispanics living in the U.S.A. tend to perform worse on the serial 7s and backwards spelling task on the MMSE (Hohl *et al.*, 1999) than non-Hispanics. As spelling “MUNDO” forwards and backwards clearly depends on literacy, it is not surprising that the effect of mutation status on performance of this task was reduced when education was taken into account. It should be noted that in our study of a Mexican population, the lowest number of years of education achieved was six, so all subjects had at least a minimal ability to read and write. As MMSE scores can be adjusted according to educational level (Mungas *et al.*, 2000), we consider that it has utility as a cognitive screening test for literate persons.

An important limitation to this study is the degree to which the results can be applied to sporadic AD. There are phenotypic differences between *PSEN1*-related AD and sporadic AD of later onset. Therefore, our results may not generalize directly to the elderly population at risk for AD. Nonetheless, studying a population at risk for inheriting a fully penetrant form of AD has several advantages. As this is a relatively young population, the contribution from cognitive changes associated with aging and its comorbidities (cerebrovascular disease, etc.) are minimized. In addition, using NCs from the same families as controls helps to control for socioeconomic status and other cultural factors as well as non-*PSEN1* genetic influences.

The current study was intended to explore the utility of sub-items of a well-characterized and widely used cognitive screening test, the MMSE, for incipient AD. We acknowledge that more difficult tests of episodic memory are more sensitive to early AD (Estevez-Gonzalez *et al.*, 2003; Ringman *et al.*, 2005) and we do not consider that the MMSE has utility in making the specific diagnosis of AD. Our data suggest that impairment on the attention item and orientation to date on the MMSE might in some cases herald incipient AD. Furthermore, the consistency between our results and those found in studies of MMSE sub-items in sporadic AD supports the utility of autosomal dominant AD as a model for the more common form of the disorder.

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Table 1

Demographic data and MMSE and subscale score differences

	***PSEN1* MUTATION PRESENT (MCs, *n* = 29)**	***PSEN1* MUTATION NOT PRESENT (NCs, *n* = 21)**	***p*-VALUE**
Age in years (S.D.)	28.7 (7.9)	29.2 (8.8)	0.807
Female, *n* (%)	17 (59)	16 (76)	0.196 (χ^2)
Education in years (range, S.D.)	11 (6–17, 2.51)	12.7 (9–18, 2.99)	*0.039*
Total MMSE score (range, S.D.)	28.1 (25–30, 1.37)	29.2 (27–30, 0.83)	*0.003*
Orientation subscore (range, S.D.)	9.7 (8–10, 0.55)	9.9 (9–10, 0.30)	*0.046*
Attention subscore (range, S.D.)	4.5 (1–5, 0.91)	4.9 (4–5, 0.22)	*0.019*
Language subscore (range, S.D.)	3.9 (3–4, 0.35)	4 (4, 0)	*0.043*
Immediate registration (range, S.D.)	(3, 0)	(3, 0)	N.A.
Delayed recall (range, S.D.)	2.2 (0–3, 0.94)	2.4 (0–3, 0.75)	0.375
Three-step command (range, S.D.)	2.93 (2–3, 0.26)	3.0 (3, 0)	0.161
Writing, no. correct (%)	29 (100)	20 (95)	0.420 (χ^2)
Copying, no. correct (%)	29 (100)	21 (100)	N.A.

MMSE = Mini-mental State Examination; *PSEN1* = *presenilin-1*; MC = mutation carrier; NC = non-carrier; S.D.= standard deviation; N.A. = not applicable.