Journal of the International Neuropsychological Society (2012), **18**, 144–150.

doi:10.1017/S1355617711001287

BRIEF COMMUNICATION

Probable Alzheimer's Disease Patients Presenting as "Focal Temporal Lobe Dysfunction" Show a Slow Rate of Cognitive Decline

Camillo Marra,[1] Giampiero Villa,[1] Davide Quaranta,[1] Alessandro Valenza,[2] Maria Gabriella Vita,[1] AND Guido Gainotti[1]

[1]Department of Neuroscience – Center for Neuropsychological Research, Catholic University of Sacred Heart, Rome, Italy
[2]Neurological Unit, Ospedale Belcolle, Viterbo, Italy

(RECEIVED June 7, 2011; FINAL REVISION August 25, 2011; ACCEPTED August 25, 2011)

Abstract

Several authors have recently shown that anterograde amnesia is often associated with semantic memory impairment in amnesic MCI patients. Similarly, after the MCI condition, some patients who convert to Alzheimer's disease (AD) show the classic onset (cAD) characterized by the impairment of memory and executive functions, whereas other AD patients show isolated defects of episodic and semantic memory without deficits in other cognitive domains. The latter have been considered an AD variant characterized by 'focal Temporal Lobe Dysfunction' (TLD). The aim of the present study was to assess the differences in disease progression between cAD and TLD. For this purpose a continuous series of newly diagnosed probable AD patients presenting as cAD ($n = 30$) and TLD ($n = 25$), matched for severity, and 65 healthy controls underwent a comprehensive neuropsychological evaluation at baseline; TLD and cAD were re-evaluated at a 24-month follow-up. At follow-up, TLD patients showed no significant worsening of cognitive functions, whereas cAD subjects displayed a significant worsening in all explored cognitive domains. In conclusion, our results confirm that probable AD presenting as TLD represents a specific onset of AD characterized by a slower rate of progression. (*JINS*, 2012, *18*, 144–150)

Keywords: Focal onset Alzheimer's disease, Cognitive decline, Neuropsychology, Memory impairment, Semantic disturbance, Alzheimer's disease progression

INTRODUCTION

Several authors have described an association between anterograde amnesia and semantic memory impairment both in amnesic MCI patients (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; Dudas, Clague, Thompson, Graham, & Hodges, 2005; Howieson et al., 2008; Murphy, Rich, & Troyer, 2006) and at the onset of AD, defined according to the classical NINCDS-ADRDA (McKhann et al., 1984) criteria. Indeed, even if according to these criteria Alzheimer's disease (AD) usually sets out with severe episodic memory disorders that are later accompanied by defects of the executive functions, timed attentional tasks, naming and visual-spatial abilities, the neuropsychological patterns of presentation are not similar among AD patients. Some patients with AD pathology present with progressive focal neocortical syndromes (Alladi et al., 2007; Galton, Patterson, Xuereb, & Hodges, 2000) and other patients show isolated defects of episodic and semantic memory (Butters, Lopez, & Becker, 1996; Cappa et al., 2001). These isolated defects of episodic and semantic memory have been attributed to a bilateral dysfunction of the temporal lobes and have been labeled 'focal Temporal Lobe Dysfunction' (TLD). These AD patients have been distinguished from those showing the classic AD pattern (cAD) characterized by a more diffuse cognitive impairment mainly involving executive functions, divided attention, and constructive abilities in addition to memory disorders.

Butters et al. (1996) proposed that TLD patients may constitute a distinct subgroup of AD, probably affected by a biological variant. This hypothesis was supported by Cappa et al. (Cappa et al., 2001), who showed that patients affected by probable AD, with a neuropsychological profile characterized by isolated defects of episodic and semantic memory, display also specific perfusion deficits at HMPAO-SPET (bilateral

Correspondence and reprint requests to: Camillo Marra, Department of Neuroscience, Catholic University of Sacred Heart, Largo A. Gemelli, 00168 – Roma, Italy. E-mail: cmarra@rm.unicatt.it

hypoperfusion in mesial temporal regions *vs*. bilateral temporo-parietal hypoperfusion in cAD).

The results of these studies may alternatively lead to the assumption that TLD and cAD represent distinct phenotypic variants of AD, with different functional involvement of neuroanatomical structures, or different stages of the disease.

The aim of the present study was to compare the clinical course of subjects affected by classic, ''diffuse'' AD (cAD) with patients with TLD. Our predictions are that if the two groups represent two different stages of the disease no differences in the rate of progression between baseline and follow-up should be observed and some TLD patients are expected to convert to cAD in the course of the disease.

METHODS

Subjects

Fifty-five subjects fulfilling the NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984) and with CDR ≥ 1, were included in the study among all subjects referring to the Neuropsychology Unit of our University Hospital for suspect dementia. None of them had a history of epilepsy, alcoholism, or other major neurologic or psychiatric diseases. All patients and/or proxy care-givers gave an informed consent to participate to the study, according to the guidelines of our Ethical Committee.

Each patient underwent a complete medical and neurologic examination and blood tests to rule out possible secondary dementias. None of the sample subjects met the criteria for possible Frontotemporal Dementia (Neary et al., 1998).

To exclude structural abnormalities of mesial temporal structures (e.g., hippocampal sclerosis) a detailed MRI study of these regions was performed. Furthermore, as in our previous study on this subject (Cappa et al., 2001) perfusion deficits at HMPAO-SPET were investigated in all patients.

All subjects were medication-free at the inclusion; after the baseline, all of them were started on the same cholinesterase inhibitor (ChEi) at the same dosage (donepezil 5 mg). At the follow-up examination 12 TLD and 18 cAD had increased the donepezil dose to 10 mg whereas 3 TLD and 2 cAD had discontinued therapy for side effects. Patients taking other ChEi and Memantine were not included in the study. Follow-up was conducted 24 months (± 2 months) after the baseline evaluation.

At baseline, a control group (healthy controls, HC; $N = 65$, 35 women) was formed from the Italian care-givers of patients referring to our Unit; most of whom were spouses or relatives accompanying the patients to the study. Eligibility was made after excluding the presence of any neurological, psychiatric or any other major medical illnesses potentially interfering with neuropsychological performances.

Neuropsychological Examination

To establish a global index of their cognitive decline, each patient underwent the CDR and MMSE (Folstein, Folstein, & McHugh, 1975). In addition, patients were administered an extensive neuropsychological battery; including tasks of verbal memory [Rey's Auditory Verbal Learning Test (RAVLT)] allowing separate scores for immediate and delayed recall and forced-choice recognition (Rey, 1958), digit span forward and backward (Wechsler, 1981); phonological (PWF) and semantic (SWF) word fluency; an executive functions task (Stroop Test) (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2002); a demanding visual attentional task [Multiple Features Targets Cancellation test (MFTC)] (Gainotti, Marra, & Villa, 2001) and abstract reasoning (Raven's Colored Progressive Matrices; PM'47) (Raven, 1949). Constructional praxis was evaluated by means of copy of drawings with and without landmarks (Gainotti, Miceli, & Caltagirone, 1977).

On the basis of the pattern of neuropsychological presentation, AD patients were assigned to the TLD or cAD groups. According to the normative values for the Italian population (Carlesimo, Caltagirone, & Gainotti, 1996), in each patient the normal or pathological rank of any test was recorded. Patients were considered TLD if they performed below the cut-off scores on two or more memory scores and on the SWF, whereas cAD had to perform below the cut-off scores in memory and other neuropsychological tasks.

STATISTICAL ANALYSIS

Data were analyzed using STATISTICA software for statistics. One-way analyses of variance (ANOVAs) were carried out to analyze differences in cognitive and demographic variables among normal controls, cAD and TLD subjects.

The changes between baseline and follow-up scores in the neuropsychological variables were analyzed in AD patients by means of a two-way multivariate ANOVA (MANOVA) for repeated measures, considering AD onset (cAD or TLD) and test–retest condition as independent variables, and neuropsychological scores as dependent variables.

Within the different multivariate statistical tests, we chose to use Wilks' lambda, thus determining the presence of significant effects between the main factors and the interaction between the dependent variables (Lee, Harrell, Tolley, & Rosati, 1983). After correction for multiple comparisons, significance level was set at $p = .003$.

Post hoc comparisons between groups were performed by means of Tukey's test for unequal sample size.

RESULTS

The sample of AD patients included 30 patients (16 women) diagnosed as cAD and 25 patients (13 women) with TLD. Table 1 reports the main demographic (age and educational level) and clinical characteristics (disease duration, MMSE and CDR scores, taken as an index of general mental impairment, and scores obtained at the baseline on each test of the neuropsychological battery) of the two patient groups and of HC.

https://doi.org/10.1017/S1355617711001287 Published online by Cambridge University Press

Table 1. Demographical and neuropsychological scores comparisons at the baseline in the three groups of cAD, TLD, and HC

	cAD ($N = 30$)			TLD ($N = 25$)		HC ($N = 65$)		
	Mean	*SD*		Mean	*SD*	Mean	*SD*	*p*
Age	70.40	*9.05*	=	73.44	*7.04*	70.98	*3.98*	.16
Education	10.40	*5.04*	=	10.80	*5.09*	9.32	*4.14*	.31
Illness duration	24.81	*12.21*	=	26.42	*17.78*			.45
MMSE	21.35	*3.70*	=	22.08	*3.44*	28.29	*1.07*	**< .001**
CDR	2.1	*0.65*	=	2.2	*0.91*	0.0	*0.0*	**< .0001**
RAVLT—immediate	22.70	*6.49*	=	20.68	*3.76*	37.29	*8.13*	**< .001**
RAVLT—delayed	2.26	*2.03*	>	0.70	*1.05*	8.26	*2.66*	**< .001**
RAVLT—Recog. false alarms	6.99	*6.08*	=	6.64	*6.35*	0.83	*0.96*	**< .001**
RAVLT—Recog. accuracy	0.74	*0.098*	>	0.67	*0.09*	0.90	*0.07*	**< .001**
PWF	20.49	*11.59*	=	23.72	*8.09*	24.49	*9.60*	.18
SWF	10.75	*4.67*	=	10.28	*3.56*	14.88	*3.77*	**< .001**
Copy of figures	8.08	*3.13*	=	9.56	*2.62*	9.08	*2.95*	.15
Copy with landmarks	58.17	*10.81*	<	65.02	*5.14*	63.33	*3.51*	**< .001**
Digit Span forward	5.23	*1.03*	=	5.28	*1.10*	5.38	*1.28*	.83
Digit Span backward	2.76	*0.86*	=	3.40	*0.82*	3.92	*1.34*	**< .001**
RPM'47	17.33	*5.61*	<	24.76	*4.49*	25.18	*5.39*	**< .001**
MFTC—false alarms	6.57	*9.95*	>	0.72	*1.31*	0.55	*0.92*	**< .001**
MFTC—accuracy	0.81	*0.14*	<	0.92	*0.08*	0.94	*0.06*	**< .001**
MFTC—time	161.9	*81.13*	>	97.42	*35.23*	79.12	*33.83*	**< .001**
Stroop—interf. time	81.47	*37.72*	>	65.17	*14.01*	53.72	*16.51*	**< .001**
Stroop—Interf. errors	7.73	*9.03*	>	3.30	*2.28*	0.91	*1.62*	**< .001**

Note. In bold type are reported significant differences after Bonferroni correction; the symbols " < " and " > " indicate significant differences between TLD and cAD.
RAVLT—immediate (Rey's Auditory Verbal Learning Test immediate recall); RAVLT—delayed (Rey's Auditory Verbal Learning Test delayed recall); RAVLT Recog. False alarms and accuracy (Forced-choice recognition of RAVLT accuracy and false alarms); PWF (phonological word fluency); SWF (semantic word fluency); RPM'47 (Raven's Coloured Progressive Matrices); MFTC (Multiple Features Targets Cancellation test); Stroop (Stroop test short form).

There was no statistically significant difference in age and educational level between the groups. The groups were homogeneous for gender distribution ($\chi^2 = 0.03$; $p = .863$).

The one-way ANOVA carried out to compare TLD, cAD and HC displayed a significant main effect of the "group" variable (Wilk's lambda = 0.07; $p < .001$). Significant differences were observed in most of the neuropsychological measures, as shown in Table 1.

Post hoc comparisons revealed that at baseline TLD subjects scored worse than HC on all measures of episodic memory tasks (RAVLT immediate recall: $p < .001$; RAVLT delayed recall: $p < .001$; RAVLT Recog. False: $p < .001$; RAVLT Recog. Accuracy: $p < .001$), semantic memory (SWF: $p < .001$) and at the MMSE ($p < .001$), no differences in the other tests were found between TLD and HC. Furthermore, TLD obtained worse scores than cAD on RAVLT recognition accuracy ($p = .013$) and RAVLT delayed recall ($p = .05$) and performed better on Copy with landmarks ($p < .01$), PM '47 ($p < .001$), MFTC false alarms ($p < .001$), MFTC accuracy ($p < .001$), MFTC time ($p < .001$), Stroop interference time ($p = .039$), Stroop interference errors ($p = .004$).

It is worth noting that TLD and cAD patients reported similar MMSE and CDR scores and that cAD patients performed worse than HC on all cognitive tasks, with the exception of digit span forward, PWF and Copy of drawings.

The progression of the two AD groups was compared by means of a two-way MANOVA for repeated measures (Table 2).

The general interaction of AD subgroup (TLD *vs.* cAD) *versus* Test–retest condition (baseline *vs.* retest scores) was statistically significant (Wilks' lambda = 0.51; $p = .03$); also, group and test–retest condition showed an independent significant overall effect on change of cognitive performances between baseline and follow-up (respectively, Wilks' lambda = 0.38; $p < .0001$; and Wilks' lambda = 0.30; $p < .0001$).

When the interaction between AD subgroup and disease progression (Subgroup × Test–retest interaction) was investigated at the level of the individual test scores (see Table 2), significant specific effects were found on constructional praxis tasks (Copy of figures without and with landmarks), and semantic verbal fluency tasks (SWF). Statistical trends (considering Bonferroni Correction) in the univariate interaction analyses were obtained for MMSE, RAVLT – immediate recall, RAVLT – false alarms on recognition, phonological verbal fluency tasks, span forward and accuracy on MFTC. At the follow-up, in all these tasks, always cAD worsened more than TLD.

Post hoc comparisons were also used to evaluate separately whether any significant change occurred between first and second evaluation in cAD and TLD subjects.

https://doi.org/10.1017/S1355617711001287 Published online by Cambridge University Press

Table 2. Test retest comparisons of the two subgroups of AD with classical or focal onset

	Classic AD (cAD)					Temporal Lobe Dysfunction (TLD)					Interaction Group × Time
	Baseline		Follow-up			Baseline		Follow-up			
	Mean	*SD*	Mean	*SD*	*p*	Mean	*SD*	Mean	*SD*	*p*	*p*
MMSE	21.35	*3.70*	16.85	*5.59*	**.0001**	22.08	*3.44*	20.62	*4.14*	.31	.009
RAVLT—immediate	22.70	*6.49*	17.50	*7.39*	**.0001**	20.68	*3.76*	19.44	*4.40*	.63	.006
RAVLT—delayed	2.27	*2.03*	1.30	*2.07*	.009	0.70	*1.05*	0.44	*0.71*	.75	.145
RAVLT—Rec. false alarms	6.99	*6.09*	10.99	*7.48*	.01	6.64	*6.36*	7.41	*5.80*	.94	.082
RAVLT—Rec. accuracy	0.74	*0.1*	0.72	*0.15*	.10	0.67	*0.09*	0.58	*0.12*	.90	.293
PWF	20.49	*11.59*	14.37	*10.40*	**.0002**	23.72	*8.09*	22.08	*10.06*	.63	.018
SWF	10.75	*4.67*	6.08	*4.08*	**.0002**	10.28	*3.57*	9.24	*4.03*	.41	**<.001**
Copy of figures	8.08	*3.13*	5.43	*2.96*	**.0002**	9.56	*2.62*	9.80	*2.02*	.97	**<.001**
Copy with landmarks	58.17	*10.81*	46.90	*20.78*	**.0005**	65.02	*5.14*	65.60	*4.65*	.99	**.003**
Span forward	5.23	*1.03*	4.80	*1.21*	.088	5.28	*1.10*	5.44	*1.08*	.85	.030
Span backward	2.76	*0.86*	2.13	*1.20*	.007	3.40	*0.82*	3.16	*0.99*	.63	.165
RPM'47	17.33	*5.61*	13.97	*5.34*	**.0008**	24.76	*4.49*	22.96	*4.58*	.19	.198
MFTC—false alarms	6.57	*9.95*	11.14	*13.79*	.205	0.72	*1.31*	2.32	*7.40*	.92	.387
MFTC—accuracy	0.81	*0.14*	0.74	*0.19*	.085	0.92	*0.08*	0.93	*0.10*	.99	.068
MFTC—time	161.89	*81.13*	177.87	*80.38*	.15	97.42	*35.23*	98.04	*31.18*	.99	.170
Stroop—interf. time	81.47	*37.72*	122.68	*38.97*	**.0002**	65.17	*14.01*	89.21	*37.25*	.01	.098
Stroop—Interf. errors	7.73	*9.03*	14.75	*9.01*	**.0004**	3.30	*2.28*	6.86	*6.62*	.19	.150

Note. In bold type are reported significant differences after Bonferroni correction.
RAVLT—immediate (Rey's Auditory Verbal Learning Test immediate recall); RAVLT—delayed (Rey's Auditory Verbal Learning Test delayed recall); RAVLT Recog. False alarms and accuracy (Forced-choice recognition of RAVLT accuracy and false alarms); PWF (phonological word fluency); SWF (semantic word fluency); RPM'47 (Raven's Coloured Progressive Matrices); MFTC (Multiple Features Targets Cancellation test); Stroop (Stroop test short form).

As shown in Table 2, cAD patients displayed a general worsening of cognitive performances at the follow-up evaluation. In particular, scores obtained on MMSE and on tasks exploring episodic memory (RAVLT: immediate recall); visual-praxis abilities (copy of figures with and without landmarks); word list generation (PWF, SWF); and executive tasks (Stroop test interference time and errors) showed a significant decline at follow-up. A tendency toward a worsening was also observed on RAVLT delayed recall and on RAVLT recognition accuracy.

On the other hand, cognitive performances of TLD patients were relatively unchanged between baseline and follow-up, as only Stroop interference time score displayed a trend toward worsening ($p = .01$). It's worth noting that in TLD a 'floor effect' could have concealed the decline on RAVLT delayed recall.

DISCUSSION

Several studies have already described different cognitive pattern of amnesic MCI and the association of episodic and semantic deficit have been largely reported in the past (Adlam et al., 2006; Howieson et al., 2008; Murphy, Rich, & Troyer, 2006). The present paper represents an attempt to detect if this peculiar pattern still extends when the cognitive decline progress to a condition of overt AD. On this purpose, we compared two groups of AD patients with distinctive neuropsychological profiles at onset.

At baseline, the global severity of cognitive impairment (assessed by means of the MMSE and CDR) was similar in TLD and cAD patients, but the pattern of neuropsychological impairment shown by the two AD groups was different as expected by the selection criteria. TLD patients obtained pathological scores only on tests of episodic memory (RAVLT immediate and delayed recall, recognition accuracy, and false alarms) and semantic fluency, whereas cAD patients obtained pathological scores on episodic memory (RAVLT immediate and delayed recall, recognition accuracy and false alarms) attentional-executive (digit span backward, Stroop test and MFTC) and visual-spatial tests (RPM'47 and constructional praxis). Furthermore, when the two AD groups were directly compared, TLD subjects showed greater impairment in the accuracy on RAVLT recognition subtest and in the RAVLT delayed recall, whereas cAD patients obtained significantly lower scores on attentional-executive (digit span backward, Stroop test and MFTC) and visual-spatial tests (RPM'47 and constructional praxis).

The most relevant difference between the two groups of AD consisted in the different rate of progression. Indeed, no significant worsening as a whole was observed in TLD patients with the exception of a slight worsening in the time of execution of the Stroop test. Interestingly enough TLD patients were even more impaired in long term memory than at the baseline but, due to a floor effect, this further worsening was not significant. On the other hand, a wider significant decline was observed in cAD patients both on the global MMSE scores and on various memory, executive and visual-spatial measures. Executive functions were the most impaired over time in cAD and even the worsening shown on memory

https://doi.org/10.1017/S1355617711001287 Published online by Cambridge University Press

tests was partly due to an impairment of control functions. In fact, the most important change on the RAVLT concerned the recognition subtest and was due to a strong increase of false alarms, causing a decline of the accuracy score.

The main criticism advanced to explain the specific neuropsychological features of TLD has been advanced by Bien et al. (Bien, Helmstaedter, & Elger, 2001), who suggested that some patients classified as TLD do not actually have AD, but rather hippocampal sclerosis (HS). This suggestion stemmed from the necropsy observation of HS in one of the patients of the Butters' study (Butters et al., 1996). Indeed, HS patients show characteristic memory impairments, the progression of memory impairment is very slow, and other cognitive functions are mostly preserved (Helmstaedter & Elger, 1999). However this condition is quite rare and could hardly affect the majority of our TLD patients; moreover none of our patients was affected by epilepsy and the MRI study of mesial temporal structures allowed the exclusion of features of hippocampal sclerosis.

Two main interpretations can, in our opinion, be advanced to explain the specific neuropsychological features and the slow cognitive decline of TLD patients.

The first interpretation assumes that TLD represents a distinct phenotypic variant of AD, with a functional involvement of specific temporal structures and slower spreading of the pathological process to the frontal and parietal association areas. As mentioned above, this variant is probably detectable also in the MCI condition (Adlam et al., 2006; Murphy et al., 2006) and could represent a continuum since from the onset of the pathological process. Moreover, a recent study by Libon et al. (2010) identifies three subtypes of neuropsychological patterns in the MCI condition. One of them is characterized by amnesia associated only with semantic impairment. This pattern could maintain its cognitive profile also after the conversion to overt AD and thus could represent a prodromal condition of TLD group.

The same authors also suggest that a different neuropathology could underlie these manifestations compared to the other MCI characterized by an amnesic and dysexecutive condition.

Argyrophilic Grain Disease (AGD), first described by Braak & Braak (1987, 1989) could partially correspond to the neuroimaging, neuropsychological and evolutionary features of TLD. This disease is characterized by the presence of argyrophilic grains (AGs) and pre-tangle neurons in the mesial temporal lobe limbic structures (Braak & Braak, 1989). Amnesia is its most common initial symptom (Ferrer, Santpere, & van Leeuwen, 2008), whereas other cognitive functions are relatively spared. However AGD usually appears in very old patients (in our sample only three patients were above 75); in addition, our TLD patients lack the behavioral disturbances (irritability agitation, delusions, and apathy) frequently reported in dementia associated with AGD (Steuerwald et al., 2007; Togo et al., 2005).

The hypothesis that TLD represents a phenotypic AD variant is also supported by a voxel based morphometric MRI study (Shiino et al., 2006), that identified four patterns of brain atrophy at onset in AD patients over 65 years of age, one of which, analogously to our TLD group, shows a slower progression.

The second interpretation assumes that TLD represents an earlier stage of disease progression than cAD. According to this interpretation, the neuropsychological features of TLD could be due to the early selective involvement of the entorhinal cortex and hippocampus and to the subsequent circumscribed spreading of the pathological process to the adjacent temporal neocortex, subsuming the associated semantic memory disorders (Ahmed, Arnold, Thompson, Graham, & Hodges, 2008; Convit et al., 2000; Hodges & Patterson, 1995). Only at a later stage the pathological process would spread to the frontal and parietal association areas, causing the executive, attentional and visual-spatial disorders typical of cAD patients. However, a strict version of this interpretation is at variance with the fact that the global severity of cognitive and functional impairment (assessed by means of CDR and MMSE) and the illness duration did not differ at baseline between TLD and cAD patients and that no conversion was observed from the TLD to the cAD category during the 24-month follow-up.

The main weakness of our study consists of the fact that AD was not diagnosed on the basis of pathology, but of clinical, SPET, and MRI data. We cannot, therefore, exclude that some of our patients were suffering from semantic dementia (SD), HS or AGD. The diagnosis of SD was discarded because none of the TLD patients met the criteria for possible Frontotemporal Dementia (Neary et al., 1998) and atrophic lesions (at the MRI) and perfusion deficits (at HMPAO-SPET) prevailed in mesial temporal regions, whereas in SD the mesial temporal structures are relatively spared and the atrophy prevails on the anterior, inferior and lateral aspects of the temporal lobes (Nestor, Fryer, & Hodges, 2006). Some authors (Davies, Graham, Xuereb, Williams, & Hodges, 2004) have, however, shown that at the individual level mesial temporal regions can be at least as atrophic in SD, when compared with AD.

In a similar manner, MRI data and lack of seizure history were used to rule out a diagnosis of hippocampal sclerosis, and the lack of a very old age and of behavioral disturbances led us to exclude a diagnosis of AGD. It must be acknowledged, however, that it is difficult to identify HS in the elderly, because they do not have the characteristic signal intensity noted for HS in the context of epilepsy (Zarow, Sitzer, & Chui, 2008) and that the clinical overlap between AD and AGD symptoms renders very difficult a differential diagnosis between these two degenerative diseases. It is, therefore, difficult to say if TLD must be considered as a phenotype of AD or as a syndrome that can result from different pathologies.

The main prediction that we had made at the beginning of our study was that, if TLD and cAD patients represent two different stages of AD, some TLD patients should convert to cAD in the course of the disease. Even if we cannot say if TLD must be considered as a phenotype of AD or as a syndrome resulting from different pathologies, our data clearly

https://doi.org/10.1017/S1355617711001287 Published online by Cambridge University Press

show that TLD does not represent an early stage of evolution of 'classical' AD, because no conversion from TLD to cAD was observed during the 2-year follow-up. Furthermore, the same data show that patients classified as TLD from the neuropsychological and neuroradiological point of view, show a slower rate of cognitive decline and/or a better response to ChEi therapy than cAD patients. Such data are also in agreement with the complementary observations made by several authors (Burns, Jacoby, & Levy, 1991; Drachman, O'Donnell, Lew, & Swearer, 1990; Marra, Silveri, & Gainotti, 2000; Ortof & Crystal, 1989; Teri, Hughes, & Larson, 1990) that the early occurrence of failures on executive function or on attentional tasks predicts a quicker decline in the clinical course of AD. Our observations might represent an important source of variance that should be taken into account when evaluating results of both therapeutic trials and clinical studies on the progression of 'probable' AD. In any case, the distinction between TLD and cAD deserves further investigation and confirmation by larger independent studies that should consider also neuropathological investigations.

ACKNOWLEDGMENTS

We thank Dr. Livia Wright for revising the English form of the manuscript. All the authors disclose any financial or non-financial competing interest related to the content of this manuscript. The study was supported by a grant of the 'Strategic Research Program 2006' (''Strumenti e procedure diagnostiche per le demenze utilizzabili nella clinica ai fini della diagnosi precoce e differenziale, della individuazione delle forme a rapida o lenta progressione e delle forme con risposta ottimale alle attuali terapie'') of the Italian Ministry of Health.

REFERENCES

Adlam, A.L., Bozeat, S., Arnold, R., Watson, P., & Hodges, J.R. (2006). Semantic knowledge in mild cognitive impairment and mild Alzheimer's disease. *Cortex*, *42*(5), 675–684.

Ahmed, S., Arnold, R., Thompson, S.A., Graham, K.S., & Hodges, J.R. (2008). Naming of objects, faces and buildings in mild cognitive impairment. *Cortex*, *44*(6), 746–752.

Alladi, S., Xuereb, J., Bak, T., Nestor, P., Knibb, J., & Patterson, K. (2007). Focal cortical presentations of Alzheimer's disease. *Brain*, *130*(Pt 10), 2636–2645.

Bien, C.G., Helmstaedter, C., & Elger, C.E. (2001). Is it really Alzheimer's disease? *Journal of Neurology, Neurosurgery, and Psychiatry*, *71*(3), 416–417.

Braak, H., & Braak, E. (1987). Argyrophilic grains: Characteristic pathology of cerebral cortex in cases of adult onset dementia without Alzheimer changes. *Neuroscience Letters*, *76*(1), 124–127.

Braak, H., & Braak, E. (1989). Cortical and subcortical argyrophilic grains characterize a disease associated with adult onset dementia. *Neuropathology and Applied Neurobiology*, *15*(1), 13–26.

Burns, A., Jacoby, R., & Levy, R. (1991). Progression of cognitive impairment in Alzheimer's disease. *Journal of the American Geriatric Society*, *39*(1), 39–45.

Butters, M.A., Lopez, O.L., & Becker, J.T. (1996). Focal temporal lobe dysfunction in probable Alzheimer's disease predicts a slow rate of cognitive decline. *Neurology*, *46*(3), 687–692.

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2002). Una versione abbreviata del test di Stroop: dati normativi nella popolazione italiana. *Nuova Rivista di Neurologia*, *12*(4), 111–115.

Cappa, A., Calcagni, M.L., Villa, G., Giordano, A., Marra, C., & De Rossi, G. (2001). Brain perfusion abnormalities in Alzheimer's disease: Comparison between patients with focal temporal lobe dysfunction and patients with diffuse cognitive impairment. *Journal of Neurology, Neurosurgery, and Psychiatry*, *70*(1), 22–27.

Carlesimo, G.A., Caltagirone, C., & Gainotti, G. (1996). The Mental Deterioration Battery: Normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery. *European Neurology*, *36*(6), 378–384.

Convit, A., de Asis, J., de Leon, M.J., Tarshish, C.Y., De Santi, S., & Rusinek, H. (2000). Atrophy of the medial occipitotemporal, inferior, and middle temporal gyri in non-demented elderly predict decline to Alzheimer's disease. *Neurobiology of Aging*, *21*(1), 19–26.

Davies, R.R., Graham, K.S., Xuereb, J.H., Williams, G.B., & Hodges, J.R. (2004). The human perirhinal cortex and semantic memory. *European Journal of Neuroscience*, *20*(9), 2441–2446.

Drachman, D.A., O'Donnell, B.F., Lew, R.A., & Swearer, J.M. (1990). The prognosis in Alzheimer's disease. 'How far' rather than 'how fast' best predicts the course. *Archives of Neurology*, *47*(8), 851–856.

Dudas, R.B., Clague, F., Thompson, S.A., Graham, K.S., & Hodges, J.R. (2005). Episodic and semantic memory in mild cognitive impairment. *Neuropsychologia*, *43*(9), 1266–1276.

Ferrer, I., Santpere, G., & van Leeuwen, F.W. (2008). Argyrophilic grain disease. *Brain*, *131*(Pt 6), 1416–1432.

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). ''Mini-mental state''. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198.

Gainotti, G., Marra, C., & Villa, G. (2001). A double dissociation between accuracy and time of execution on attentional tasks in Alzheimer's disease and multi-infarct dementia. *Brain*, *124*(Pt 4), 731–738.

Gainotti, G., Miceli, G., & Caltagirone, C. (1977). Constructional apraxia in left brain-damaged patients: A planning disorder? *Cortex*, *13*(2), 109–118.

Galton, C.J., Patterson, K., Xuereb, J.H., & Hodges, J.R. (2000). Atypical and typical presentations of Alzheimer's disease: A clinical, neuropsychological, neuroimaging and pathological study of 13 cases. *Brain*, *123*(Pt 3), 484–498.

Helmstaedter, C., & Elger, C.E. (1999). The phantom of progressive dementia in epilepsy. *Lancet*, *354*(9196), 2133–2134.

Hodges, J.R., & Patterson, K. (1995). Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia*, *33*(4), 441–459.

Howieson, D.B., Carlson, N.E., Moore, M.M., Wasserman, D., Abendroth, C.D., & Payne-Murphy, J. (2008). Trajectory of mild cognitive impairment onset. *Journal of the International Neuropsychological Society*, *14*(2), 192–198.

Lee, K.L., Harrell, F.E., Jr., Tolley, H.D., & Rosati, R.A. (1983). A comparison of test statistics for assessing the effects of concomitant variables in survival analysis. *Biometrics*, *39*(2), 341–350.

Libon, D.J., Xie, S.X., Eppig, J., Wicas, G., Lamar, M., & Lippa, C. (2010). The heterogeneity of mild cognitive impairment: A neuropsychological analysis. *Journal of the International Neuropsychological Society*, *16*(1), 84–93.

Marra, C., Silveri, M.C., & Gainotti, G. (2000). Predictors of cognitive decline in the early stage of probable Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *11*(4), 212–218.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E.M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*(7), 939–944.

Murphy, K.J., Rich, J.B., & Troyer, A.K. (2006). Verbal fluency patterns in amnestic mild cognitive impairment are characteristic of Alzheimer's type dementia. *Journal of the International Neuropsychological Society*, *12*(4), 570–574.

Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., & Black, S. (1998). Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology*, *51*(6), 1546–1554.

Nestor, P.J., Fryer, T.D., & Hodges, J.R. (2006). Declarative memory impairments in Alzheimer's disease and semantic dementia. *Neuroimage*, *30*(3), 1010–1020.

Ortof, E., & Crystal, H.A. (1989). Rate of progression of Alzheimer's disease. *Journal of the American Geriatrics Society*, *37*(6), 511–514.

Raven, J.C. (1949). *Progressive matrices (1947): Sets A, Ab, B: board and book forms*. London: H.K. Lewis.

Rey, A. (1958). Mémorisation d'une serie de 15 mot en 5 répétitions. In A. Rey (Ed.), *L'examen clinique en psychologie*. Paris: Presses Universitaire de France.

Shiino, A., Watanabe, T., Maeda, K., Kotani, E., Akiguchi, I., & Matsuda, M. (2006). Four subgroups of Alzheimer's disease based on patterns of atrophy using VBM and a unique pattern for early onset disease. *Neuroimage*, *33*(1), 17–26.

Steuerwald, G.M., Baumann, T.P., Taylor, K.I., Mittag, M., Adams, H., & Tolnay, M. (2007). Clinical characteristics of dementia associated with argyrophilic grain disease. *Dementia and Geriatric Cognitive Disorders*, *24*(3), 229–234.

Teri, L., Hughes, J.P., & Larson, E.B. (1990). Cognitive deterioration in Alzheimer's disease: Behavioral and health factors. *Journal of Gerontology*, *45*(2), P58–P63.

Togo, T., Isojima, D., Akatsu, H., Suzuki, K., Uchikado, H., & Katsuse, O. (2005). Clinical features of argyrophilic grain disease: A retrospective survey of cases with neuropsychiatric symptoms. *The American Journal of Geriatric Psychiatry*, *13*(12), 1083–1091.

Wechsler, D. (1981). *Wechsler Adult Intelligence Scale: WAIS-R manual*. New York: Psychological Corporation.

Zarow, C., Sitzer, T.E., & Chui, H.C. (2008). Understanding hippocampal sclerosis in the elderly: Epidemiology, characterization, and diagnostic issues. *Current Neurology and Neuroscience Reports*, *8*(5), 363–370.