ORIGINAL CONTRIBUTION

Platelet Amyloid Precursor Protein Abnormalities in Mild Cognitive Impairment Predict Conversion to Dementia of Alzheimer Type

A 2-Year Follow-up Study

Barbara Borroni, MD; Francesca Colciaghi, PhD; Carlo Caltagirone, MD; Luca Rozzini, MD; Laura Broglio, MD; Flaminio Cattabeni, PhD; Monica Di Luca, PhD; Alessandro Padovani, MD, PhD

Background: Alteration of the amyloid precursor protein (APP) forms ratio has been described in the platelets of patients with dementia of Alzheimer type (DAT) and in a subset of subjects with mild cognitive impairment (MCI).

Objective: To evaluate the potential role of the platelet APP forms ratio in predicting progression from MCI to DAT.

Design: Thirty subjects with MCI underwent a clinical and neuropsychological examination and a determination of the platelet APP forms ratio. Subjects were followed up periodically for 2 years, and the progression to dementia was evaluated.

Setting: Community population-based sample of patients admitted for memory complaints.

Results: Patients who progressed to DAT at the 2-year follow-up (n=12) showed a significant decrease of baseline platelet APP forms ratio values (mean±SD, 0.36±0.28) compared with stable MCI subjects (mean±SD, 0.73±0.32) ($P<.01$) and patients who developed other types of dementia (mean±SD, 0.83±0.27) ($P=.03$). By fixing a cutoff score of 0.6, 10 (83%) of the 12 DAT patients showed baseline values below the cutoff, whereas 10 (71%) of 14 subjects who either developed non-Alzheimer–type dementia or maintained cognitive functions had values in the normal range.

Conclusion: Mild cognitive impairment is a major risk factor for DAT, and Alzheimer disease–related pathological changes can be identified in patients converting to DAT within a 2-year follow-up.

Arch Neurol. 2003;60:1740-1744

From the Department of Neurology, University of Brescia, Brescia (Drs Borroni, Rozzini, Broglio, and Padovani), the Institute of Pharmacological Sciences, Centre of Excellence for Neurodegenerative Disorders, University of Milan, Milan (Drs Colciaghi, Cattabeni, and Di Luca), and the Department of Neurology, University "Tor Vergata," Rome (Dr Caltagirone), Italy.

A SLIGHT impairment in cognitive functions, notably memory, with otherwise normal performances has been designated as mild cognitive impairment (MCI), and has become a topic of considerable research in the past few years.[1-3]

Individuals with MCI represent the population at higher risk to develop dementia of Alzheimer type (DAT), with a rate of progression 10 times faster than a healthy elderly subject. In this regard, some investigators[4-6] have suggested that all MCI subjects have Alzheimer disease (AD).

Nevertheless, the proposed criteria for MCI may well apply to a heterogeneous population whose memory complaints could be secondary to systemic disease, a drug-induced state, affective disorders, or other neurodegenerative diseases, rather than to an ongoing AD-related process.

Detection of AD among MCI subjects is, therefore, mandatory to maximize the benefit of available therapies that maintain cognitive functions over time.[7] In this view, biological and neuroimaging markers hold the promises to disclose the identification of the so-called preclinical stage.

Several researchers[8,9] have tried to identify peripheral markers of AD, and high-accuracy diagnostic values since the mild stages have been obtained by the combination of tau and Aβ protein concentrations in cerebrospinal fluid. More recently, it has been demonstrated that altered tau and Aβ42 protein concentrations may already be detectable in those subjects who were clinically diagnosed as having MCI before developing dementia.[10,11]

Other researchers[12] have focused attention on the amyloid precursor protein (APP), a protein expressed in several splice variants in neural compartment and in nonneural tissues.

Interestingly, it has been demonstrated that patients with sporadic DAT show an alteration of APP pattern forms expression in platelets when compared with age-matched control subjects and

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with patients affected by non-AD–related dementia.[13-15] A platelet APP forms alteration has already been found in many MCI subjects, suggesting its potential role in identifying patients who will convert to DAT.[16]

This observation defined the frame of the present work, which aimed to investigate the platelet APP forms ratio (APPr) prospectively as a biomarker for the diagnosis of preclinical AD among MCI subjects. To this aim, a population of MCI subjects was observed through a 2-year follow-up study, and the platelet APPr at enrollment was evaluated.

METHODS

SUBJECTS

Among a large sample of patients with memory complaints, 30 MCI patients were recruited from the Centre of Ageing Brain and Neurodegenerative Disorders, University of Brescia. The study was conducted in accord with local clinical research regulations, and informed consent was required from all subjects and caregivers when indicated.

All subjects underwent a somatic and neurologic examination and laboratory studies, including the determination of apolipoprotein E genotype. All individuals underwent a brain imaging study (computed tomography or magnetic resonance imaging). The behavioral and global cognitive evaluation was performed according to a standardized battery that included the following tools: Clinical Dementia Rating Scale,[17] Mini-Mental State Examination,[18] Alzheimer Disease Assessment Scale,[19] Neuropsychiatric Inventory,[20] Geriatric Depression Scale,[21] Hamilton Anxiety Rating Scale,[22] and instrumental activities of daily living[23] and activities of daily living indexes.[24] The diagnosis was accomplished by tests tapping different domains such as verbal and nonverbal memory, abstraction, executive functions, visuospatial skills, and language (data not presented).

The diagnosis of MCI was based on Mayo Clinic criteria.[4,25]

A diagnosis of probable DAT was based on National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[26] A diagnosis of frontotemporal dementia and dementia with Lewy bodies was made according to standardized clinical criteria.[27,28] The inclusion and exclusion criteria are reported elsewhere.[15,16]

STUDY DESIGN

This is a longitudinal open study. At baseline, subjects underwent the neuropsychological assessment previously described, and venipuncture for platelet collection was performed. Each subject was followed up periodically for 2 years.

Subjects with MCI were reexamined, and a final diagnosis according to clinical and neuropsychological features was determined by 2 independent raters (L.R. and L.B.) who were blind to the baseline experimental findings.

PLATELET COLLECTION AND PREPARATION

The patient information and case diagnoses were unknown to the laboratory investigator (Dr Colciaghi) who received and analyzed the samples.

According to previous studies,[15,16] platelets from each subject were processed for Western blot analysis by a monoclonal antibody (22C11) raised against the N-terminal domain of the APP, therefore recognizing all APP forms present in the samples.

Table 1. Demographic and Clinical Characteristics at Baseline According to the 2-Year Follow-up Diagnosis*

Characteristic	MCI to DAT (n = 12)†	MCI to NADD (n = 4)‡	MCI to MCI (n = 10)§	*P* Value
Female-male ratio	9:3	3:1	6:4	.47
Age, y	70.8 ± 7.7	62.2 ± 10.8	70.2 ± 5.9	.13
MMSE score	27.7 ± 2.3	26.4 ± 1.5	28.7 ± 1.6	.18
ADAS, cognitive, score	11.9 ± 4.2	15.7 ± 1.5	9.2 ± 4.8	.06
NPI score	14.6 ± 10.8	16.2 ± 9.3	11.2 ± 12.6	.46

Abbreviations: ADAS, Alzheimer Disease Assessment Scale; DAT, dementia of Alzheimer type; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NADD, non-Alzheimer–type dementia; NPI, Neuropsychiatric Inventory.

*Data are given as mean ± SD unless otherwise indicated. The mean ± SD Clinical Dementia Rating Scale score was the same (0.5 ± 0.0) in the 3 groups. No instrumental activities of daily living were lost in the 3 groups.

†Subjects with MCI who progressed to DAT at the 2-year follow-up.

‡Subjects with MCI who progressed to NADD at the 2-year follow-up (3 had frontotemporal dementia and 1 had Lewy body dementia).

§Subjects with MCI who were still diagnosed as having MCI at the 2-year follow-up.

This antibody recognized 3 different APP forms, with the apparent molecular weight of 130, 110, and 106 kDa. The results were expressed as the platelet APPr between the optical density of the upper (130 kDa) and the lower (106-110 kDa) APP immunoreactive bands. The ratio was determined for each individual from at least 3 replications (SD among replications, <10%).

STATISTICAL ANALYSIS

Comparisons among groups were performed using factor analysis of variance with post hoc analyses (Scheffé test) and Spearman rank correlation analysis. From a study[15] performed on a large sample of DAT and control individuals, a cutoff score of 0.6 was calculated, and APPr values below this cutoff were considered pathological.

Results were averaged and expressed as mean±SD. Differences were considered statistically significant at $P<.05$.

RESULTS

The 2-year follow-up data were available for 26 of 30 patients. Among these 26 patients, 12 (46%) progressed to DAT and 4 (15%) progressed to non-Alzheimer–type dementia (3 with frontotemporal dementia and 1 with Lewy body dementia); 10 (38%) were diagnosed as having stable MCI (percentages do not total 100 because of rounding).

The demographic and clinical characteristics at baseline of the sample, classified according to diagnosis at the 2-year follow-up, are reported in **Table 1**. At baseline, the APPr of the 26 MCI subjects was 0.58±0.35.

Patients who progressed to DAT showed a significant decrease of baseline APPr values (0.36±0.28) compared with stable MCI subjects (0.73±0.32) ($P<.01$) and patients who developed other types of dementia (0.83±0.27) ($P=.03$) (**Figure 1**).

In **Table 2**, the values of cognitive and functional performances at the 1- and 2-year follow-up are shown. Through Spearman rank correlation analysis, diagnosis at the 2-year follow-up was significantly associated with the APPr at baseline ($P<.01$), but there was no associa-

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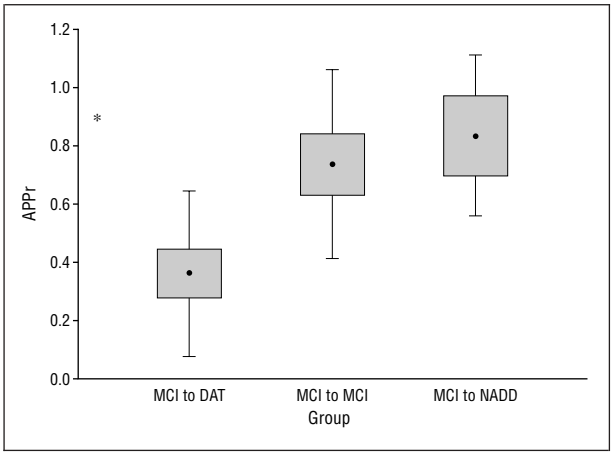

Figure 1. The mean±SD amyloid precursor protein forms ratio (APPr) according to the 2-year follow-up diagnosis. MCI indicates mild cognitive impairment; DAT, dementia of Alzheimer type; NADD, non-Alzheimer–type dementia; MCI to DAT, subjects with MCI who progressed to DAT at the 2-year follow-up; MCI to MCI, subjects with MCI who were still diagnosed as having MCI at the 2-year follow-up; MCI to NADD, subjects with MCI who progressed to NADD at the 2-year follow-up; circle in center of squares, mean value; and asterisk, the mean APPr values of control subjects previously described.[15,16]

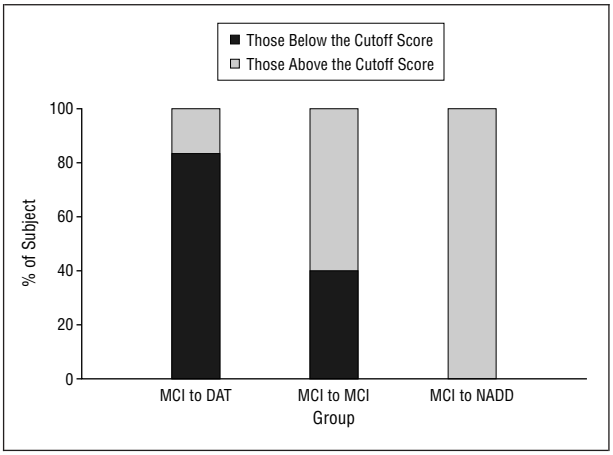

Figure 2. Percentage of subjects below and above the cutoff score in the different groups. The abbreviations and the groups are explained in the legend to Figure 1.

Table 2. Clinical Scores at the 1- and 2-Year Follow-up in the 3 Groups*

Time	MCI to DAT	MCI to NADD	MCI to MCI	*P* Value
		CDR Score		
Baseline	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	NA
1 y	0.6 ± 0.2	0.8 ± 0.28	0.5 ± 0.0	.06
2 y	1.0 ± 0.49	1.3 ± 0.5	0.5 ± 0.0	.01
		MMSE Score		
Baseline	27.7 ± 2.3	26.4 ± 1.5	28.7 ± 1.6	.18
1 y	26.3 ± 3.1	24.4 ± 2.9	29.0 ± 1.2	.01
2 y	23.3 ± 4.4	20.7 ± 4.2	29.0 ± 1.9	.001
		ADAS, Cognitive, Score		
Baseline	11.9 ± 4.2	15.7 ± 1.5	9.2 ± 4.8	.06
1 y	14.3 ± 7.6	28.0 ± 7.4	4.45 ± 8.7	.001
2 y	20.4 ± 11.9	32.5 ± 11.7	8.7 ± 4.3	.001
		NPI Score		
Baseline	14.6 ± 10.8	16.2 ± 9.3	11.2 ± 12.6	.46
1 y	15.5 ± 12.8	27.0 ± 18.5	9.1 ± 7.7	.09
2 y	15.5 ± 7.7	18.5 ± 7.0	7.9 ± 7.1	.04
		IADL (Lost)		
Baseline	0	0	0	NA
1 y	−0.8 ± 1.1	−2.0 ± 2.1	0	.05
2 y	−2.6 ± 1.3	−3.2 ± 2.6	0	<.001

Abbreviations: ADAS, Alzheimer Disease Assessment Scale; CDR, Clinical Dementia Rating Scale; DAT, dementia of Alzheimer type; IADL, instrumental activities of daily living; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NA, data not applicable; NADD, non-Alzheimer–type dementia; NPI, Neuropsychiatric Inventory.

*Data are given as mean ± SD unless otherwise indicated. The 3 groups are described in the third through fifth footnotes to Table 1.

tion with demographic and clinical variables and apolipoprotein E genotype ($P=.52$).

By fixing a cutoff score of 0.6, previously chosen among a large sample of subjects, at baseline, there were 14 (54%) of 26 MCI subjects with pathological APPr scores. Among these 14 subjects, 10 (71%) developed DAT, whereas 4 (29%) were classified as having stable MCI. In particular, 10 of 12 patients with DAT (sensitivity, 83%) showed baseline pathological values below the cutoff, whereas 10 of 14 subjects who either developed non-AD–type dementia (all 4 patients with non-Alzheimer–type dementia) or maintained cognitive functions (6 of 10 MCI patients) had normal values above the cutoff (specificity, 71%) (**Figure 2**).

COMMENT

In the present study, we confirmed that MCI is a major risk factor for developing dementia and that AD-related pathological changes can be identified in patients converting to DAT within the 2-year follow-up.

Mild cognitive impairment is a heterogeneous condition, and the literature data[1,29] indicate a varying degree of rate of conversion toward DAT, ranging from 10% to 25%. To limit this heterogeneity, a consensus defined subtype features of MCI, such as amnestic MCI, to find a subgroup at a much higher risk of progression to dementia.[25] In fact, in our sample, adopting strict criteria to keep confounding factors at a minimum and excluding patients with depression, somatic disorders, or cardiovascular pathological features, we found a high rate of progression (23% per year).

Moreover, the platelet APPr was significantly altered in those MCI subjects who progressed to DAT, as more than 80% of these subjects showed a pathological decrease of the platelet APPr at baseline.

Thus, the demonstration of an APPr decrease in MCI subjects and its association with progression to DAT suggests that a subgroup of these subjects already has the biological hallmarks of AD.

During the past 3 years, the research on biological and neuroimaging markers of AD has moved from early to preclinical diagnosis, because neuropathological studies[30] supported the view that AD-related features precede the clinical onset of symptoms.

In this regard, it has been recently shown that cerebrospinal fluid markers, such as Aβ, tau, and phos-

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phorylated tau proteins, correlate with either progressive cognitive decline or conversion to DAT with high accuracy values.[10,11]

Similar to these studies, we found high sensitivity (83%) and specificity (71%) values, thus supporting the view that biomarkers might represent a useful tool for identifying converter MCI from nonconverter MCI.

We acknowledge that our study has some limitations. A longer follow-up of a larger sample of subjects who still have MCI is needed, along with neuropathological data to confirm the clinical diagnosis of DAT. Furthermore, the inclusion and exclusion criteria might have determined a selection bias that favored the recruitment of MCI patients at higher risk of AD, thus limiting the generalization of our findings.

Despite these limitations, these observations have several implications at theoretical and clinical levels.

From the theoretical point of view, our data support the view that MCI represents a predementia stage, although not uniquely associated with AD. In fact, there is a relatively small proportion of MCI subjects who either do not progress or do convert to other forms of dementia than DAT, thus questioning the claim that criteria for MCI are highly specific for subjects with incipient AD. Nevertheless, converging evidence derived from an autopsy series clearly demonstrates that AD-related changes precede the stage at which standardized clinical criteria for DAT apply. In fact, typical AD neuropathological markers are found in persons with and without dementia; these persons are labeled as having preclinical AD. All together, these findings argue for a distinction to be made between AD and DAT, according to which AD should properly refer to a neuropathological entity that is distinct but overlapping with dementia.[31]

Indeed, taking into account all different prospective studies on MCI, accuracy values compare favorably with National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association clinical criteria for probable DAT.[32] Consequently, it might be speculated that the accommodation of the predementia stage on a biological profile argues for the real possibility of diagnosing AD before patients satisfy the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for dementia. It might well turn out that a single biomarker will not ever be reliable enough to become the gold standard for the diagnosis of AD before DAT, but rather that a combination of different biological markers will be required to identify AD before dementia develops.[33,34] The operational approach to a preclinical diagnosis of AD by including markers from different sources will have relevant consequence in clinical practice because it might be the more appropriate approach through which to evaluate the effectiveness of therapeutic options for DAT prevention, emphasizing when the available treatments should take place.

In conclusion, our study suggests that in MCI patients, biological disease-related changes are already detectable and the APPr may represent a helpful predictor of progression. In the future, the better characterization of the biological and neuroimaging alterations in this population will open a new chapter on biomarker criteria for preclinical AD diagnosis and will prompt clinicians to communicate the diagnosis of AD when dementia symptoms are not already overt.

Accepted for publication July 3, 2003.

Author contributions: *Study concept and design* (Drs Borroni, Di Luca, and Padovani); *acquisition of data* (Drs Colciaghi, Rozzini, and Broglio); *analysis and interpretation of data* (Drs Borroni, Caltagirone, and Cattabeni); *drafting of the manuscript* (Drs Borroni, Di Luca, and Padovani); *critical revision of the manuscript for important intellectual content* (Drs Colciaghi, Caltagirone, Rozzini, Broglio, and Cattabeni); *statistical expertise* (Drs Borroni and Rozzini); *obtained funding* (Drs Caltagirone, Di Luca, and Padovani); *administrative, technical, and material support* (Drs Borroni and Colciaghi); *study supervision* (Dr Cattabeni).

This study was supported by a grant from the Ministry of Health (Progetto Finalizzato Alzheimer–Regione Lombardia and Progetto Finalizzato Alzheimer–Istituto Di Ricovero E Cura A Carattere Scientifico Santa Lucia), Rome, Italy; and grants 9906158271-004 (Dr Di Luca) and 9906158271-003 (Dr Padovani) from the Ministero dell'istruzione e dell'università e della ricerca, Roma, Italy.

We thank Elisabetta Cottini, MD; Chiara Agosti, MD; and Barbara Vicini Chilovi, MD, for performing the neuropsychological assessments.

Corresponding author and reprints: Alessandro Padovani, MD, PhD, Clinica Neurologica, c/o Spedali Civili di Brescia, Università degli Studi di Brescia, Pza Spedali Civili, 1, Brescia, Italy (e-mail: padovani@bshosp.osp.unibs.it).

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