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Late and early onset dementia: What is the role of vascular factors? A retrospective study

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ABSTRACT

Background: Neuropathology of Alzheimer's disease (AD) demonstrates that the common occurrence of vascular lesions and vascular factors is suggested to contribute significantly to the clinical progression of the disease. This study has assessed the presence of vascular brain lesions and risk factors in subjects with diagnosis of AD and their influence on the disease course both in Late Onset Dementia (LOD) and in Early Onset Dementia (EOD).

Methods: MRI scans of 374 LOD and of 67 EOD patients were evaluated for the presence of vascular associated lesions and rated according to the age-related white matter changes (ARWMC) scale as "pure degenerative", "mixed" and "vascular" cases of dementia. Vascular risk factors burden (hypertension, diabetes, dyslipidemia, myocardial infarction) and disease progression were also assessed.

Results: 44% of LOD cases and 46% of EOD were classified as "mixed dementia cases". The vascular risk factors burden showed an increase from the pure degenerative to the pure vascular forms. Disease progression, calculated in two years using the Mini Mental State Evaluation (MMSE), Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scores, did not reveal differences among the three different classes of dementias.

Conclusions: Vascular lesions are found in the majority of LOD cases and in about one half of EOD. This observation is consistent with the hypothesis of a synergistic effect of the degenerative and vascular factors on the development of cognitive dysfunction. The linear increase of the vascular burden supports the idea of a continuum spectrum between the pure degenerative and the pure vascular forms of adult-onset dementia disorders.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by an insidious and gradual progression of memory and other cognitive dysfunctions leading to difficulties in daily life activities [1,2]. Its prevalence is age related, averaging at 0.001% before 65 years of age (Early Onset Dementia, EOD), 2% at 65 years and up to 50% at ≥85 years (Late Onset Dementia, LOD) [3,4]. Vascular features have been suggested to contribute to AD pathophysiology as shown by necropsy investigations demonstrating approximately one third of cases of obvious brain vascular lesions [5,6]. These results were supported by more recent data [7–9] suggesting that in AD the vascular injury may contribute to the clinical expression of the disease.

Re-evaluation of vascular lesions in AD suggests to reconsider the strong distinction of dementias in neurodegenerative and vascular forms as in the majority of patients degenerative and vascular damage co-exist. Pure neurodegenerative or vascular processes probably account for a minority of cases [10]. A more reasonable hypothesis is that the presence of vascular lesions contributes significantly to the clinical expression of AD [11,12]. On the other hand, in the majority of AD patients neurodegenerative and vascular injury coexist [10]. Therefore AD and Vascular Dementia (VaD), should be considered to lie in a continuum spectrum, where pure AD is at one extreme and pure VaD on the other. Likely in the daily clinical practice most patients are in an intermediate situation [10].

The present study has investigated the presence of vascular brain lesions and risk factors in subjects with diagnosis of adult-onset dementia and their influence on the disease course both in LOD and EOD. Patients were recruited among all subjects evaluated in the Alzheimer Unit, A. Cardarelli Hospital in Naples, and were adequately informed about the purpose of processing their personal data after the ethical approval by the IEC.

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2. Material and methods

2.1. Diagnostic procedures

The overall sample included 374 LOD patients (229 F and 145 M) and 67 EOD patients (38 F and 29 M). Patients were examined by the Memory Clinic of Cardarelli Hospital in Naples and diagnosis was made according to NINCDS-ADRDA criteria [13] for AD, and NINDS-AIREN criteria [14] for VaD. We carefully excluded from the initial sample subjects potentially affected by other dementias. This retrospective study included only patients monitored in our clinic for at least 24 months. In all subjects general cognitive abilities were evaluated by the Mini Mental State Examination (MMSE) and Clock Drawing Test. Living autonomy was assessed by Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales. At the enrollment patients did perform a Magnetic Resonance Imaging (MRI) scan and were followed up for at least two years. MRI was done at baseline and after 24 months in all subjects. This second evaluation allowed a comparison to previous data and excluded any significant change. Disease progression was evaluated every 6 months by MMSE, ADL and IADL assessment. Baseline characteristics of the sample are shown in Table 1. All patients were treated with acetylcholinesterase inhibitors and/or memantine; all received also antihypertensive agents, lipid lowering agents and other drugs if needed, and medication adherence was good in all. All patients having vascular risk factors were strongly encouraged to control them (e.g. aerobic exercise, walking, stop smoking etc.).

2.2. Reclassification of the cases

Mixed dementia (MD), refers to a combination of definite Alzheimer disease (AD) and vascular encephalopathy, but the distinction between both disorders is controversial. For the diagnosis of MD the clinical/neuroimaging criteria of possible AD plus cerebrovascular diseases (CVD) separate entities are used, but causal relations between vascular brain lesions and dementia are unclear.

According to the NINDS-AIREN criteria for the diagnosis of vascular dementia the term "AD with CVD" should be reserved to classify patients fulfilling the clinical criteria for possible AD and who also present clinical or brain imaging evidence of relevant CVD.

For diagnosis reclassification, MRI scans of single patients with AD diagnosis were rated according to the New Rating Scale for Age-Related White Matter Changes (ARWMC) [15]. This scale, that estimates the extent of brain vascular injury, assesses independently vascular damages in the white matter and basal ganglia, in the frontal, parietal–occipital, temporal, cerebellar/infratentorial areas. A score ≥ 2 at the scale indicates the presence of significant vascular damages.

We used a cut-off ≥ 2 at the ARWMC scale, because, in this scale, starting from a score of 2 points are identified early confluent lesions. Lower scores indicate the presence of a limited number of lesions that do not exceed 5 mm in diameter.

Patients scoring <2 were then considered as "pure" AD, whereas those scoring ≥ 2 as "mixed" dementia cases. The presence of vascular risk factors was then calculated in pure AD, mixed dementia and in pure VaD cases. Two neurologists evaluated the clinical papers and MRI scans of all AD patients and independently made the diagnosis of "pure" AD or mixed dementia, and if any controversy arise, the opinion of a third neurologist was asked.

Table 1
Baseline characteristics of the patient groups.

No. of patients	Sex		Age		Years of schooling	
Late Onset Dementia						
374	Male	145 (38.8%)	Range	Mean	Range	Mean
	Female	229 (61.2%)	68–90	73 ± 8	0–18	7 ± 5
Early Onset Dementia						
67	Male	38 (56.7%)	Range	Mean	Range	Mean
	Female	29 (43.3%)	49–69	63 ± 5	0–18	7 ± 5

2.3. Statistics

The analysis of changes in scores for each of the parameters included in this was made using Hotelling's T-squared test to evaluate the changes within each group during the course of the therapy, and the analysis of variance (ANOVA) was made for the identification of possible significance in the differences of disease progression between pure AD, mixed dementia and in pure VaD cases, both in LOD and EOD.

3. Results

Original diagnosis for the sample of LOD patients (374 individuals) included 66% of AD, 14% of VaD and 20% of other adult-onset dementias. When AD cases were re-evaluated for the presence/absence of vascular lesions in MRI by the ARWMC scale, 164 of the 246 patients with original diagnosis of AD (44% of the sample) revealed lesions going from multiple lacunar infarcts to white matter confluent lesions. Only in the 22% of cases (82 patients) that no vascular lesions were noticeable. For patients of this last group, a final diagnosis of "pure" AD was placed, whereas the remaining patients with vascular lesions were included in the group of "mixed dementias" (Fig. 1).

From the global sample of EOD patients (67 subjects), VaD was found in 18% of cases and AD in 82% of them. When AD subjects were reclassified in terms of expression of vascular injury, 31 of the 67 individuals (46% of the sample) displayed vascular lesions, whereas only 13 patients (36% of the sample) did not show cerebrovascular damage. These last patients were then re-classified as "pure" AD cases, whereas those with vascular lesions were included in the group of "mixed dementias" (Fig. 2).

Analysis of the global burden of risk vascular factors in LOD and EOD samples resulted in the data summarized below. LOD cases: Arterial hypertension in 36.8% of pure AD, 69.3% of mixed dementias

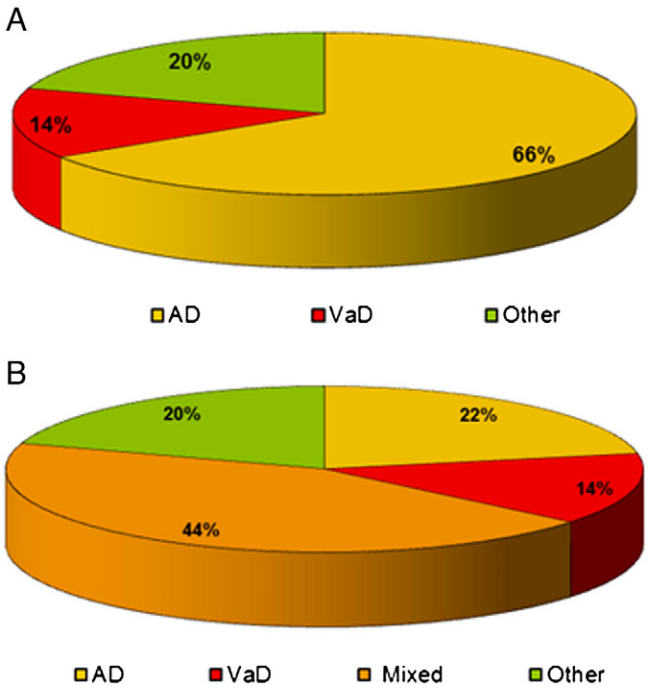

Fig. 1. Late Onset Dementia cases before (left) and after the reclassification based on MRI assessment.

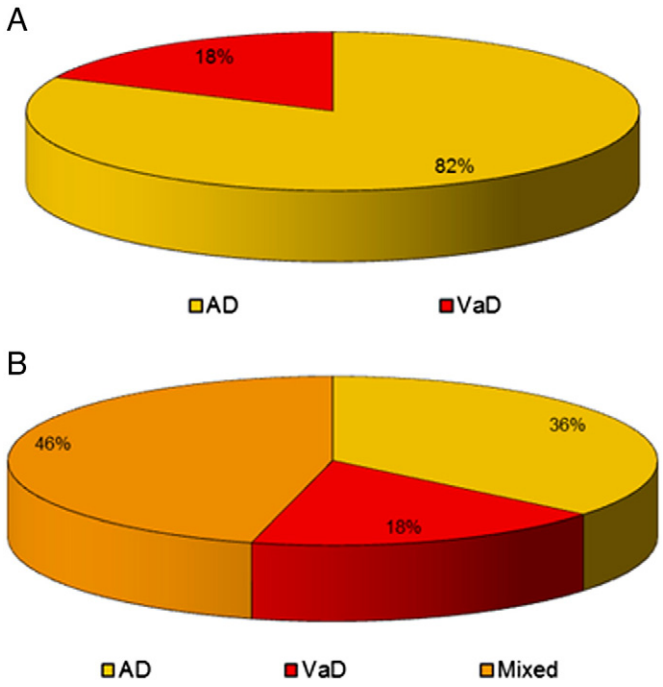

Fig. 2. Early Onset Dementia cases before (left) and after the reclassification.

and 80% of VaD patients; Diabetes in 15.2% of pure AD, 29.9% of mixed dementia and 39% of VaD patients; Dyslipidemia in 11.1% of pure AD, 25.7% of mixed dementia and 29.3% in VaD patients; Myocardial infarction in 10.3% of pure AD, 21.9% of mixed dementia and 17. 5% of VaD patients (Fig. 3). EOD cases: Arterial hypertension in 25% of pure AD, 61% of mixed dementia, and 61% of VaD patients; Diabetes in 12% of AD, in 35% of mixed dementia and 15% of VaD patients; Dyslipidemia in 12.5% of pure AD, 16% of mixed dementias and 30% of VaD patients; Myocardial infarction in 12% of pure AD, 12.9% of mixed dementia and 23% of VaD patients (Fig. 4).

Analysis of disease progression throughout the 2 years using MMSE, ADL and IADL (Figs. 5–7), shows that VaD has a significative decrease of the values in the scale during the first year and a slight recovery during the second. Mixed dementias and Alzheimer's dementia show instead a slow decrease that becomes significative after the first year; data are summarized in Table 2.

The difference between the dementias is most of all between Vascular Dementia and the other cases; considering the MMSE the difference is significative only in the LOD, while the difference is significative both in LOD and EOD in the functional evaluation (ADL and IADL); these differences disappear at the second year of follow up.

No significant differences were noticeable between disease progression and different vascular factors (data not shown).

4. Discussion

Increasing evidence supports the relevance of vascular factors as a cause of cognitive impairment and dementia, although the complex interplay between AD and VaD is not clearly elucidated yet [16]. A possible overlapping between forms of AD and VaD is suggested by several studies pointing out that pure AD and VaD could be placed at the extremes of a curve showing the peak with AD and VaD mixed cases, which probably represent the most diffused forms in the elderly [17–19]. The present investigation was designed to further contribute to define the influence of vascular injury and vascular risk factor on adult-onset dementia disorders.

At the beginning all patients have been classified in two categories: Alzheimer disease and Vascular Dementia, according with the NINCDS-ADRA and NINCDS-AIREN criteria. Only patients who have had the previous classification of AD were reclassified. The reclassification of these patients as “pure” AD or “mixed” cases was done only according with the MRI imaging (ARWMC scale). Subsequently we only evaluated the vascular risk factors in each, “pure” and mixed groups.

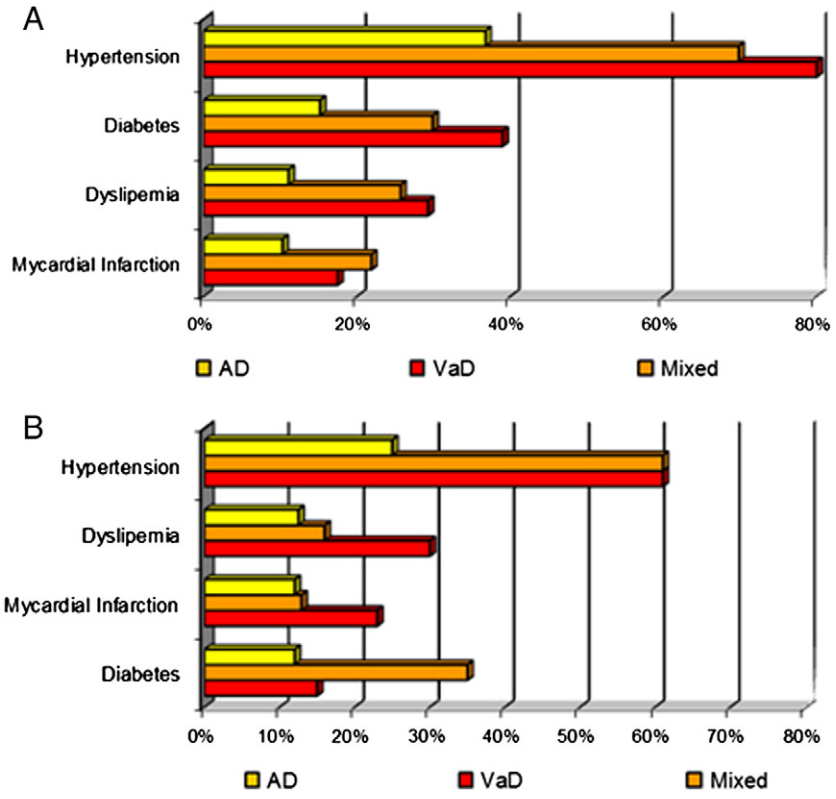

Fig. 3. Vascular risk factors burden in Late Onset Dementia (LOD).

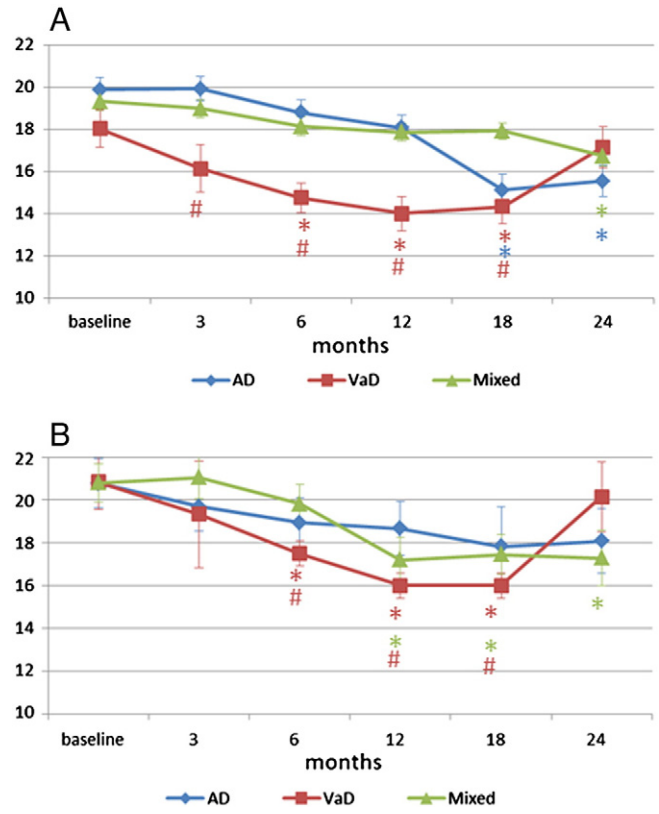

Fig. 4. Vascular risk factors burden in Early Onset Dementia (EOD).

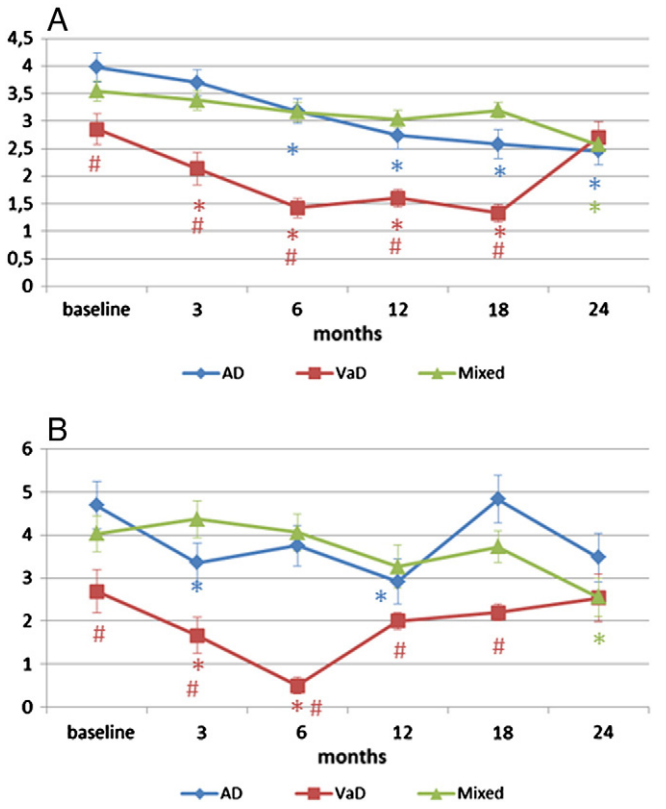

Fig. 6. ADL progression in Late Onset Dementia (left) and Early Onset Dementia (follow up at 3–6–12–18–24 months). Data are the means ± S.E.M. * = significative difference $p<0.05$ vs. baseline; # = significative difference VaD vs. other cases.

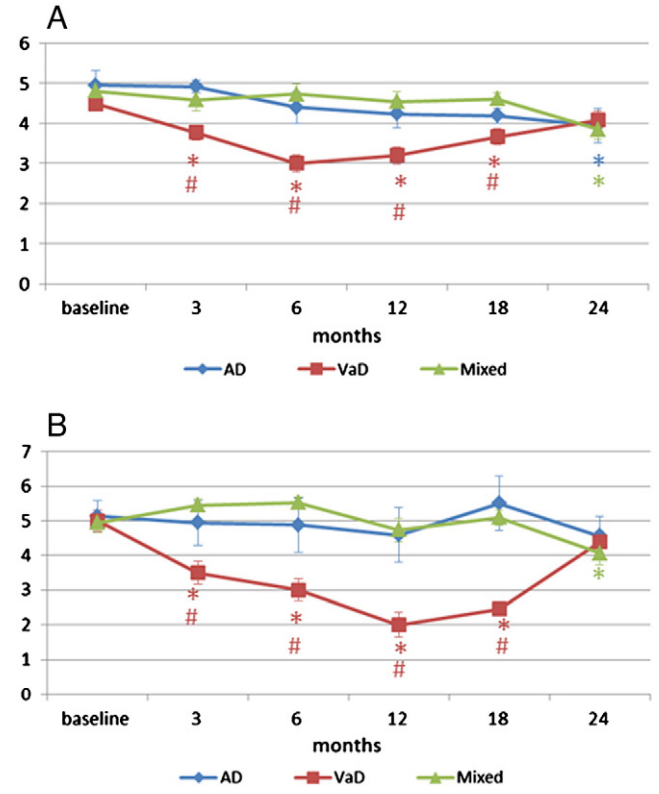

Fig. 5. MMSE progression in Late Onset Dementia (left) and Early Onset Dementia (follow up at 3–6–12–18–24 months). Data are the means ± S.E.M. * = significative difference $p<0.05$ vs. baseline; # = significative difference VaD vs. other cases.

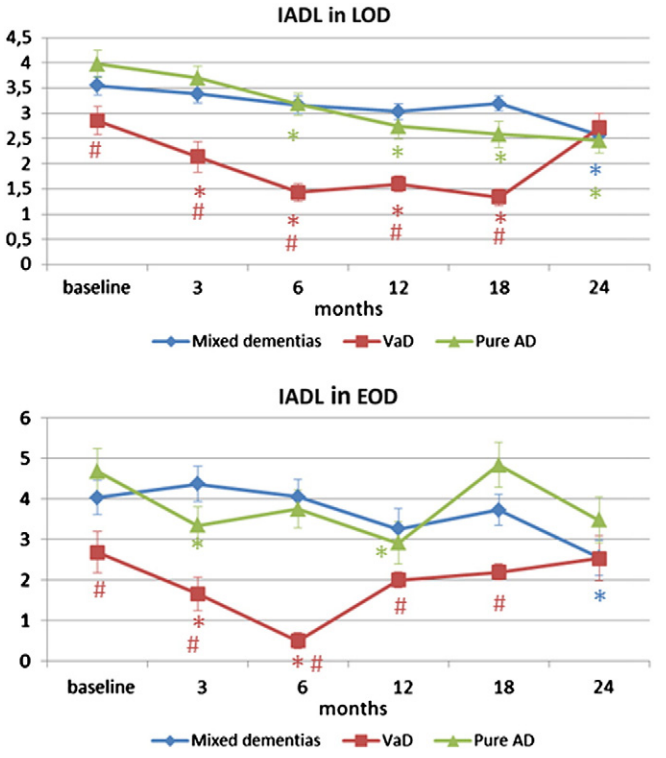

Fig. 7. IADL progression in Late Onset Dementia (left) and Early Onset Dementia (follow up at 3–6–12–18–24 months). Data are the means ± S.E.M. * = significative difference $p<0.05$ vs. baseline; # = significative difference VaD vs. other cases.

Table 2
Progression of MMSE, ADL and IADL scores over time. MMSE score is in a range of 0–30, ADL score is in a range of 0–6 and IDAL score is in a range of 0–8.

	Baseline	3 months	6 months	12 months	18 months	24 months
MMSE score						
Late Onset Dementia						
Mixed dementias	19.3	19.0	18.1	17.9	17.9	16.7
VaD	18.0	16.1	14.8	14.0	14.3	17.2
Pure AD	19.9	19.9	18.8	18.1	15.1	15.5
Early Onset Dementia						
Mixed dementias	20.8	21.1	19.8	17.2	17.5	17.3
VaD	20.8	19.3	17.5	16.0	16.0	20.2
Pure AD	20.8	19.7	18.9	18.7	17.8	18.1
ADL score						
Late Onset Dementia						
Mixed dementias	4.8	4.6	4.7	4.5	4.6	3.9
VaD	4.5	3.8	3.0	3.2	3.7	4.1
Pure AD	5.0	4.9	4.4	4.2	4.2	4.0
Early Onset Dementia						
Mixed dementias	4.9	5.5	5.5	4.7	5.1	4.1
VaD	5.0	3.5	3.0	2.0	2.5	4.4
Pure AD	5.1	4.9	4.9	4.6	5.5	4.6
IADL score						
Late Onset Dementia						
Mixed dementias	3.5	3.4	3.2	3.0	3.2	2.6
VaD	2.9	2.1	1.4	1.6	1.3	2.7
Pure AD	4.0	3.7	3.2	2.7	2.6	2.5
Early Onset Dementia						
Mixed dementias	4.0	4.4	4.1	3.3	3.7	2.6
VaD	2.7	1.7	0.5	2.0	2.2	2.5
Pure AD	4.7	3.4	3.8	2.9	4.8	3.5

So, the first step of this work has investigated in MRI scans of subjects with both early and late onset dementia those with vascular lesions to establish the possible burden of vascular injury on the development of dementia, and the second step was to assess vascular risk factors in pure AD or mixed dementia patients as well as in the individuals with clear diagnosis of VaD.

Initially we found that vascular lesions were in the majority of LOD cases and in about one half of EOD. This observation is consistent with the hypothesis of a synergistic effect of the degenerative and vascular factors on the development of cognitive dysfunction. Similarly as found for cerebrovascular lesions, vascular risk factors showed an increasing frequency from pure AD, to mixed dementia and VaD. Our findings are consistent with the hypothesis that a "continuum" seems then to exist between the degenerative and the vascular processes in the majority of adult-onset dementias [10] and are in agreement with the investigation of Agüero-Torres et al. reporting that in old subjects with AD vascular involvement was frequent, with pure AD cases representing only a minority [7]. Our investigation has also revealed that vascular lesions and risk factor are present in a relevant proportion of EOD. In our sample, consistent with the findings of literature [20] vascular risk factors burden had a similar distribution in EOD and LOD, although, as expected, their entity was lower compared to LOD individuals. This suggests the validity of the "continuum" hypothesis also in this group. The only risk factor displaying a different trend was diabetes, the occurrence of which had a similar trend in pure AD, mixed dementia and VaD groups. This observation, which is in line with the results of wide population studies [21,22], and the Memory in Diabetes (MIND) part of the ACCORD study [23], suggests that hyperglycemia leads to both degenerative and vascular damage. APOe factor is probably involved in the relationship between insulin resistance and amyloid deposition [24].

Cerebral amyloid angiopathy, microvascular degeneration affecting the cerebral endothelium and smooth muscle cells, basal lamina alterations, hyalinosis, and fibrosis are frequently evident in AD [5]. In addition, amyloid beta protein appears directly involved in the degeneration of both the larger perforating arterial vessels as well as cerebral capillaries, which represent the blood–brain barrier [6]. The cerebrovascular pathology in AD also encompasses macro- and micro-infarctions, hemorrhages, lacunas, and ischemic white-matter changes. An interaction of both perivascular mediators and derived factors would perturb the brain vasculature. Peripheral vascular factors such as long-standing hypertension, atrial fibrillation, coronary or carotid artery disease, and diabetes mellitus are also apparent in AD. These factors would modify the cerebral circulation such that a sustained hypoperfusion or oligemia is impacted upon the aging processes to induce the characteristic pathology [8].

To sum up, vascular factors probably contribute significantly to the clinical appearance of adult-onset dementia disorders including AD. Very likely subjects with pure AD are on one extreme and subjects with pure VaD on the other, whereas the intermediate area, which is the largest one includes mixed cases. These findings therefore suggest the inappropriateness of a neat split between the degenerative and the vascular processes in the majority of cases of adult-onset dementia.

The second step of the study has investigated the disease progression. Disease progression is probably not influenced by vascular factors, as, both in LOD and EOD subjects, the vascular burden was not associated with differences in the MMSE, ADL and IADL scores. Our results, which are not consistent with studies of other groups [25] may reflect the particular sample we have examined. All patents we did examine were treated with acetyl-cholinesterase inhibitors and/or other drugs and were encouraged, to accurately control their vascular risk factors. The limit of the present study is the relatively small number of reported cases. The strength of it includes accuracy of diagnosis and of follow up, based on clinical, neuropsychological and imaging evaluations.

In conclusion, vascular factors are relevant in adult-onset dementia disorders including AD. Prevention and adequate therapeutic strategies to reduce the incidence of dementia are of great importance to lower the global dementia burden.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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