

Vascular Disease and Dementia: Lipoprotein(a) as a Neglected Link

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In a recent article published in this issue of the journal, de Mello Gomide Loures et al report their comprehensive review and meta-analysis on the association between hemostatic abnormalities and dementia,¹ concluding that patients with Alzheimer's disease (AD) display a variety of hemostasis related changes including increased values of von Willebrand factor (VWF), D-dimer, plasminogen activator inhibitor-1, thrombomodulin, and homocysteine. They also report that patients with vascular dementia (VD) show increased values of fibrinogen, activated factor VII, factor VIII, VWF, D-dimer, and homocysteine. These findings lead to the conclusion that hemostasis abnormalities may play an important role in the pathogenesis of dementia. Indeed, these scenarios are entirely plausible, and many hemostasis components evidenced to be raised in AD and VD, as representing important disorders leading to cognitive decline, are otherwise recognized to represent prothrombotic markers when elevated.²

Sometimes, however, it is not what is reported to be linked to a particular disease, but what is missing from such reports that also deserves attention, and thus we also wish to highlight the possible contribution of lipoprotein(a), Lp(a), to these adverse conditions. Lp(a) is cholesterol-enriched lipoprotein particle, sharing biochemical and structural homology with low-density lipoproteins (LDLs).³ Unlike LDL, whose main protein moiety is represented by apolipoprotein B100 (apoB100), Lp(a) also contains apolipoprotein(a), apo(a), which is covalently linked by a disulfide bridge to apoB100.⁴ Apo(a) displays a complicated and repetitive structure, highly homologous to that of human plasminogen, and is characterized by the presence of an inactive protease domain and five other structurally related domains, conventionally called "kringles." Unlike plasminogen, apo(a) contains a unique copy of kringle V and multiple kringle IV repeats, which are responsible for considerable size heterogeneity of this apolipoprotein and whose number is inversely associated with blood concentration (i.e., the lower the size, the higher the concentration, and vice versa).⁴

The presence of apo(a) confers to Lp(a) unique and exclusive metabolic features, which may also contribute to make it a potential player in the pathogenesis of dementia.

Reliable epidemiological evidence has been published on the association between Lp(a) and dementia. The very first study was published by Urakami et al in 1987,⁵ in which the authors found that patients with VD had significantly higher Lp(a) levels than age-matched healthy subjects (15 vs. 10 mg/dL; $p < 0.05$), whereas Lp(a) concentration was found to be similar in AD patient and healthy controls (9 vs. 10 mg/dL; $p < 0.05$).

In an ensuing cross-section study, Kuriyama et al studied 22 patients with senile AD, 29 with VD, and 68 matched healthy controls.⁶ The concentration of Lp(a) was found to be significantly higher in both patients with VD (36 ± 22 mg/dL) and AD (33 ± 30 mg/dL) compared with healthy controls (14 ± 4 mg/dL; $p < 0.001$ for both comparisons). No significant difference was observed between VD and AD cohorts. Unlike these findings, Caramelli failed to find a significant difference of Lp(a) concentration between 24 patients with AD and 32 elderly controls (25 ± 25 vs. 26 ± 18 mg/dL; $p = 0.32$).⁷

Urakami et al measured Lp(a) in 14 patients with VD, 18 with AD, and 47 healthy individuals,⁸ reporting that Lp(a) values were significantly increased in patients with VD compared with both AD patients and healthy controls (no final concentration reported; $p < 0.05$ for both comparisons). Regarding apo(a) phenotypes, low molecular weight isoforms were more frequent in patients with VD than in healthy individuals.

Mooser et al performed a case-control study including 285 patients with AD and 296 healthy controls,⁹ concluding that Lp(a) was associated with a reduced risk of AD in noncarriers of the apolipoprotein E $\epsilon 4$ allele (odds ratio [OR]: 0.4; 95% confidence interval [CI]: 0.2–0.9), whereas it was associated with an enhanced risk of late-onset AD in those with $\epsilon 4$ allele (OR: 6; 95% CI: 1.2–30.8).

Zuliani et al measured Lp(a) in 60 patients with VD, 40 with late onset AD, and 54 nondemented older controls.¹⁰ The concentration of Lp(a) was found to be nonsignificantly different across the three cohorts (healthy controls: 21 mg/dL; AD: 17 mg/dL, VD: 16 mg/dL; $p =$ nonsignificant for all comparisons).

Solfrizzi et al performed a cross-sectional study including 61 patients with AD and 63 healthy age-matched healthy controls,¹¹ concluding that Lp(a) values > 70 mg/dL were significantly associated with an enhanced risk of AD (OR: 4.7; 95% CI: 1.6–13.5), independently of sex and apolipoprotein E genotype.

In an ensuing case–control investigation, Emanuele et al measured Lp(a) in 54 patients with frontotemporal dementia and in 77 matched nondemented controls.¹² The concentration of Lp(a) was slightly but nonsignificantly increased in frontotemporal dementia patients compared with healthy controls (16 vs. 11 mg/dL; $p = 0.22$). Notably, patients with frontotemporal dementia had a significantly higher frequency of low molecular weight isoforms than the cognitively healthy controls. The same team of authors published another cross-sectional study including 50 patients with VD, 162 with AD, and 105 matched nondemented controls.¹³ The concentration of Lp(a) was found to be similar in patients with AD and in the control group (10.6 vs. 7.9 mg/dL; $p =$ nonsignificant), whereas Lp(a) levels were found to be substantially higher in patients with VD than in the other two cohorts (24 mg/dL; $p \leq 0.01$ for both comparisons). The frequency of low molecular weight isoforms was significantly higher in VD patients than in the cohorts. The same authors published almost simultaneously another work (73 AD patients compared with 73 matched healthy controls), displaying virtually identical data (Lp(a) concentration 11 vs. 12 mg/dL; $p =$ nonsignificant),¹⁴ but emphasizing that AD patients with the null apo(a) allele, which is associated with undetectable levels of Lp(a), had a delayed onset of AD compared with those with other apo(a) alleles (i.e., 77 ± 8 vs. 67 ± 10 years; $p = 0.010$).

Iwamoto et al studied 150 patients with late-onset AD, 46 with VD, and 150 healthy controls,¹⁵ concluding that Lp(a) values were similar in AD patients and controls (25 ± 25 vs. 21 ± 19 mg/dL; $p =$ nonsignificant), whereas Lp(a) concentration was significantly higher in VD patients (46 ± 36 mg/dL) than in the other two groups ($p < 0.05$ for both comparisons).

Watanabe et al measured Lp(a) in 37 patients with VD, 34 with AD, and 63 healthy controls,¹⁶ reporting that the concentration of Lp(a) was slightly but nonsignificantly higher in AD patients than in the control group (25 ± 22 vs. 14 ± 13 mg/dL; $p =$ nonsignificant), whereas Lp(a) was substantially higher in patients with VD than in the other two cohorts (45 ± 46 mg/dL; $p \leq 0.005$ for both comparisons).

Pantoni et al described the cases of three patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL),¹⁷ one of whom displayed an extremely elevated value of Lp(a) (i.e., 143 mg/dL; normal reference range: < 30 mg/dL).

Cankurtaran studied 120 patients with AD, 55 with VD, and 803 subjects with normal cognitive status.¹⁸ No signifi-

cant differences of Lp(a) values were found among the three cohorts of patients (normal cognitive status: 25 ± 18 mg/dL; AD: 25 ± 12 mg/dL; VD: 29 ± 35 mg/dL; $p =$ nonsignificant for all comparisons).

Ban et al performed a cross-sectional study including 197 with AD, 42 with VD, and 47 healthy controls,¹⁹ reporting that Lp(a) values were similar between AD patients (20 ± 4 mg/dL) and the healthy control group (19 ± 1 mg/dL; $p =$ nonsignificant), whereas its concentration was substantially higher in patients with VD than in the other two groups (32 ± 4 mg/dL; $p < 0.001$ for both comparisons).

In another report, Gong et al described the case of a family with CADASIL and increased values of Lp(a).²⁰ Similar findings were then reported by Valenti et al,²¹ who also studied three families with CADASIL and reported that the affected members displayed extremely high concentration of Lp(a), comprised between 32 and 143 mg/dL.

More recently, Ray et al performed a cross-sectional study including 40 patients with AD, 40 with VD, and 40 age-matched healthy controls.²² Interestingly, although the concentration of Lp(a) was found to be virtually identical in patients with AD and in the control group (both ~ 25 mg/dL), Lp(a) levels were found to be nearly twice higher in patients with VD (~ 50 mg/dL) than in the other two cohorts ($p < 0.001$ for both comparisons).

The only prospective study on the relationship between Lp(a) and dementia was published by Kunutsor et al in 2016.²³ Briefly, the authors measured Lp(a) concentration at baseline in 2,532 men aged between 42 and 61 years, who were then followed up for a median period of 24.9 years. Overall, 228 incident cases of dementia were recorded. In age-adjusted analysis, Lp(a) was found to be inversely associated with the risk of incident dementia (hazard ratio: 0.68; 95% CI: 0.46–0.99).

Taken together, these findings would suggest that although the link between Lp(a), impaired cognitive performance, and AD remains elusive,²⁴ it cannot be discounted that in the vast majority of published studies, Lp(a) concentration was found to be higher in subjects with VD or CADASIL than in those with normal cognitive status (– **Table 1**). Therefore, this lipoprotein seems to play a certain role in the pathogenesis of VD and to be supported by at least four plausible biological mechanisms (i.e., enhanced atherogenesis, endothelial dysfunction, impaired fibrinolysis, and platelet hyperactivation) (– **Fig. 1**), which are also strongly involved in the pathogenesis of dementia, especially in that of the vascular form (i.e., VD).²⁵

Atherogenesis is indeed the most historically known pathological effect of Lp(a). Lp(a) contains a large amount of cholesterol and is known to amplify the atherogenic process in blood vessels through many different mechanisms (comprehensively reviewed elsewhere).²⁶ On the other hand, atherosclerosis is also commonplace in patients with AD and, especially, VD.²⁵

Endothelial dysfunction is a second putative mechanism possibly linking Lp(a) with (vascular) dementia. Reliable evidence has been published that an increased value of Lp(a) is strongly associated with endothelial dysfunction,

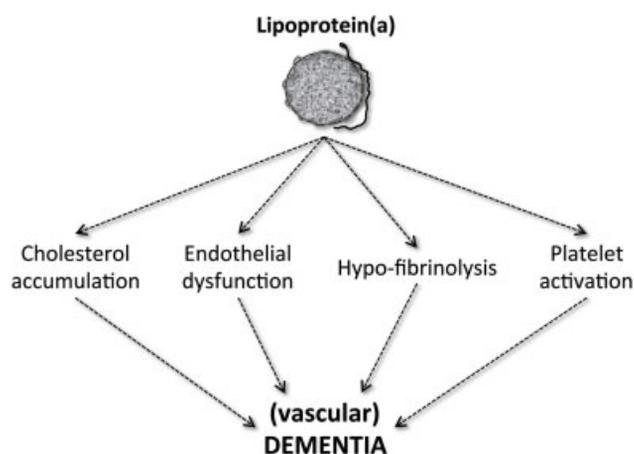
Table 1 Summary of epidemiological evidence on Lp(a) levels in patients with dementia

Authors	Study	Results
Urakami K et al, 1987 ⁵	Cross-sectional	Lp(a) higher in VD patients than in AD patients and healthy controls
Kuriyama et al, 1992 ⁶	Cross-sectional	Lp(a) higher in patients with AD and VD than in healthy controls
Caramelli et al, 1999 ⁷	Cross-sectional	Lp(a) similar in AD patients and healthy controls
Urakami et al, 2000 ⁸	Cross-sectional	Lp(a) higher in VD patients than in AD patients and healthy controls
Mooser et al, 2000 ⁹	Cross-sectional	Lp(a) associated with AD in carriers of apolipoprotein E $\epsilon 4$ allele but not in those without
Zuliani et al, 2001 ¹⁰	Cross-sectional	Lp(a) similar in patients with VD, AD, and healthy controls
Solfrizzi et al, 2002 ¹¹	Cross-sectional	High values of Lp(a) associated with an enhanced risk of AD
Emanuele et al, 2003 ¹²	Cross-sectional	Lp(a) similar in patients with frontotemporal dementia and healthy controls
Emanuele et al, 2004 ¹³	Cross-sectional	Lp(a) higher in VD patients than in AD patients and healthy controls
Emanuele et al, 2004 ¹⁴	Cross-sectional	Lp(a) similar in patients with AD and healthy controls
Iwamoto et al, 2004 ¹⁵	Cross-sectional	Lp(a) higher in VD patients than in AD patients and healthy controls
Watanabe et al, 2004 ¹⁶	Cross-sectional	Lp(a) higher in VD patients than in AD patients and healthy controls
Pantoni et al, 2004 ¹⁷	Case report	High Lp(a) value in a patient with CADASIL
Cankurtaran et al, 2005 ¹⁸	Case report	Lp(a) similar in patients with AD or VD and healthy controls
Ban et al, 2009 ¹⁹	Cross-sectional	Lp(a) higher in VD patients than in AD patients and healthy controls
Gong et al, 2010 ²⁰	Case report	High Lp(a) values in a family with CADASIL
Valenti et al, 2012 ²¹	Case report	High Lp(a) values in three families with CADASIL
Ray et al, 2013 ²²	Cross-sectional	Lp(a) higher in VD patients than in AD patients and healthy controls
Kunutsor et al, 2016 ²³	Perspective	Lp(a) inversely associated with the risk of incident dementia

Abbreviations: AD, Alzheimer's disease; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Lp(a), lipoprotein(a); VD, vascular dementia.

proliferation, and migration of smooth muscle cells,²⁷ which are also key events in the pathogenesis of both AD and VD.²⁸

Besides its well-established atherogenic properties, Lp(a) seems to play a role also in the pathogenesis of venous thrombosis.²⁹ This is probably attributable to its antifibrinolytic properties, because the high structural homology between apo(a) and plasminogen leads both proteins to compete for binding to fibrin and cell membrane.³⁰ Therefore, in patients with high Lp(a) values, plasminogen binding to its receptors is partially disrupted, and fibrinolysis would be finally impaired.

**Fig. 1** Potential links between lipoprotein(a) and cognitive decline.

Platelet hyperactivation is another important aspect in the pathogenesis of dementia and AD,³¹ whereas it has been demonstrated that both Lp(a) and apo(a) are capable to enhance platelet activation and aggregation.²⁷

While it seems therefore plausible to conclude that Lp(a) may be both epidemiologically and biologically associated with (vascular) dementia and that Lp(a) may effectively interplay with other well-known risk factors of dementia such as hyperhomocysteinemia or apolipoprotein E $\epsilon 4$ allele, reliable evidence has also been published that this lipoprotein may be actively participating in cognitive decline. Takechi et al showed apoB colocalization with amyloid β (A β) within dense neuritic amyloid plaque, which are hallmarks of dementia.³² Leung et al also performed a large study including 344 patients with AD and 325 cognitively normal subjects from whom cerebrospinal fluid (CSF) samples were collected and analyzed.³³ Overall, Lp(a) and A β_{1-42} levels in CSF were found to be significantly associated ($p = 0.012$).

In conclusion, several lines of evidence would lead us to conclude that the role of increased Lp(a) values should not be neglected in dementia, especially in those forms with predominantly vascular nature. This aspect is especially important considering that high values of Lp(a) are compatible with longevity,³⁴ thus potentially exposing many elderly people to an increased risk of developing some forms of cognitive impairment. Nevertheless, this correspondence is not meant as a criticism of the review and meta-analysis

prepared by de Mello Gomide Loures et al.¹ Why Lp(a) was not identified as a putative marker associated with (vascular) dementia most likely simply relates to their search limitations and their focus on “hemostatic factors.” Although Lp(a) shares some structural homology to plasminogen, a precursor of plasmin, and thus involved in fibrinolysis and linked to hemostasis, it is not really considered to be a hemostasis-related protein. Thus, the findings reported by de Mello Gomide Loures et al, focused on hemostasis, should not be considered as definitive in terms of vascular markers associated with dementia. Moreover, although it is unlikely that their report covers only the tip of an iceberg, it is likely that their report represents but a sampling of the potential involvement of hemostasis and vascular-associated proteins in conditions that present with considerable clinical adversity—namely, dementia and cognitive decline—and especially as related to any vascular contributors.

Conflicts of Interest

None.

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