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Argyrophilic Grain Disease: Demographics, Clinical, and Neuropathological Features From a Large Autopsy Study

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Abstract (words: 249)

Background: Argyrophilic grain disease (AGD) is a frequent late-onset, 4-repeat tauopathy in Caucasians with high educational attainment. Little is known about AGD in non-Caucasian and individuals with low educational attainment. Due to the lack of distinctive antemortem features, studies on AGD require using well-characterize clinicopathological series. Here, we describe AGD demographics, clinical and neuropathological features in a large multiethnic, population-based, postmortem sample of 983 subjects.

Methods: Participants dwelled in São Paulo, Brazil and were 50 years or older. Demographics and clinical data were collected through semi-structured interviews with an informant and included the Informant Questionnaire on Cognitive Decline in the Elderly, the Clinical Dementia Rating, and the Neuropsychiatric Inventory. Neuropathologic assessment included immunohistochemistry and relied on internationally accepted criteria.

Results: AGD was frequent (15.2%) and was the only neuropathological diagnosis in 8.9% of all cases (mean age 78.9 ± 9.4 years), although it rarely occurred as an isolated pathological finding. AGD was associated with older age, lower socioeconomic status (SES), and appetite disorders.

Conclusion: This is the first study to our knowledge that examines demographic, clinical and neuropathological aspects of AGD in different ethnicities and subjects from all socioeconomic strata. We hope that our findings will instigate other groups to explore AGD further in prospective clinicopathological studies. Changes in hormonal levels related to appetite control could also be explored as antemortem markers of AGD. Moreover, understanding the mechanisms behind the higher susceptibility to AGD in

subjects at the lowest SESs may disclose novel environmental risk factors for neurodegenerative diseases.

Key words: neurodegeneration, dementia, tauopathy, postmortem, neuropathology

1. Introduction

Argyrophilic grain disease (AGD) is an age-related 4-repeat tauopathy, first described as a novel neuropathological entity in 1987.(1, 2) AGD affects both genders equally and shows an age-related increase in prevalence varying from about 9.3% in 65 years old to 31.3% in centenarians.(3-7) These numbers make AGD the second most common neurodegenerative disease after Alzheimer's disease (AD) in subjects of European descent.(5, 8) AGD often overlaps with other neurodegenerative diseases, including AD, Pick's Disease, tangle-only dementia, progressive supranuclear palsy, corticobasal degeneration, Creutzfeldt-Jakob disease, Parkinson's disease, dementia with Lewy bodies, and TDP-43 proteinopathies.(3, 4, 9-13)

The high degree of overlapping between AD-type pathology and AGD lead to the speculation that AGD was rather a part of the AD spectrum. Only recently, studies showing distinct AGD characteristics such lack of acetylated tau settled AGD as an independent entity.(6, 14-21) AGD features three principal neuropathological hallmarks, all containing phospho-tau: 1) argyrophilic grains (AGs), 2) oligodendrocytic coiled bodies, and 3) neuronal intracytoplasmic pretangles. Associated changes include balloon neurons and phospho-tau positive bush-like astrocytes.(1, 9, 22-25) AGD remains a predominantly sporadic disease. Recently studies described two rare MAPT mutations (MAPT S305I and S305S) causing pathological features consistent with AGD in individuals with memory decline and behavioral changes.(26, 27) Furthermore, AGD is associated with DNA copy number variations at 17p13.2.(60)

An early study suggested an increased risk of AGD in individuals with apolipoprotein E (APOE) ε2 allele, but further studies failed to confirm this relationship.(28-30)

The lack of antemortem distinctive features makes AGD virtually unknown to clinicians.(9, 20) Clinicopathological studies suggest that AGD manifests mainly as very

slowly progressive amnestic mild cognitive impairment (MCI), similar to early AD stages.(31-33) In rare instances, AGD changes spread beyond their usual limbic localization and the disease presents as a behavioral-variant frontotemporal dementia.(33-35) Intriguingly, AGD has been found in up to 31% of cognitively normal individuals, leading to the speculation that AGD is rather a benign condition. (36-38) On the other hand, AGD subjects show neuropsychiatric symptoms including personality changes and emotional instability failure more frequently than age-matched controls, probably reflecting the prominent involvement of the limbic system.(3, 9, 39-43)

Despite being comprehensive, all these studies on AGD relied mostly on highly educated Caucasians. Little is known about AGD in other ethnicities, subjects with low school attainment, or low socioeconomic status. Here, we describe AGD demographics, clinical and neuropathological features in a large multiethnic, population-based, postmortem sample.

2. Methods

2.1. Participants

The participants belonged to the Brain Bank of the Brazilian Aging Brain Study Group (BBBABSG) from the University of São Paulo, Brazil. The BBBABSG receives brain donations from individuals who die in the metropolitan area of São Paulo (11 million inhabitants) and receive an autopsy in the São Paulo Autopsy Service.(44) From February 2004 to March 2014, 983 brain bank donors received a complete clinicopathological workup and were included in this study. This study was approved by the University of Sao Paulo ethical committee and written informed consent for brain donation and provision of clinical information was obtained from the next-of-kin.(45)

2.2. Clinical evaluation

Trained gerontologists obtained clinicofunctinoal data from a knowledgeable informant who had, at least, weekly contact with the subject over the six months preceding death, using a semi-structured interview.(45) This interview included information about demographics, cardiovascular risk factors, socioeconomic status (SES) and validated questionnaires covering multiple cognitive domains. SES was categorized using a validated Brazilian scale that grouped subjects into five categories (A to E).(46) SES categories were then grouped as high (A/B), middle (C), and low D/E). The Clinical Dementia Rating scale (CDR; informant section only) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) determined participant's cognitive function before death.(47, 48) Behavioral and psychological symptoms of dementia were assessed using the Neuropsychiatric Inventory (NPI).(49) We analyzed the NPI both as a total score and as individual scores for each item (delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time disturbances, and appetite and eating abnormalities).

2.3. Apolipoprotein E (APOE) genotyping

Genomic DNA was extracted from blood samples in a subset of the cases. APOE genotyping was performed using real-time polymerase chain reaction assay, as described by Calero et al.(50)

2.4. Neuropathological assessment

Brain procurement was performed within 20 hours of death. One hemisphere was fixed in 4% buffered paraformaldehyde and the other hemisphere was coronally sectioned and snapped frozen. Samples from the fixed hemisphere were embedded in paraffin

representing the following areas: middle frontal gyrus, middle and superior temporal gyri, angular gyrus, superior anterior cingulate gyrus, visual cortex, hippocampal formation at the level of lateral geniculate body, amygdala, basal ganglia at the level of the anterior commissure, thalamus, midbrain, pons, medulla oblongata, and cerebellum. All areas were stained with hematoxylin and eosin (H & E) and selected sections were immunostained with antibodies against β-amyloid (4G8, 1:10.000; Signet Pathology Systems, Dedham, MA), phosphorylated tau (PHF-1, 1:2.000; gift from Peter Davies, NY), transactivation response DNA-binding protein of 43 kDa (TDP-43; 1:500, Proteintech, Chicago, IL), and α-synuclein (EQV-1, 1:10.000; gift from Kenji Ueda, Tokyo, Japan), as previously described.(44) Internationally accepted neuropathological criteria and guidelines were used for diagnosing and staging.(51-53)

AD-type pathology was scored using the Braak and Braak staging system, the Consortium to Establish a Registry for AD (CERAD) criteria and the Thal et al. phase system for β-amyloid plaques.(54) A neuropathological diagnosis of AD was granted to individuals showing, at least, intermediate ADNC.(51) Diagnosis of AGD required the presence of abundant phosphorylated tau-positive grains in the CA1 sector of the hippocampus, pre-tangles-especially in the hippocampal CA2 sector, and oligodendrocytes with coiled bodies in the hippocampal/temporal white matter; regardless of the presence of other neurodegenerative disease-related lesions.(9, 55-57)

Cerebrovascular lesions were analyzed on gross examination and using H & E stained histological slides in all of the sampled areas. The presence of small vessel disease (SVD), lacunae, and large infarcts was registered by topography, size, and number. SVD diagnosis required widespread and at least moderately severe microvascular changes in three cortical regions. A diagnosis of vascular dementia (VaD) was made in subjects with either one large (> 1 cm) chronic infarct or three lacunae, which could be in any of the

following strategic areas (thalamus, fronto-cingular cortex, basal forebrain and caudate, medial temporal area, or angular gyrus).(58)

2.5. Statistical Analysis

First, we divided the cases into two groups according to the presence of AGD (AGD and non-AGD). Table 1 depicts sociodemographics, clinicofunctional and neuropathological variables, and APOE genotype for these two groups. Subsequently, we divided the AGD group in "pure" and mixed (AGD plus another neurodegenerative disease or AGD plus vascular dementia). Table 2 depicts sociodemographics, clinicofunctional and neuropathological variables, and APOE genotype for these two subgroups. Finally, we compared pure-AGD to pure-AD subjects.

For the analysis, we dichotomized some of the variables. Subjects with a CDR=0 (47) were rated as cognitively normal, whereas a CDR > 0 granted a label of cognitive impairment. As the NPI curves were skewed to 0 because of the large number of controls in this series, NPI score was considered positive if ≥ 1. APOE allele frequencies were counted considering the number of times that each allele was present in each individual. Out of the neuropathological variables, cases were grouped as Braak AD stages 0-II and III-VI. For the CERAD score, cases were grouped into absent/sparse or moderate/frequent groups.

Chi-square or Fisher's exact tests were used to analyze categorical variables, and unpaired t-tests were used for continuous ones. Variables that were associated with AGD in univariate analyses (age, sex, education attainment, and SES) were included in a multiple logistic regression model to investigate their independent association with AGD. The level of statistical significance was set at 5%. The statistical analyses were performed using SAS 9.3 (Cary, NC, USA).

3. Results

In the 983 participants, the mean age at death was 74.0 ± 11.7 years; 52% were female, the mean education was 4.2 ± 3.7 years, and 30% were cognitively impaired (CDR > 0).

3.1. AGD vs. non-AGD

AGD was identified in 15.2% of the sample; it was the third most common neuropathological diagnosis after AD (23%) and VaD (16%). The prevalence of AGD, with or without concomitant neurodegenerative disease, increased considerably with older age (Figure 1). Only three subjects were younger than 60 years. Participants with AGD were significantly older, more likely to be female, had fewer years of education, and lower SES (Table 1). However, after including age, sex, education, and SES in a multiple logistic regression, AGD was only associated with age (OR=1.05; 95% CI=1.03-1.07; p<0.0001) and SES (OR=1.80; 95% CI=1.39-2.32; p<0.0001). Finally, there was no difference in race, cognitive status or frequency of cerebrovascular risk factors between non-AGD and AGD groups. APOE genotype was available for 368 participants (Table 1). No association between AGD and APOE genotyping was found. In non-AGD group, subjects with an APOE ε4 showed a higher burden of AD-type hallmarks (neurofibrillary tangles and neuritic plaques) and cerebral amyloid angiopathy (Supplementary Table 1).

Some degree of behavioral and psychological symptoms (NPI≥ 1) was observed in 70% of AGD subjects (Table 1). Appetite changes were more frequent in the AGD group. Among the 62 AGD subjects with appetite changes according to the NPI, the severity of the symptom was moderate to severe in 79%. Hallucinations tended to be more frequent in the non-AGD group, but the results did not reach statistical significance.

Concerning neuropathological parameters, the AGD group had a higher proportion of subjects with moderate to high Braak stages. The neuritic plaques burden, presence of lacunar infarcts, arteriolosclerosis, and Lewy-type pathology were similar between AGD and non-AGD groups (Table 1). Hippocampal sclerosis was present in only a few cases (3% of the series) and was not included in this analysis. In 5% (8/152) of participants in the AGD group, no other neuropathologic changes were identified, including a total absence of neurofibrillary tangles (Braak 0) and senile plaques. Four of these eight participants showed cognitive impairment: two with a CDR = 0.5, one with CDR = 1, and one with CDR = 3.

3.2. Pure-AGD versus mixed-AGD

Out of the 65 subjects with mixed-AGD, over half (34) also had AD. VaD was found in 16 subjects and Lewy body disease in 12. Mixed-AGD subjects were significantly older ($p< 0.001$) (Figure 1). There was no difference in sex, race, years of schooling, SES, frequencies of cerebrovascular risk factors, and APOE genotyping between pure- and mixed-AGD (Table 2).

There was a higher rate of cognitively normal subjects in pure-AGD (75%) compared to the mixed group (37%). In fact, dementia (CDR $\geq$1) was found in only 10% of pure AGD compared to almost 48% in mixed-AGD ($p<0.001$).

Behavioral and psychological symptoms were frequently observed independently of the presence of a concomitant neurodegenerative disease (Table 2) or cognitive impairment (Supplementary Figure 1). Behavioral and psychological symptoms were found in 55% of pure-AGD subjects without cognitive impairment (CDR =0) and 63% of AGD with only mild neurofibrillary pathology (Braak stage I-II). Delusions, hallucinations, and aberrant motor activities were more frequent in the mixed-AGD group (Supplemental

Figure 1). We failed to find differences in appetite/eating changes between pure- and mixed AGD.

By definition, pure-AGD was more likely to have a low burden of neurofibrillary pathology (57%) than mixed-AGD (20%) ($p< 0.001$).

3.3. Pure-AGD X Pure-AD (Supplementary Table 2)

As predicted, pure-AGD subjects were younger, had a lower proportion of APOE ε4 allele, and better functional scores (according to the IQCODE and CDR) than pure-AD subjects. Surprisingly, pure-AGD subjects belonged to a lower SES. Regarding behavioral and psychological symptoms, pure-AGD subjects were less prone to show delusions, hallucinations, agitation, disinhibition, irritability and aberrant motor activity. The frequency of appetite disorders was similar in pure-AGD and pure-AD subjects.

4. Discussion

In this study, we analyzed 983 subjects from a multi-ethnic population-based clinicopathological series to investigate possible distinctive demographics and clinical aspects associated with AGD. As novel findings, we identified that AGD is associated with a lower SES and equally affects Caucasians, Africans and Asians. We also found a correlation between AGD and appetite disorders measured by the NPI.

This study corroborates findings from other series of unselected subjects. AGD prevalence is high, second only to AD among the neurodegenerative diseases. AGD is associated with older age and affects both genders equally.(3, 9, 33, 57) In fact, since advanced age is also a risk factor for other neurodegenerative diseases, it is not a surprise that the average age in the mixed-AGD group was higher than in the pure-AGD group.

The prevalence of AGD in the current series (15.2%) is slightly higher than in other studies (3, 4, 9, 33, 40, 57) except Josephs et al. that identified AGD in 16% of 359 autopsy cases from a dementia clinic (age range 74-101).(20) Tolnay et al. found AGD in 9% of 301 consecutive autopsies of individuals over 65 years old (age range 67-100) from a hospital series.(38) Braak and Braak, using silver staining, a method less sensitive than immunohistochemistry, found an AGD prevalence of 5% among 2,261 non-selected autopsies (age range 25-96) from a general hospital.(3) Saito et al. reported AGD in 4% of 1,241 serial autopsy cases (age range 48-104) from a geriatric hospital. (57) Martinez-Lange et al. observed that the prevalence of AGD was 6% in 300 unselected consecutive autopsies of patients older than 30 years (no age range provided), but 12% in those older than 65 years, reaching 31% in centenarians.(4) It is plausible that improvements on immunohistochemistry may partially explain our and Josephs et al. higher AGD frequencies, since our studies are the most recent ones. Nevertheless, demographics differences among the series may also have contributed to the differences. Although not explicitly described, it is possible to infer than other series on AGD were enriched for individuals belonging to high SES, as oppose to the current series that included a broad range of SESs and 1/3 of the subjects in the lower SESs. In fact, the strong association between low SES and AGD even after multivariate analyses were surprising. As the cross-sectional nature of our series precludes investigating the causes of this association, further studies using longitudinal clinicopathological series including subjects belonging to different SESs may confirm if a low SES is a risk factor to AGD and by which mechanisms. Most importantly, longitudinal series may have information about the subject's SES during chilhood and early adulthood when enviromental factors as nutrition, exposure to toxins, and quality of health care may have an higher impact on the

risk of developing neurodegenerative conditions in late life.(59-62). Unfortunately, our questionnaires were not designed to capture SES status at different life stages.

We failed to find an association between AGD and a specific APOE allele, in line with most of the previous studies.(29, 30, 63) It is possible to speculate that our results could be related to particular features of the Brazilian population. As we identified a similar distribution of APOE alleles in our non-AGD group and series from the EUA and Europe (Supplementary Table 1), we hypothesize that the lack of association between a particular APOE allele and AGD is independent of the multiethnic composition of our sample.

The lack of distinctive antemortem clinical features of AGD and the extensive overlap between AGD and other dementing conditions represent considerable challenges to the understanding of AGD's impact on cognitive decline.(19, 20, 64, 65) We detected a total absence of other neuropathological changes in only 8 AGD cases (5%). Half of those had some degree of cognitive decline. Martinez-Lange and Munoz observed intellectual deterioration in 18% (n=11) and Tolnay et al. reported dementia in 54% of 35 clinically well-documented AGD cases.(4, 38) However, it is unclear which percentage of these cases had no overlapping neuropathological changes. It is possible that neurofibrillary pathology/ β-amyloid pathology under the threshold for AD could have had a role in the cognitive decline.(30) Overlapping between AGD and low levels of AD-type pathology is common. In our series, 41% of the AGD cases showed a scarce amount of neurofibrillary tangles (Braak I-II) and 71% had low burden of β-amyloid pathology.

Previous studies suggested that AGD could be benign or even protective against cognitive decline.(17) In fact, 59% of the participants with AGD pathology in the present study were cognitively normal, in line with several previous studies that have also identified a high prevalence of AGD pathology in controls. Davis et al. found AGD in 23% of a total sample of 59 older cognitively normal subjects.(36) In addition, Knopman et al. found 12

AGD cases in a sample of 39 older cognitively normal individuals.(37) Unfortunately, the cross-sectional and retrospectively nature of our study precludes identifying subtle cognitive differences between subjects with or without AGD or to capture a possible slowdown in cognitive decline rate associated to AGD.

Several studies pointed to a correlation between AGD and behavioral and psychological symptoms. Braak and Braak described that personality changes tend to precede memory failure distinguish in AGD from AD patients.(3) In our series, behavioral and psychological symptoms were found in 55% of pure AGD subjects without cognitive impairment and 63% of AGD with mild neurofibrillary pathology (Braak stage I-II). Curiously, appetite and eating disorders were the most frequent neuropsychiatric change identified in AGD. Unfortunately, the NPI does not provide specific information on the type of appetite change detected and the neuroanatomical substrate for these changes in appetite remains unclear. It is possible to infer that the appetite changes reflect changes in the hypothalamus, a region vulnerable to AGD.(9, 66) A previous human postmortem investigation identified an early and prominent involvement of the hypothalamic lateral tuberal nucleus and moderate involvement of the ventromedial nucleus (associated to satiety) with relative resistance of tuberomamillary nucleus, the latter susceptible to AD.(66) Moreover, the hypothalamus connects to the hippocampal CA2 sector in mice, including the paraventricular nucleus that participates in appetite regulation.(67-69) CA2 is extremely vulnerable to AGD pathology, although it is resistant to other tauopathies, including AD.(56) We failed to identify differences in appetite disorders between pure-AGD and pure-AD groups. We believe that this result does not invalidate our findings because the pure-AD group has much worse cognitive status and a higher frequency of other behaviors and neuropsychiatric changes that may impact the appetite.

This study was limited by the lack of complete medical history data and its cross-sectional, retrospective design. The frequency of AGD pathology in subjects with severe AD-type pathology could be underestimated in our sample as a specific antibody for AGD is yet to be developed. Despite these limitations, this study has considerable strengths. This is the first study, to our knowledge, that examines demographic, clinical and neuropathological aspects of AGD in different ethnicities and subjects from all socioeconomic strata.

Despite growing research interest in AGD, its pathophysiological mechanisms and clinical impact remain poorly understood. We hope that this manuscript will instigate other groups to further explore our findings. Prospective clinicopathological studies are needed to investigate the neuronal basis of appetite changes in AGD and investigate if other functions associated with the hypothalamus including sleep and circadian rhythm are part of the AGD clinical phenotype. Hormonal changes reflecting hypothalamic lesions such as leptin and ghrelin could also be explored as antemortem markers of AGD. Moreover, understanding the mechanisms behind the higher susceptibility to AGD in subjects in the lower SESs may disclose novel environmental risks factors for neurodegenerative diseases.

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Figure legends

Figure 1. Frequency of AGD cases in different age groups in pure-AGD and mixed-AGD subjects.

Supplementary Figure 1. Frequency of behavioral and psychological symptoms in AGD subjects, according the presence of cognitive impairment (%).

Table 1. Characteristics of the sample by AGD status (n=983)

Variables	Non-AGD (n=831)	AGD (n=152)	*p*
Sociodemographic features			
- Age, mean (SD)	73.1 (11.9)	78.9 (9.4)	***<0.001****
- Female, n (%)	417 (50.2)	93 (61.2)	***0.01***[¥]
- Race			0.44[¥]
White	575 (69.3)	108 (71.1)	
Black	88 (10.6)	19 (12.5)	
Brown	153 (18.4)	21 (13.8)	
Asian	14 (1.7)	4 (2.6)	
- Years of schooling, mean (SD)	4.3 (3.8)	3.6 (3.3)	***0.02****
- SES, n (%)			
High	214 (25.9)	27 (17.9)	***<0.001***[¥]
Middle	348 (42.1)	45 (29.8)	
Low	264 (32.0)	79 (52.3)	
APOE, n (%)			
- ε2	38 (12.3)	4 (7.0)	
- ε3	177 (56.7)	39(67.2)	0.27[¥]
- ε4	97 (31.1)	15 (25.9)	
Cardiovascular risk factors, n (%)			
- Diabetes mellitus	229 (28.2)	43 (28.9)	0.87[¥]
- Hypertension	521 (64.2)	102 (68.5)	0.31[¥]
- Dyslipidemia	75 (9.2)	15 (10.1)	0.75[¥]
- Smoking	219 (27.0)	33 (22.1)	0.44[¥]
- Alcohol use	138 (17.0)	19 (13.0)	0.48[¥]
- Stroke	123 (17.2)	16 (14.5)	0.48[¥]
Cognitive, behavioral/psychological, and functional evaluations			
- IQCODE, mean (SD)	3.4 (0.7)	3.4 (0.6)	0.63*
- CDR sum of boxes, mean (SD)	4 (6.4)	4 (6.2)	0.90*
- CDR			0.90[¥]
No impairment, n (%)	487 (58.6)	89 (58.6)	
Impairment, n (%)	344 (41.4)	63 (41.4)	
- NPI, n (%)	536 (64.7)	106 (69.7)	0.22[¥]
- NPI symptoms			
Delusions,n (%)	85 (10.3)	11 (7.2)	0.24[¥]
Hallucinations, n (%)	125 (15.1)	14 (9.2)	0.056[¥]
Depression, n (%)	199 (24.0)	25.7 (39.0)	0.66[¥]
Anxiety, n (%)	198 (23.9)	38 (25.2)	0.73[¥]
Agitation/aggression, n (%)	176 (21.3)	24 (15.8)	0.12[¥]
Euphoria, n (%)	29 (3.5)	3 (2.0)	0.24[£]
Disinhibition, n (%)	70 (8.4)	9 (5.9)	0.29[¥]
Irritability/lability, n (%)	143 (17.2)	21 (13.8)	0.29[¥]
Apathy, n (%)	166 (20.0)	26 (17.1)	0.40[¥]
Aberrant motor activity, n (%)	72 (8.7)	13 (8.6)	0.95[¥]
Nighttime behaviors, n (%)	193 (23.3)	36 (23.7)	0.92[¥]
Appetite/eating changes, n (%)	249 (30.0)	62 (40.8)	***0.009***[¥]
Neuropathological lesions			
- Braak, n (%)			***<0.001***[£]
0-II	568 (68.8)	60 (41.4)	
III-VI	258 (31.2)	85 (58.6)	
- CERAD, n (%)			0.22[¥]
none/sparse	630 (75.9)	108 (71.1)	
moderate/frequent	200 (24.1)	44 (28.9)	
- Lacunar infarct, n (%)	100 (12.2)	18 (11.9)	0.93[¥]
- Hyaline arteriolosclerosis, n (%)	131 (15.8)	17 (11.3)	0.15[¥]
- Lewy-type pathology, n (%)	83 (10.2)	17 (11.3)	0.70[¥]

[£] Fisher´s Exact Test; [¥] Pearson Chi-Square; ***** Student *t* Test

Table 2. Characteristics of the AGD sample according the presence of concomitant neuropathological diagnosis (n=152)

Variables	AGD pure (n=87)	AGD mixed (n=65)	*p*
Sociodemographic features			
- Age, mean (SD)	76.5 (9.8)	82.1 (7.8)	***<0.001****
- Female, n (%)	50 (57.0)	43 (66.2)	0.27¥
- Race			
White	58 (66.7)	50 (76.9)	0.23¥
Black	10 (11.5)	9 (13.8)	
Brown	16 (18.4)	5 (7.7)	
Asian	3 (3.4)	1 (1.5)	
- Years of schooling, mean (SD)	3.9 (3.6)	3,17 (2.8)	0.13*
- SES, n (%)			
High	12 (14.0)	15 (23.1)	0.35¥
Middle	27 (31.4)	18 (27.7)	
Low	47 (54.7)	32 (49.2)	
APOE, n (%)			0.46£
- ε2	3 (11.5)	1 (3.2)	
- ε3	16 (61.5)	23 (71.9)	
- ε4	7 (26.9)	8 (25.0)	
Cardiovascular risk factors, n (%)			
- Diabetes mellitus	14 (22.2)	29 (33.7)	0.12¥
- Hypertension	59 (68.6)	43 (68.3)	0.96¥
- Dyslipidemia	5 (7.9)	10 (11.6)	0.45¥
- Smoking	22 (25.6)	11(17.5)	0.37¥
- Alcohol use	11 (13.3)	8 (12.7)	0.42¥
- Stroke	7 (14.9)	9 (14.3)	0.92¥
Cognitive, behavioral/psychological, and functional evaluations			
- IQCODE, mean (SD)	3.2 (0.4)	3.67 (0.7)	***<0.001****
- CDR sum of boxes, mean (SD)	2.1 (4.7)	6.4 (7.1)	***<0.001****
- CDR			
No impairment, n (%)	65 (74.7)	24 (36.9)	***<0.001***¥
Impairment, n (%)	22 (25.3)	41 (63.1)	
- NPI, n (%)	55 (63.2)	51 (78.5)	***0.04***¥
- NPI symptoms			
Delusions,n (%)	3 (3.4)	8 (12.3)	***0.04***£
Hallucinations, n (%)	4 (4.6)	10 (15.4)	***0.02***£
Depression, n (%)	21(24.1)	18 (27.7)	0.62¥
Anxiety, n (%)	20 (23.0)	18 (28.1)	0.47¥
Agitation/aggression, n (%)	13 (14.9)	11 (16.9)	0.74¥
Euphoria, n (%)	2 (2.3)	1 (1.6)	0.61£
Disinhibition, n (%)	3 (3.4)	6 (9.2)	0.12£
Irritability/lability, n (%)	13 (14.9)	8 (12.3)	0.64¥
Apathy, n (%)	12 (13.8)	14 (21.5)	0.21¥
Aberrant motor activity, n (%)	4 (4.6)	9 (13.8)	***0.04***£
Nighttime behaviors, n (%)	20 (23.0)	16 (24.6)	0.81¥
Appetite/eating changes, n (%)	34 (39.1)	28 (43.1)	0.62¥
Neuropathological lesions			
- Braak, n (%)			***<0.001***¥
0-II	47 (57.3)	13 (20.6)	
III-VI	35 (42.7)	50 (79.4)	
- CERAD, n (%)			***<0.001***£
none/sparse	85 (97.7)	23 (35.4)	
moderate/frequente	2 (2.3)	42 (64.6)	
Lacunar infarct, n (%)	3 (3.4)	16 (25.0)	***<0.001***£
Hyaline arteriolosclerosis, n (%)	6 (6.9)	11 (17.2)	***0.05***¥
Lewy-type pathology, n (%)	1 (1.1)	16 (25.0)	***<0.001***£

£ Fisher´s Exact Test; ¥ Pearson Chi-Square; * Student *t* Test

Figure 1

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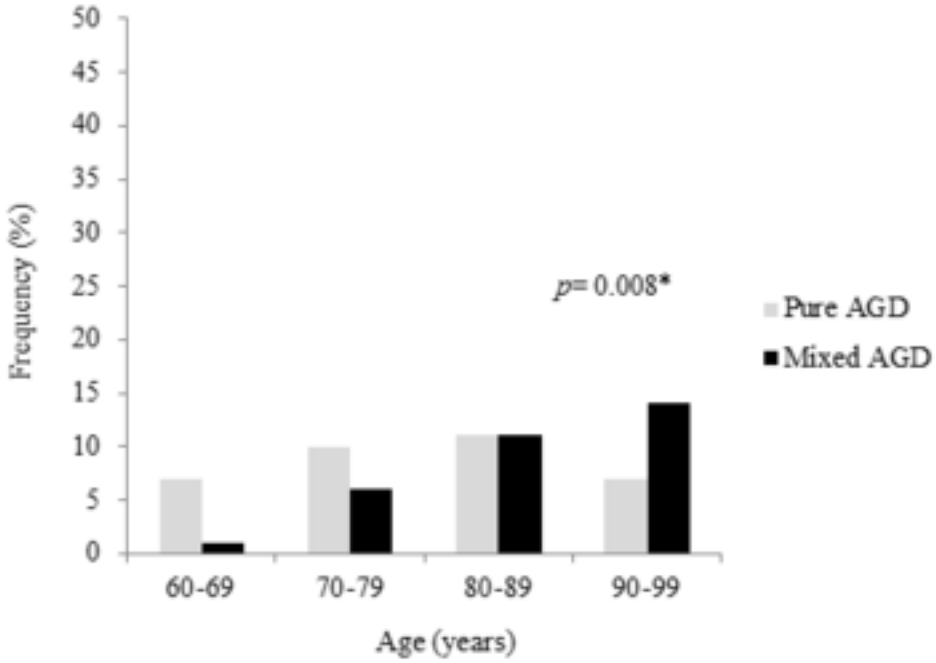

Supplementary Figure 1