Published in final edited form as:

Alzheimer Dis Assoc Disord. 2009 ; 23(3): 229–233. doi:10.1097/WAD.0b013e318199d833.

Correlation of Clinical Features with Argyrophilic Grains at Autopsy

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Abstract

Argyrophilic grains (AGs) are a pathologic feature found in association with neurodegenerative disease. Some have suggested that these features may occur as a distinctive condition. We reviewed 80 subjects from our tissue bank with pathologically confirmed AGs and identified their clinical features. We compared these subjects' features to the features of subjects with matched clinical diagnoses but without AGs. Subjects with AGs represented 21.7% of the entire autopsy sample from 1999 through 2005 (80/367). Of AD subjects, 43 /233 had AGs (18.4% of AD subjects); 11 /42 PD-D subjects had AGs (26.1% of PDD subjects); 2 / 9 DLB subjects had AGs (22.2% of DLB subjects); 4 /15 MCI subjects had AGs (26.7% of MCI subjects); and 20 /68 cognitively normal subjects had AGs (29.4% of NC). Subjects with AGs tended to be older but only significantly so in AD. Many co-morbid non-neurological health conditions were seen in cases of AGs without any single predilection emerging. AGs occur in approximately 22% of the entire autopsy cohort and likely are associated with advanced age. No distinctive antemortem clinical features were overrepresented in the AG cases. AGs can occur with or without neurodegenerative conditions and can occur in the absence of significant cognitive decline. AGs are not clearly associated with any single co-morbid health condition.

Keywords

Argyrophilic grains; dementia; neurodegeneration; neuropathology

Introduction

Argyrophilic grains (AG's) are a pathological feature seen in many elderly persons at autopsy. Argyrophilic grains are identified using silver stains or tau immunohistochemical stains and are most frequently located in mesiotemporal and limbic brain regions. Morphologically, they are spindle or comma- shaped neuropil elements and consist of ubiquitinated and abnormally phosphorylated tau protein.¹⁻³

What is not clear is whether AG's constitute a independent disease entity (it has been suggested that the terms argyrophilic grain disease or Braak's disease be used) or are an incidental finding. AGs have been reported with a variety of neurodegenerative diseases. Here we report the clinical features and conditions seen in subjects with pathologically confirmed AGs.

Methods

Subjects

This study took place at Sun Health Research Institute (SHRI) Brain Donation Program (SHRI-BDP), a longitudinal clinicopathologic study of aging and neurodegenerative disease⁴.

The Brain Donation Program is approved by the Sun Health Corporation Institutional Review Board and written informed consent for entry into the Brain Donation Program was obtained from all subjects and/or from the legal representatives of subjects with dementia. All Brain Donation Program subjects coming to autopsy between January 1, 1999 and December 31, 2005 and receiving selected clinicopathologic diagnoses were included in the study. The neuropathologic diagnoses included were 1) neuropathologically and clinically within normal limits for age 2) Mild cognitive impairment with neuropathology within normal limits for age 3) Alzheimer's disease 4) Parkinson's disease with dementia 5) dementia with Lewy bodies.

Clinical Assessments

Clinical data available for the subjects in this study were derived from review of the private medical records as well as from standardized assessments that are routinely conducted annually as part of the Brain Donation Program (insert our reference here again). Data gathered included medical history, family history, physical and neurological examination, movement testing, Unified Parkinson Disease Rating Scale (UPDRS)⁵, functional staging, and neuropsychological testing. The private medical records consisted of at least 4 years of private medical records from the subjects' primary care physicians and, for those under a neurologist's care, their neurologists. Some subjects did not receive a standardized neuropsychologic assessment, largely because they died before a clinical assessment could be scheduled. Information obtained from the private medical records included the neurological diagnosis, presence or absence of dementia, Mini Mental State Examination scores⁶ and results of private neuropsychologic assessments. All data were tabulated in a database.

Parkinson's Disease with Dementia was clinically diagnosed according to the UK brain bank criteria for Parkinson's Disease, i.e. the presence of two of three cardinal features (rest tremor, bradykinesia, rigidity) without atypical features (e.g. early falls, early dementia, gaze palsy, etc) or obvious secondary cause (e.g. arthritis, strokes, drugs, hydrocephalus, etc).⁷⁻⁸ DSM-IV criteria for dementia in Parkinson's disease were used: abnormalities in memory and one other domain of cognition, functional decline related to cognitive deficit(s), and preservation of consciousness⁹.

AD was diagnosed using National Institute of Neurological Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for a clinical diagnosis of probable or possible AD¹⁰ as well as NIA-Reagan¹¹ postmortem criteria for intermediate or high probability of AD and also classified by the Consortium to Establish a Registry for Alzheimer Disease (CERAD)¹² postmortem criteria.

Dementia with Lewy bodies was diagnosed according to criteria established by the Dementia with Lewy Bodies Consortium¹³⁻¹⁴ The distinction between PDD and dementia with Lewy bodies (DLB) was made clinically, on the basis of relative time of appearance of motor and cognitive signs.¹³⁻¹⁴

The MCI subjects included in this study were diagnosed clinically using Petersen criteria¹⁵⁻¹⁶. All had subjective complaints of memory loss, objective impairment in memory and were without significant functional decline. All were categorized as single or multi-domain amnesic MCI.

Normal control subjects were defined as having no demonstrable cognitively based limitations of activities of daily living including, when applicable, employment. Rigorous criteria were used to exclude anyone with any type of symptomatic or severe brain-related neurologic or psychiatric illnesses. This was done by prospective interview of the participant and careful scrutiny of the medical records. Examples of excluded conditions included mental retardation, epilepsy, cerebral infarction or hemorrhage, multiple sclerosis, brain tumor, schizophrenia, traumatic brain injury, and substance abuse.

Neuropathologic Procedures

All subjects received a standardized neuropathologic examination after death. Both paraffin-embedded blocks and large fixed frozen blocks were utilized as previously described⁴. Briefly, paraffin-embedded sections were stained with H & E as well as an immunohistochemical method for α -synuclein. Large fixed frozen blocks (3 × 4 cm, 40 μ m) were stained with H & E, Campbell-Switzer, Gallyas¹⁷, Thioflavine S to demonstrate cerebral white matter rarefaction, senile plaques and neurofibrillary tangles. Argyrophylic grains (AGs) were detected with the Gallyas silver method for all cases, with selected cases also identified by immunohistochemistry for phosphorylated tau protein with the AT8 antibody.

Grains were graded for severity, in the amygdala, entorhinal/transentorhinal areas and hippocampal CA1 field, as sparse, moderate and frequent by analogy with the CERAD grading diagrams for neuritic plaques and neurofibrillary tangles¹². Additionally, the presence or absence of glial tauopathy was recorded. Glial tauopathy was defined as Gallyas and/or AT8-positive cellular elements with glial morphology, including but not limited to tufted astrocytes, thorned astrocytes and coiled bodies.

Neuropathologic Diagnostic Criteria

Universally agreed-upon clinicopathologic criteria for the diagnosis of PD do not exist.⁷⁻⁸ The CERAD consensus diagnostic criteria for AD¹² contain suggested criteria for PD, which stipulate the diagnosis is made if there is a clinical diagnosis of parkinsonism (at least 2 of the 3 cardinal signs of bradykinesia, rigidity and tremor) as well as Lewy bodies and pigmented neuron loss in the substantia nigra. Additionally, we followed the consensus criteria for dementia with Lewy bodies (DLB)¹³⁻¹⁴ that give specific instructions on how DLB should be differentiated from PD with dementia.

Cases with dementia were rated according to NIA-Reagan criteria, which assign a probability estimate ("high", "intermediate" or "low"), based on the abundance of plaques and tangles, of the likelihood that dementia is due to AD¹⁸⁻¹⁹. All cases were also classified according to CERAD criteria for the diagnosis of AD¹², and all cases were assigned a Braak stage.¹⁷ When cases met neuropathologic diagnostic criteria for both PD and AD, both diagnoses were assigned. For this report, cases of PD with AD were combined with those cases that were PD and dementia but without AD.

Statistical Analysis

The data were analyzed for significant differences between groups using t-tests, Fisher's exact tests and analysis of variance with posthoc paired significance testing.

Results

Grains were always located in the mesiotemporal lobe, including the entorhinal and transentorhinal areas, hippocampal CA1 field and the amygdala (Figure 1a). Occasionally AGs were also seen in the inferomesial temporal neocortex, especially the fusiform gyrus, and also in the hypothalamus, insula and cingulate gyrus. Rarely the frontal lobe also contained AGs. Typically, grains were rice-grain, spindle or comma-shaped (Figure 1b) but in the CA1 field of the hippocampus they more often appeared as short, fine threads (Figure 1c). Dot-like neuropil elements were often seen in association with AGs but when present without the classic AG types these were not diagnosed as AGs. Gallyas-positive and/or tau-immunoreactive glia, corresponding to forms known as tufted astrocytes, thorned astrocyte, coiled bodies and intermediate morphologies (Figures 1d-f) were often present in a similar distribution to grains, and frequently were also present in the putamen and globus pallidus.

The sample included 80 subjects with argyrophilic grains at autopsy. Specifically, there were 43 subjects with AD, 11 with PDD, 2 with DLB, 4 with MCI and 20 that were cognitively normal and without parkinsonism. They were compared to subjects matched by disease category. The data are summarized in Table 1.

All subjects had advanced ages with no significant differences for age between the groups except AD subjects with AGs were significantly older than AD subjects without AGs. There were no differences in education and there was no gender predilection for subjects with AGs. The MMSE was significantly lower in the AD, DLB and PDD groups.

Table 1 also shows selected co-morbid health conditions. The fraction of subjects having each health condition differed across diagnostic categories. There were no differences among the groups in terms of the prevalences of these health conditions except NC subjects with AGs had significantly more CAD than NC subjects without AGs and AD subjects with AGs had significantly more cancer than AD subjects without AGs.

Subjects with AGs represented 23.6% of the entire autopsy sample at SHRI from 1999 through 2005 (98/415). Of AD subjects, 43 of 233 had AGs (18.4% of AD subjects); 11 of 42 PD-D subjects had AGs (26.1% of PDD subjects); 2 of 9 DLB subjects had AGs (22.2% of DLB subjects); 4 of 15 MCI subjects had AGs (26.7% of MCI subjects); and 20 of 68 cognitively normal subjects had AGs (29.4% of NC). The prevalence and severity of AGs did not differ significantly between groups (Table 2). A glial tauopathy accompanied AGs in 30 of 50 cases for which this was assessed.

The prevalence and severity of AGs were greater in subjects that were rated as Braak stages III and IV, in terms of classic neurofibrillary pathology (Table 3). Sixty-four percent of subjects with AGs were Braak stage III and IV while only 36 percent were Braak stages I, II, V or VI. Braak stage IV cases had the most severe AG score, followed by Braak stages III, V, I, II and VI.

Discussion

This study of cases with pathologically confirmed argyrophilic grains revealed several findings. First, AGs are relatively common in mentally normal subjects of advanced age. Second, no distinctive antemortem clinical findings were overrepresented in the AG cases, although an exhaustive study of the neuropsychological and behavioral data was not performed. Third, AGs occur with a number of different neurodegenerative conditions at about the same prevalence and severity as in normal aging individuals. Fourth, an accompanying glial tauopathy is common in subjects with AGs, being present in about 54% of all cases with AGs. Finally, AGs are not clearly associated with any non-neurological co-morbid health conditions.

Argyrophilic grains have been found in several degenerative brain conditions as well as in elderly individuals without specific neurological diagnoses. Others report argyrophilic grains in Pick's disease²⁰, Alzheimer's disease²¹, Parkinson's disease²², progressive supranuclear palsy²³, Creutzfeldt Jacob disease²⁴ and hippocampal sclerosis.²⁵ Argyrophilic grains have been reported in MCI.²⁶ Our findings confirm these reports, however we have found that AGs are more prevalent than has been previously reported.

It remains unclear whether AGs are an incidental finding associated with advanced age or are an independent disease entity. Our data suggest that AGs do not represent a distinct disease but rather a non-specific aging change. Also, it is not clear what their contribution to the severity or phenotype of dementia might be. Other groups have coined the term argyrophilic grain disease (AGD) or Braak's disease for cases in which AGs are an isolated finding in cases with dementia.²⁷⁻³³ Some have proposed that argyrophilic grain disease is a unique 4-repeat tauopathy.^{3,26} We have found that a glial tauopathy frequently coincides with AGs but is not present in all cases. Although some diagnostic groups appeared to have a higher prevalence of glial tauopathy, the total numbers of cases in these groups were too small to determine whether this is a genuine finding. The grains themselves, however, undoubtedly represent a neuronal tauopathy, so in that sense all cases of AGs are tauopathies. Our data show that all cases of AGs coincide with neurofibrillary pathology, typically cases at Braak stages III and IV. The distribution of AGs is very similar to that of classic neurofibrillary pathology at Braak stages III and IV, with the most heavily-affected regions being the entorhinal and transentorhinal areas, hippocampal field CA1 and amygdala. We suggest that AGs simply represent a transient phase of neurofibrillary degeneration, as axons, presynaptic terminals and dendrites break up and are ultimately destroyed by phagocytic cells. The fact that they are composed predominantly of 4-repeat tau may just be peculiarity related to their situation in axons and dendrites rather than cell bodies.

In conclusion, future studies with greater numbers of cases in the different diagnostic groups might yet find some significant disease associations for AGs but at present the results indicate that they are equally common in diseased and normal individuals, suggesting a linkage with general aging processes.

Acknowledgments

This research is supported by grants to the Sun Health Research Institute Brain Donation Program and the Arizona Parkinson's Disease Consortium by the Michael J. Fox Foundation for Parkinson's Research (The Prescott Family Initiative), the Arizona Biomedical Research Commission (contracts 4001, 0011 and 05-901) and the National Institute on Aging (P30 AG19610).

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Figure 1. Microscopic Appearance of Argyrophilic Grains and Glial Tauopathy

a) Grains were most frequently present in the mesiotemporal lobe; in this low-magnification photomicrograph, a dense cloud of grains are seen close to the surface of the ambient gyrus. b) Grains were usually shaped like rice grains, spindles or commas, like these in the ambient gyrus. c) In the CA1 field of the hippocampus, grains were more frequently seen as short fine threads. d) Glial tauopathy commonly accompanies argyrophilic grains; this is a tufted astrocyte in the putamen. e) Thorned astrocyte in the globus pallidus. f) Coiled body in the globus pallidus. All of the sections depicted were stained with the Gallyas silver stain.

Table 1
Clinical Summary of Subjects with and without Argypophilic Grains at Autopsy

	AD with AGs n= 43	AD w/o AGs n= 190	PDD with AGs n= 11	PDD w/o AGs n= 31	DLB with AGs n= 2	DLB w/o AGs n= 7	NC with AGs n= 20	NC w/o AGs n= 48	MCI with AGs n=4	MCI w/o AGs n=11
Age	85.81 ±6.98	82.15 ±8.80 [*]	80.91 ±5.26	78.54 ±6.89	84.5 ±7.78	81.43 ±8.50	86.00 ±5.63	84.42 ±6.12	89.75 ±3.33	86.18 ±7.44
Education	14.30 ±2.23	14.48 ±2.61	13.89 ±1.76	15.0 ±2.47	14.0 ±1.0	11.5 ±4.12	15.41 ±2.83	15.85 ±2.68	16.0 ±3.27	15.27 ±2.61
Gender M/F	24/19	93/97	5/6	22/9	1/1	4/3	8/12	24/24	3/1	4/7
MMSE	11.86 ±9.18	11.91 ±8.81	20.43 ±2.94	17.70 ±9.29	22.5 ±2.12	12.67 ±7.23	28.31 ±1.35	28.61 ±1.63	27.3 ±1.15	27.0 ±1.95
Diabetes Mellitis	5/43	16/190	1/11	1/31	1/2	2/7	1/20	8/48	1/4	3/11
Hypertension	20/43	60/190	4/11	7/31	1/2	4/7	12/20	21/48	0/4	7/11
Coronary Artery Disease	4/43	18/190	4/11	3/31	1/2	5/7	5/20	2/48 [§]	0/4	0/11
Depression	14/43	38/190	6/11	7/31	1/2	3/7	7/20	10/48	0/4	3/11
Hypercholesterolemia	4/43	16/190	1/11	2/31	1/2	2/7	3/20	3/48	0/4	0/11
Cerebrovascular accident or transient ischemic attack	1/43	11/190	1/11	1/31	0/2	4/7	2/20	6/48	0/4	4/11
Arthritis	11/43	42/190	4/11	6/31	1/2	4/7	6/20	16/48	0/4	7/11
Cancer	9/43	16/190 [‡]	3/11	2/31	1/2	2/7	8/20	25/48	0/4	4/11

^{*} p<0.05 difference in mean age between AD subjects with AGs compared to subjects without AGs

[§] p<0.05 difference in Coronary Artery Disease between NC subjects with AGs compared to NC subjects without AGs

[‡] p<0.05 difference in cancer between AD subjects with AGs compared to subjects without AGs

Argyrophilic Grain Prevalence, Severity and Glial Tauopathy in the Diagnostic Groups

Table 2

	NC Subjects	MCI Subjects	AD Subjects	DLB Subjects	PDD Subjects
Prevalence	29.4%	26.7%	18.4%	22.2%	26.1%
Severity Grade	6.80 (2.2)	6.87 (2.4)	6.30 (2.9)	8.25 (1.1)	5.43 (2.7)
Glial tauopathy	42%	100%	40%	100%	80%

Figures in parentheses are standard deviations.

Table 3
Prevalence and Severity of Argypophilic Grains and Braak Neurofibrillary Stage

	Stage I	Stage II	Stage III	Stage IV	Stage V	Stage VI
Prevalence	2%	10%	36%	28%	18%	5%
Severity Grade	5.25 (3.6)	4.45 (1.9)	6.11 (2.5)	6.48 (2.3)	6.04 (2.4)	3.07 (1.8)

Figures in parentheses are standard deviations.