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Argyrophilic grains: A distinct disease or an additive pathology?

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Abstract

Background: Argyrophilic grains (AG) are silver-positive spindle-shaped lesions found at postmortem. Their significance is controversial.
Objective: To determine clinical correlates of AG and MRI patterns of atrophy that could allow premortem recognition of this pathology.
Methods: Cases with AG were identified from a longitudinal study of aging and dementia. Clinical features were compared between subjects with and without dementia. Voxel-based morphometry (VBM) was used to assess patterns of grey matter atrophy in subjects compared to controls. Whole brain volumes (WBV) were compared across groups.
Results: Twenty-two cases (14 females; median age at death of 90 years; range: 70–101) with AG were identified. Eight of the 22 were demented. Those with dementia had higher Braak ($p = 0.02$) and lower Mini-Mental State Examination (MMSE) ($p = 0.002$). VBM demonstrated hippocampal atrophy in those with dementia ($N = 3$) but no atrophy in those without ($N = 9$). There was no difference in WBV between groups.
Conclusion: AG is a feature of old age commonly occurring in non-demented subjects. In this age group, the presence of AG may reduce the threshold for dementia.

Keywords: Voxel-based morphometry; Total intracranial volume; Argyrophilic; MRI; Volume loss; Alzheimer's disease

1. Introduction

Pathologically, argyrophilic grains (AG) are characterized by the finding of spindle-shaped lesions in neuronal processes, and coiled bodies in oligodendrocytes in the neuropil of the hippocampus, entorhinal cortex and other limbic areas (Braak and Braak, 1987, 1989). The significance of finding AG during a postmortem evaluation is controversial. Since the original description of AG almost two decades ago (Braak and Braak, 1987), only a few series have described clinical features that may correlate with the presence of this pathology (Botez et al., 2000; Ikeda et al., 2000; Jicha et al., 2006; Martinez-Lage and Munoz, 1997; Togo et al., 2005; Tolnay et al., 1997). Some of these reports have suggested that the presence of AG correlates with dementia characterized by behavioral disturbances including agitation and violence, personality changes, and later by forgetfulness.

Controversy arises because of two main reasons. First, although AG have been found in subjects with cognitive impairment and dementia, large clinicopathological studies have found AG in subjects without any cognitive impairment (Martinez-Lage and Munoz, 1997; Tolnay et al., 1997). Secondly, AG is rarely the sole pathological finding in cognitively impaired subjects, and is most commonly found

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to co-exist with other pathologies (Braak and Braak, 1989, 1998; Jicha et al., 2006; Martinez-Lage and Munoz, 1997; Togo et al., 2002), especially neurofibrillary tangles (NFT) (Jellinger, 1998), one of the hallmark lesions of Alzheimer's disease. Currently, there are no prospective studies that have assessed clinicopathological and MRI correlates of AG.

The primary aims of this study were therefore to determine what clinical features correspond to the presence of AG, and to determine if there is an MRI signature pattern of volume loss that would allow premortem recognition of this pathology. Given prior evidence that AG is found in cognitively normal, as well as demented individuals, we also set out to compare demographic and imaging features between cases with AG, with and without dementia.

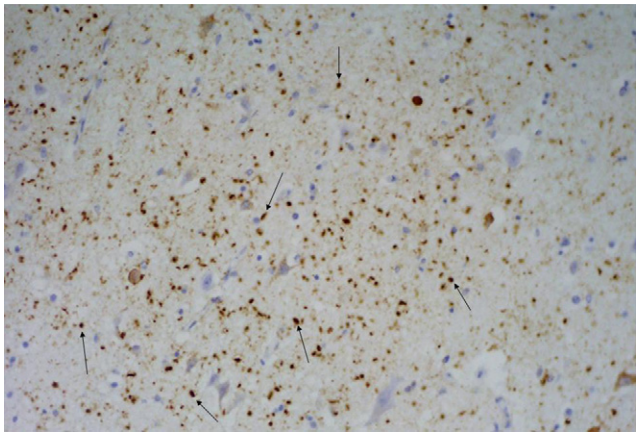

Fig. 1. Tau immunohistochemistry demonstrating the presence of typical AG (arrows highlight a few examples) in the entorhinal cortex. The AG are seen as spindle-shaped dot-like structures of varying size throughout the brain parenchyma.

2. Methods

2.1. Subjects and recruitment

In order to best address the aims of this study, we needed to attend to two important concerns. First, all subjects would have to have been clinically well characterized, and second, only subjects without any additional pathology that could account for cognitive impairment, would be included in the study. Based on these two concerns, we developed our inclusion and exclusion criteria.

2.1.1. Inclusion criteria

All subjects must have been enrolled in our Alzheimer's Disease Research Center (ADRC) or Alzheimer's Diseases Patient Registry (ADPR), Mayo Clinic, Rochester, MN. Both the ADRC and ADPR are longitudinal studies with well characterized clinical histories, serial yearly head MRI scans, and pathological material. All subjects must have had autopsy examination by at least one of our neuropathologists with expertise in degenerative neuropathology (JEP or DWD) and confirmation of the presence of AG. In order to be included in the imaging component of this study, all subjects must have had one volumetric head MRI scan.

2.1.2. Exclusion criteria

We excluded any subject in which in addition to the presence of AG, there was another pathology that could have account for, or is associated with cognitive impairment. Therefore, we excluded any case in which there was pathological features of high probability for Alzheimer's disease as defined by the NIA Reagan criteria (Hyman and Trojanowski, 1997), hippocampal sclerosis (Dickson et al., 1994), frontotemporal lobar degeneration (McKhann et al., 2001), progressive supranuclear palsy (Hauw et al., 1994), corticobasal degeneration (Dickson et al., 2002), or Lewy body disease (McKeith et al., 2005). In addition, we excluded any case that did not meet NIA Reagan criteria for Alzheimer's disease (Hyman and Trojanowski, 1997), but had a Braak Stage of V, or VI (Braak and Braak, 1991) (e.g. tangle dominant cases). We also excluded any subject in which the historical records were incomplete. For the imaging component of this study, we excluded any subject in which the volumetric MRI was of poor quality which could have affected the analysis.

2.2. Pathological analysis

All subjects underwent a standard battery of routine, silver and immunohistochemical analysis as have been previously described in detail (Knopman et al., 2005). Tau immunohistochemistry was completed with antibodies that recognize hyperphosphorylated tau (AT8, 1/1000 dilution: Endogen, Woburn, MA). All subjects were diagnosed as having AG if on histological sections there was the finding of silver and tau-positive spindle-shaped lesions in transentorhinal and entorhinal cortex, amygdala or temporal allocortex (Fig. 1) (Jellinger, 1998). The density of NFT was also assessed and all subjects were given a Braak stage according to published criteria (Braak and Braak, 1991). The presence of diffuse and neuritic plaque density was also document according to both Khachaturian (1985) and CERAD criteria (Mirra et al., 1991). Khachaturian criteria was determined with modified Bielschowsky, while CERAD criteria was determined with tau immunohistochemistry as previously reported (Knopman et al., 2003).

We also identified a control group for the MRI analysis only, which consisted of a pathologically defined cohort of individuals without pathological finding of AG, or any neurodegenerative or vascular disease who had been followed longitudinally in our ADRC or ADPR and had one volumetric head MRI scan. A control group was identified as this is a necessity in order to perform the image analysis.