**Review** paper

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# Argyrophilic grain disease: a clinicopathological review of an overlooked tauopathy

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**Abstract**

*Argyrophilic grain disease (AGD) is a sporadic tauopathy and actually the second most frequent cause of dementia after Alzheimer's disease. Patients can present with slowly progressive cognitive decline as well as psychiatric manifestations such as depression. Definite diagnosis of AGD can only be made by post-mortem examination of the brain. Neuropathological features include argyrophilic grains in limbic areas along with oligodendroglial coiled bodies in hippocampal and amygdaloid white matter, and ballooned neurons in the amygdala. AGD, however, can often be overlooked and missed on neuropathologic examination as there are actually no specific clinical manifestations that would be considered highly suggestive of AGD. Thus, it is not uncommon to find neuropathological features of AGD in patients who do not present with any apparent neurological manifestations. The aim of this review is to provide an overview of what is currently known about AGD as well as raise its awareness among both neurologists and neuropathologists who may otherwise overlook this interesting tauopathy. We believe that patients above the age of 60 years should undergo post-mortem screening for AGD to avoid missed opportunity for diagnosis and enable future clinicopathological studies.*

***Key words:*** *argyrophilic grain disease, clinical, neuropathology, tauopathy.*

## Introduction

Argyrophilic grain disease (AGD) is said to be the second most common neurodegenerative disease that causes dementia in the elderly after Alzheimer's disease [8,10,21,29,34,39]. In neuropathological practice however, it seems to be an underdiagnosed entity at post-mortem examinations. AGD was first described by Braak *et al.* in 1987 as a progressive, late-onset neurodegenerative disease characterized by small spindle- or comma-shaped lesions in neuronal processes, referred to as argyrophilic grains, which can be highlighted by silver stains [7]. Neuropathologic changes of AGD may be found in isolation or in association with other neurodegenerative disorders such as Alzheimer's disease (AD), Pick's disease, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Parkinson's disease, and TDP-43 proteinopathies [14,19,20,37,38]. AGD has also been reported in association with dementia with Lewy bodies, Creutzfeldt-Jakob disease and multiple system atrophy, albeit rarely [11,43]. The frequency of AGD increases with age without specific gender predilection [8]. The reasons for AGD being underdiagnosed in clinical neurological practice and

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post-mortem neuropathological examination may vary from one institution to another, but is partially due to the fact that AGD does not consist of so-called unique signs and symptoms that would help distinguish it from other neurodegenerative disorders in the clinical setting. This review aims to raise the awareness of AGD among both neurologists and neuropathologists and encourage post-mortem screening for AGD in elderly individuals.

## Epidemiology

The epidemiology and etiology of AGD are poorly understood. Nevertheless, AGD is generally recognized as a disease of older age. In a large autopsy series ($n$ = 2661), 5% of the cases ($n$ = 125) were classified as having AGD [8]. Patients aged 81-85 had the highest frequency of the disease ($n$ = 40), whereas only 5 patients aged 60 years or less were found to have argyrophilic grains (AGs)/AGD on post-mortem examination [8]. Another study noted that the incidence rate of AGD peaked at 80 years of age [34]. In a series of 300 consecutive autopsies of patients over the age of 30, 5.6% of the cases had evidence of AGs [16]. The mean age of the AGD cases in this series was 77 years with no patients under the age of 60 [16]. These findings are corroborated by a larger autopsy study ($n$ = 1405) that demonstrated a large increase in the incidence of AGD in patients aged 60 years and older [34]. Here, the frequency of AGs and the neuropathological stage of AGD were found to be higher in females [34]. Therefore, evidence from large autopsy studies points towards age as a prominent risk factor for the disease. This is supported by a study investigating the frequency of AGD in centenarians that found AGs in 31.3% of the cases [10].

## Clinical presentation

AGD does not present with distinct neurological features that could be considered pathognomonic. The only method to conclusively diagnose AGD is post-mortem examination of the brain. The most common clinical presentation is progressive mild cognitive impairment followed by irritability and agitation [40,44]. Patients retain the ability to articulate and verbalize as well as to solve problems on average two years longer than patients with AD [17]. Knopman *et al.*'s examination of 39 brains from cognitively normal elderly individuals (24 women, 15 men; age range 74-95) however found AGD pathology in 31% of examined brains [23]. In Rodriquez's autopsy study of brains from 983 patients, 59% of participants with AGD pathology were found to be cognitively normal [32]. Interestingly, this same study found an association between AGD and low socioeconomic status. Few authors have even suggested that AGD may be protective against cognitive decline [18]. Neuropathologic changes of AGD can therefore be found even in patients with no apparent history of cognitive decline. These studies would seem to suggest that screening for pathologic features of AGD in elderly individuals regardless of cognitive status may lead to an increased frequency of diagnosis of this entity in clinical neuropathologic practice.

AGD may also present with disinhibited behaviour reminiscent of frontotemporal dementia, as well as hallucinations, delusions, anxiety, depression, and even urinary incontinence [4,44]. Some studies have suggested that early stages of AGD present primarily with psychiatric manifestations. For example, Nagao *et al.* studied the pathological bases of 23 cases of schizophrenia and delusional disorders in cognitively normal individuals older than 40 years and found five (21.7%) of these cases to have neuropathological characteristics of AGD [28]. In another study, Shioya *et al.* performed neuropathologic examinations on brains of eleven patients clinically diagnosed with a bipolar disorder and found some degree of AGD pathology in all eleven cases [35]. A rare example of AGD has been recently described in a male suicide victim in his forties with no known significant clinical history, but who had complained to family members and colleagues of feeling weak and hypobulic [45]. Another unusual case was described in a 52-year-old male with no significant past neurological or psychiatric history and no pertinent family history or traumatic injury, who presented with late-onset psychosis and catatonia and was ultimately diagnosed with AGD on post-mortem examination [26]. One may argue that given these examples perhaps it is worthwhile to rule out AGD on post-mortem examination of patients with a clinical history of psychiatric manifestations or change in behaviour even without any known history of cognitive impairment. Even more interesting are studies suggesting that neuropathologic changes of AGD may even be found in patients without ever presenting with apparent neurologic and/or psychiatric manifestations. In our past twelve-month clinical experience, three of four patients pathologically diag-

nosed with AGD did not have a known neurological or psychiatric history (not published).

## Neuropathology

AGD is characterized by atrophy of the ambient gyrus [24]. Microscopic pathology of AGD is largely limited to medial-temporal lobe structures including the amygdala, hippocampus, and entorhinal cortex. The neuropathological hallmarks (Fig. 1) of AGD are tau-immunopositive argyrophilic grains, intraneuronal cytoplasmic pretangles, and oligodendroglial coiled bodies. These features can also be detected with silver (e.g. Bielschowsky, Gallyas) staining as

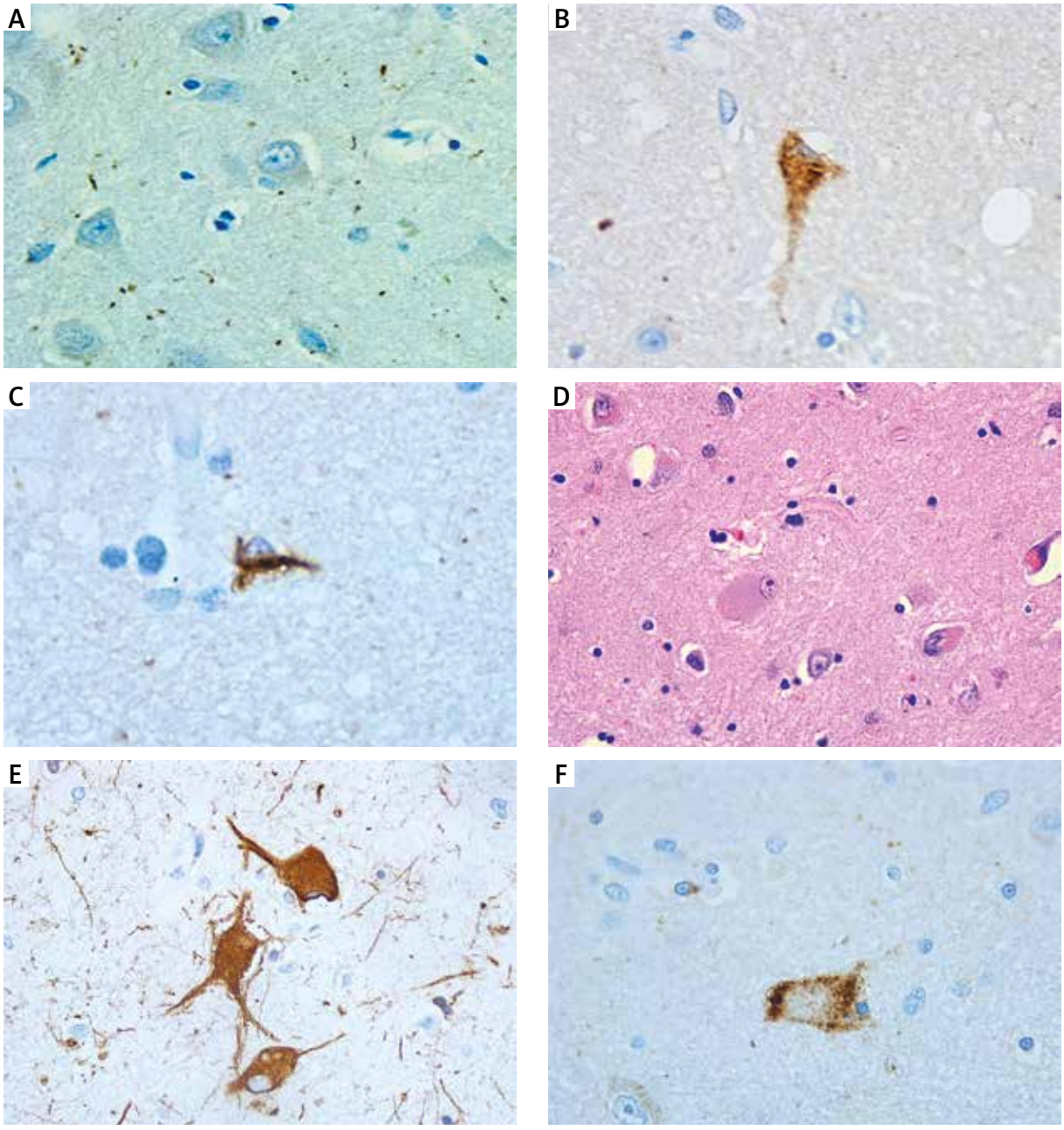


**Fig. 1. A)** Tau-positive argyrophilic grains. **B)** Tau-positive pretanglelasma. **C)** Tau-positive coiled body. **D)** An example of a balloon cell in the amygdala. **E)** Balloon cells immunopositive for α-B crystallin. **F)** Peripheral staining of balloon cell by tau protein.

well as immunostaining by p62 and ubiquitin. Argyrophilic grains are spindle-/comma-shaped neuronal lesions located in dendrites and axons. Ding *et al.*'s neuropathological study of brains from 32 centenarians found argyrophilic grains in the ambient gyrus and CA1 sector of the hippocampus in all (100%) of their cases. Within the hippocampus, the grains were observed mainly in the internal and external pyramidal layer. 3/32 cases also showed a small number of grains in CA2-CA4 sectors. A small to moderate amount of grains were also found in the insular cortex in 6/32 cases and the anterior cingulate cortex in 3/32 cases [10]. It should be noted that pathological grains can also be found in association other disorders. A recent study by Armstrong of 12 PDD cases (10 male, 2 female, age range 67-82 years) where the main pathologic correlate was the presence of Lewy bodies in cortical and limbic regions, cortical clusters of α-synuclein positive Lewy grains were identified along with Lewy bodies and Lewy neurites [2]. Tau-positive dot-like grains in cortical and hippocampal regions have also been recently described in cases of chronic traumatic encephalopathy [3]. Pretangles are characterized by diffuse or granular accumulation of tau protein in the cytoplasm of neurons with few fibrillary structures [8,44]. It should be noted that pretangles can also be found in cases of AD and primary age-related tauopathy (PART). In Ding *et al.'s* study mentioned above, 12 of 32 patients were found to display pathologic changes of both AGD and AD [10]. AGD pathology has also been suggested to contribute to the development of dementia by lowering the threshold of cognitive deficits in the presence of moderate amounts of AD pathology. In Thal *et al.*'s study, 204 post-mortem brains from 30 demented and 49 non-demented AGD patients, 39 AD patients, and from 86 non-demented controls without AGD were staged for AD-related neurofibrillary tangles and amyloid beta-protein deposition. The study found that demented AGD cases showed lower stages of AD-related pathology than did pure AD cases, but higher stages than non-demented AGD patients. AGD-associated dementia was seen in the presence of neurofibrillary (Braak)-stages II-IV and amyloid β-phases 2-3 [39]. Neuropathological examination of post-mortem brains should entail steps to rule out the concomitant presence of AGD pathology with AD and/or primary age-related tauopathy (PART). Other associated findings include tau-immunoreactive astrocytes called bush-like astrocytes as well as balloon neurons. The latter is typically found exclusively in the amygdala although we have recently encountered a case (not published) with neuropathological findings of AGD that also showed balloon neurons in the cingulate gyrus in addition to the amygdala. Ballooned neurons in the amygdala can be immunohistochemically demonstrated by α-B crystallin but they can also be stained at the periphery by anti-phospho-tau antibodies. Ballooned neurons show reduced staining of rough endoplasmic reticulum and accumulate phosphorylated neurofilament epitopes [12]. Bush-like astrocytes, which were described by Botez *et al.* as non-argyrophilic, non-neuronal tau-positive stellate cells, are said to be more commonly found in the amygdala and entorhinal cortex in cases of AGD [6,31]. Although they are not a particularly prominent feature of AGD, if present, these may help distinguish AGD from AD. The pathology of AGD can also be staged according to the following: stage I involves the ambient gyrus and the most anterior part of CA1; stage II is characterized by greater involvement of CA1 along with involvement of the dentate gyrus and presubiculum by tau pathology; in stage III, CA2-3, hypothalamic nuclei, anterior temporal, cingulate, insular and orbitofrontal cortices, nucleus accumbens and septal nuclei are affected. It is at this stage that ballooned neurons and superficial spongiosis in the ambient gyrus are said to become evident; in stage IV, tau pathology is seen extending further into neocortex and brainstem [12,34]. Adachi *et al.* examined the brain and spinal cord in 653 consecutive autopsies between 2001 and 2007 and found asymmetric density of argyrophilic grains between the left and right medial temporal lobes in patients with stage III AGD pathology. The authors of this study reported asymmetry in the posterior hippocampus commensurate with grain density in the anterior amygdala or pretangles in the dentate gyrus. Interestingly, the asymmetry in grain density of the anterior amygdala was found to be less frequent than in the posterior hippocampus, which the authors believed was partly because the former is seen in the initial stage of AGD and the grain density may be saturated in later stages [1]. This study would seem to suggest that bilateral sampling of the amygdala and posterior hippocampus and assessment of grain density on both the left and right sides may be helpful in diagnosing AGD on post-mortem examination. Further studies are needed to reach a more definitive

conclusion regarding the left-right asymmetry of tau-pathology in AGD.

It is not uncommon to find neuropathological features of AGD concurrently with those of at least one other neurodegenerative disorder. For example, multiple studies have reported the frequent finding of AGD concomitantly with progressive supranuclear palsy (PSP) [27,37,41,44]. It has also been reported that argyrophilic grains are more frequently found in patients with CBD compared with the rest of the elderly population. Tatsumi *et al.* examined 35 autopsy cases with the neuropathologic diagnosis of CBD and found argyrophilic grains in all (100%). This group also observed that the argyrophilic grains in these patients were widespread throughout the temporal lobe and that the grains were consistently found with argyrophilic threads [38]. Within the last twelve months at our institution, we encountered two autopsy cases (not published), one of which showed neuropathological features in keeping with PSP, while the other patient showed characteristics of CBD, but both displayed concurrent presence of argyrophilic grains in the medial temporal lobe structures as well as oligodendroglial coiled bodies in both the hippocampal and amygdaloid white matter. Of course, coiled bodies are also features described in the context of PSP and CBD without the presence of argyrophilic grains [22]. Balloon neurons however were not identified in either of these two cases. Interestingly, although less common, AGD has also been reported to co-exist with TDP-43 proteinopathies. In Behrouzi *et al.*'s study of 80 patients with TDP-43 proteinopathy on neuropathologic examination (41 with motor neuron disease, 23 with frontotemporal dementia, and 16 with both frontotemporal dementia and motor neuron disease) in which paraffin embedded sections of frontal, entorhinal, temporal and occipital cortex and hippocampus were immunostained for tau pathology using anti-tau antibodies, AT8, $pThr^{175}$ and $pThr^{217}$, two cases (1 with motor neuron disease, 1 with frontotemporal dementia) showed tau pathology consistent with AGD [5]. There has also been a case described of an autopsied patient (78-year-old female) who clinically presented with primary progressive aphasia which was found to have mixed tauopathy consistent with AGD and TDP-43 Type B proteinopathy [13]. In a study by Soma *et al.*, post-mortem brains from 37 autopsied patients with sporadic amyotrophic lateral sclerosis (ALS) were examined. The frontotemporal region from these patients were stained with Gallyas-Braak method and also immunostained for antibodies against phosphorylated tau, 4-repeat tau and TDP-43. The study found 14 (38%) of the 37 patients that showed tau-pathology (pretangles/tangles, coiled bodies, bush-like astrocytes) in keeping with AGD. Interestingly, TDP-43 immunohistochemistry revealed neuronal and glial cytoplasmic inclusions in the affected medial temporal lobe in 93% (13/14) and 64% (9/14), of the cases, respectively [36]. Larger scale studies however are required to determine what, if any, role AGD pathology plays in patients with ALS who also exhibit dementia or cognitive decline. AGD pathology has also been found in cases of Alzheimer's disease, Parkinson's disease, Lewy body disease and even multiple system atrophy [9,14,19,20,43].

Although neuropathologic changes of AGD have been observed in combination with other neurodegenerative disorders, AGD should still be regarded as a distinct disorder as their findings have been observed in isolation as well [32], including the four cases encountered in our institution over a twelve-month period. Some of neuropathological findings of AGD, such as atrophy of the ambient gyrus, argyrophilic grains, and bush-like astrocytes profiles are typically not described in other isolated neurodegenerative disorders thereby supporting the notion that AGD possesses unique neuropathological characteristics that make it a distinct entity rather than simply a co-pathology. This notion is also supported by Grinberg *et al.*'s finding from his post-mortem brain tissue study of 22 cases of various tauopathies that AGD inclusion differs from other tauopathies by their lack of acetylated tau [18].

## Genetics

AGD is viewed as a largely sporadic disorder [41]. To our knowledge, there have been no large-scale studies reported in the literature that have deciphered genetic alterations associated with AGD. One of the earliest studies to suggest a genetic association with AGD was Ghebremedhin *et al.*'s study, which found a higher frequency of e2 allele of apolipoprotein E (ApoE) in AGD cases (22%, $n = 48$) than in age-matched controls (4%, $n = 43$) [15]. This finding was corroborated in a later study in which the polymorphisms of the $\alpha_2$-macroglobulin ($\alpha$2M) gene and low-density lipoprotein receptor-related protein gene (LRP) were assessed in 115 cases of AGD (64 female, 51 male, ages 61-96 years) and compared with 170 controls (87 female, 83 male, ages 60-99

years) from 1986 to 2000. The authors in this study found a strong association between AGD and C766T polymorphism of LRP (102/115) as well as the valine to isoleucine (Val1000Ile) polymorphism of A2M (92/115) [16]. Villela *et al.*'s study of copy number variations (CNVs) in 29 patients whose brains showed neuropathological evidence of AGD revealed six (21%) patients with a deletion at 17p13.2 encoding the CTNS gene, which encodes a seven-transmembrane domain protein that functions to transport cysteine out of lysosomes [42]. Multiple studies have also suggested a strong association with the H1 allele of the MAPT gene [14,30]. Rönnbäck *et al.* described two siblings carrying the MAPT S305S mutation who demonstrated neuropathological features resembling AGD [33]. A single case was also reported by Kovacs *et al.* of a patient with MAPT S305I mutation and AGD-like neuropathology [25]. Further studies however are necessary to definitively link AGD with specific genetic loci.

These observations demonstrate that AGD is a distinct neurodegenerative disorder than can be distinguished not only neuropathologically, but genetically as well.

## Conclusions

AGD is a distinct neurodegenerative disorder, which although does not present with pathognomonic clinical signs and symptoms, is a frequent cause of dementia behind AD with increasing age as an established risk factor. When symptoms are present, patients most commonly present with late onset slowly progressive cognitive decline with or without psychiatric manifestations. It is also not uncommon for neuropathological features of AGD to present in patients who do not present with apparent neurological manifestations, which could explain why this entity can be missed. For this reason, it may be worthwhile to perform post-mortem screening of patients over the age of 60 years, based on epidemiological evidence, with tau immunohistochemistry on relevant anatomic areas to ensure AGD does not get overlooked. This type of screening would also facilitate further clinicopathologic studies of AGD especially into the heterogeneous clinical presentations of this entity.

## Disclosure

The authors report no conflict of interest.

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