

# Clinical Characteristics of Dementia Associated with Argyrophilic Grain Disease

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## Key Words

Argyrophilic grain disease • Dementia •  
Autopsy-confirmed • Retrospective Dementia Inventory

## Abstract

**Background/Aims:** We aimed at characterizing the clinical features of dementia associated with argyrophilic grain disease (AgD). **Methods:** Relatives or close friends of 24 individuals with autopsy-confirmed AgD and 29 patients with autopsy-confirmed Alzheimer's disease (AD) were administered a novel Retrospective Dementia Inventory to assess the cognitive, behavioral and affective symptoms of the deceased patients. **Results:** AgD patients showed less severe impairments in memory, language, attention and executive function than AD patients. **Conclusion:** Compared to AD patients, individuals suffering from AgD appear to present with comparable deficits in behavior and affect but relatively spared cognitive functioning.

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## Introduction

Argyrophilic grain disease (AgD) is a late-onset tauopathy, accounting for approximately 5–13% of neurodegenerative dementias [1–4]. In a series of old dementia patients, AgD was found to be the second most common form of degenerative dementia after Alzheimer's disease (AD) [2]. AgD is histopathologically characterized by abundant spindle-shaped argyrophilic grains (ArG) in neuronal processes and coiled bodies in oligodendrocytes. ArG consist of hyperphosphorylated and abnormally phosphorylated tau, and are primarily found in limbic regions such as the hippocampus, the entorhinal and transentorhinal cortices, and the amygdala. Saito et al. [3] proposed the following neuropathological staging paradigm: stage I = ArG restricted to the ambient gyrus and its vicinity; stage II = ArG more apparent in the anterior and posterior medial temporal lobe, including the temporal pole, as well as the subiculum and entorhinal cortex; stage III = abundant ArG in the septum, insular cortex and anterior cingulate gyrus, accompanying spongy degeneration of the ambient gyrus. Biochemical studies indicate that AgD is a 4-repeat tauopathy similar

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**Table 1.** Demographic characteristics of AgD and AD patients and their informants

	AgD	AD	Statistical significance
<i>Patients</i>	24	29	
Gender, women/men	11/13	18/11	NS
Age at death, mean years $\pm$ SD	81.8 $\pm$ 6.0	86.2 $\pm$ 6.4	t = 2.6; p < 0.02
Duration of dementia, mean years $\pm$ SD	5.6 $\pm$ 4.6	7.4 $\pm$ 6.4	NS
<i>Informants</i>	24	29	
Gender, women/men	21/3	15/14	$\chi^2$ (2) = 7.71, p < 0.01
Age, mean years $\pm$ SD	66.2 $\pm$ 11.1	63.0 $\pm$ 12.3	NS
Mini Mental Status Examination, mean $\pm$ SD	28.2 $\pm$ 1.6	28.2 $\pm$ 1.6	NS
Relationship to patient			
Spouse/partner	8 (33%)	6 (21%)	NS
Children, relatives, friends	16 (66%)	23 (79%)	NS

NS = Not significant.

to progressive supranuclear palsy and corticobasal degeneration, but distinct from AD and Pick's disease [5]. A familial form of AgD has not yet been reported, nor has a genetic alteration on the tau gene been identified. Whereas one study suggests an association of AgD with the apolipoprotein E  $\epsilon$ 2 allele, the apolipoprotein E  $\epsilon$ 4 allele does not appear to be a susceptibility factor in AgD [6].

While much progress has been made in deciphering the neuropathology and molecular pathology of AgD, the clinical characteristics of this disease, particularly its cognitive and behavioral features, have scarcely been investigated. Mental deterioration and personality changes have been reported in a number of AgD cases [1, 7], and some AgD cases have been reported who presented with the clinical features of frontotemporal dementia [8]. The goal of the present study was to determine whether AgD can be characterized by a distinctive clinical pattern in terms of onset and relevance of symptoms.

## Methods

### Subjects

Between 1994 and 2000, 115 cases were neuropathologically diagnosed [9] with AgD at the Department of Neuropathology of the University Hospital Basel, Switzerland. Sixty-one neuropathologically confirmed [10] cases with AD (diagnosed between 1997 and 2000) were available for comparison. The next of kin of the deceased patients were contacted by their family physicians and invited to participate in the study. The former caregivers of 24 deceased patients with AgD and of 29 deceased patients with

AD agreed to participate. Table 1 shows the demographics of both patient and informant groups. The 2 patient groups did not differ significantly with respect to gender distribution and duration of dementia, but age at death was significantly higher in the AD group. The AgD and AD informant groups were comparable with respect to age, Mini Mental Status Examination (MMSE) score [11] and type of relationship with the patient, but differed with respect to their gender distribution.

The local ethics committee approved this study and written informed consent was obtained from all participants.

### Neuropathology

All AgD cases were characterized by the presence of abundant ArG in limbic areas, including sector CA1 of the hippocampus, the prosubiculum, the entorhinal and transentorhinal cortices, the parahippocampal cortex, the ambient gyrus and the amygdaloid complex. In most cases, high densities of ArG were also present in the hypothalamic lateral tuberal nucleus. Many coiled bodies were found within the white matter close to cortical areas rich in ArG. ArG were sparse in the anterobasal portions of the insula, as well as in the temporopolar and frontoorbital neocortex. Mild to moderate AD pathology was found in all AgD cases, consisting of neurofibrillary tangles and neuropil threads. The distribution of neurofibrillary tangles corresponded to Braak stage I in 6 cases (25.0%), Braak stage II in 10 cases (41.7%) and Braak stage III in 8 cases (33.3%) [12]. In 11 cases (44.8%) a few scattered senile plaques were found in the hippocampal formation and the neocortex, whereas no plaques were detected in 13 cases (55.2%).  $\alpha$ -Synuclein-stained Lewy bodies were found in the amygdala of 2 AgD cases (8.3%).

Among the 29 AD cases, 6 (20.7%) corresponded to Braak stage IV, 8 (27.7%) to Braak stage V, and 15 (51.7%) to Braak stage VI. All AD cases had a CERAD neuritic plaque score of 'C' [13]. Lewy bodies were found in the amygdala of 12 AD cases (41.4%).

Few lacunar infarcts in the basal ganglia and/or the cerebral white matter were present in 5 AgD (20.8%) and in 8 AD cases (27.7%).

### *Retrospective Dementia Inventory*

Informant interviews were conducted using an extended version of the Retro Brief Clinical Rating Scale (RetroBCRS) [14], the Retrospective Dementia Inventory (RDI). The RetroBCRS has proven to be a valid method of retrospectively determining AD in autopsy-confirmed patients [14]. The new RDI was developed to assess the deceased patient's symptoms along 3 axes: (1) activities of daily living (ADL)/behavior, (2) affect and (3) cognition [15]. It comprises 140 questions, of which 117 were taken from the RetroBCRS [14], 5 from the Clinical Dementia Rating Scale [16], 4 from the Nurses' Observation Scale for Geriatric Patients [17], 3 from the Neuropsychiatric Inventory [18] and 11 were newly created questions. The symptom or symptoms queried by each question were identified and allocated to 1 of the 3 axes. In total, 42 questions assessed 8 ADL/behavioral symptoms (social behavior, ADL, hobbies, motor behavior, disturbing behavior, continence, sleep and appetite), 30 questions assessed 9 affective symptoms (aggression, depression, lability, disinhibition, mood, anxiety, delusion, hallucinations and compulsion) and 93 questions assessed 11 cognitive symptoms (language, face recognition, object recognition, recent memory, past memory, attention, concentration, problem solving, judgment, orientation and instrumental ADL). Each question asked the informant whether a particular aspect of a symptom was present, and if so, its onset (recorded as number of years prior to death). The 'extent' of each symptom was calculated as the percentage of positively answered questions per symptom. In addition, 'symptom load' was calculated as the product of symptom duration (number of years) and extent (percentage) to estimate the clinical relevance of each symptom [18].

### *Procedure*

The examiner (G.M.S.) interviewed all informants at her office or at the informant's home. On average, these interviews took about 2 h (1–2.5 h). The delay between death and time of interview differed between the 2 groups [AgD:  $3.7 \pm 2.3$  years vs. AD:  $1.7 \pm 0.9$  years;  $t(51) = 4.2$ ,  $p < 0.0001$ ]. After the interview, informants were administered the MMSE [11]. The interview material from 1 female informant in the AgD group was disregarded since she scored less than 24 points on the MMSE.

### *Statistics*

Data were analyzed with the Statistical Package for the Social Sciences (SPSS, version 10.0). The  $\chi^2$  test, t test and Bonferroni-Holm test were used as appropriate. Statistical comparisons between the AgD and AD groups were made for 'symptom onset' and 'symptom load'.

## **Results**

The rated onsets of each type of ADL/behavioral, affective and cognitive symptom in the AgD and AD patients are shown in figure 1. AgD patients experienced difficulties verbalizing and articulating approximately 2 years later than AD patients (both  $p < 0.02$ ). Moreover, AgD patients retained their problem-solving skills on average 2 years longer than AD patients ( $p < 0.05$ ), and there

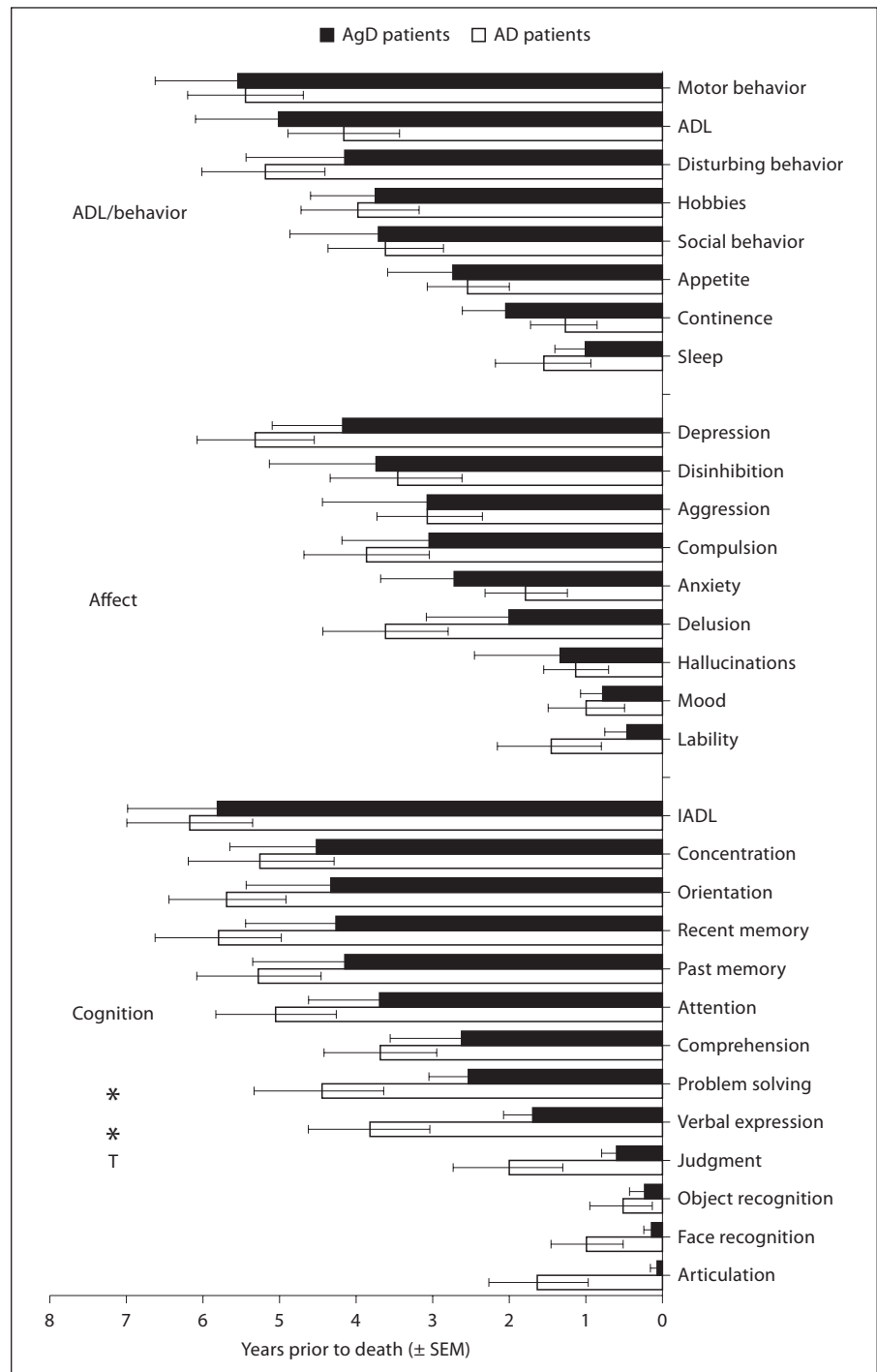
was a trend ( $p = 0.06$ ) for AgD patients to display problems in judgment later than AD patients (that is half a year vs. 2 years prior to death). The onsets of all other symptoms were comparable in the AgD and AD patient groups.

Symptom loads are shown in figure 2. The symptom loads of several cognitive symptoms were significantly lower in the AgD compared to the AD patients: attention ( $p < 0.02$ ), language (verbal expression:  $p < 0.02$ ; articulation:  $p < 0.01$ ), memory (recent memory:  $p < 0.01$ ; past memory:  $p < 0.05$ ), problem solving ( $p < 0.03$ ) and judgment ( $p < 0.05$ ). On the affect axis, delusions were significantly less prominent in AgD than in AD ( $p < 0.02$ ). Again, no differences were found in ADL/behavioral symptoms between the AgD and AD patients.

## **Discussion**

To our knowledge, this is the first study to compare the clinical features in AgD with those in AD. Thirty symptoms commonly encountered in dementia patients were retrospectively assessed in autopsy-confirmed AgD and AD patients with a novel tool, the RDI. The burden of cognitive dysfunction was smaller in AgD than in AD in several domains: memory, language, attention, and executive function. These findings do not contradict reports [7] indicating that behavioral symptoms are a characteristic feature of AgD. With relatively preserved cognitive functions, behavioral symptoms may dominate the clinical picture. Compared with AD, AgD patients generally presented with ADL/behavioral and affective symptoms at a comparable stage in the course of the disease except for later appearance of language and problem-solving difficulties. Thus, our results suggest that neuropsychological profiles eventually help in differentiating between AgD and AD. The diagnosis of AgD should be considered when patients exhibit deficits in ADL, behavior and affect characteristic of AD, yet have cognitive functions that are relatively preserved.

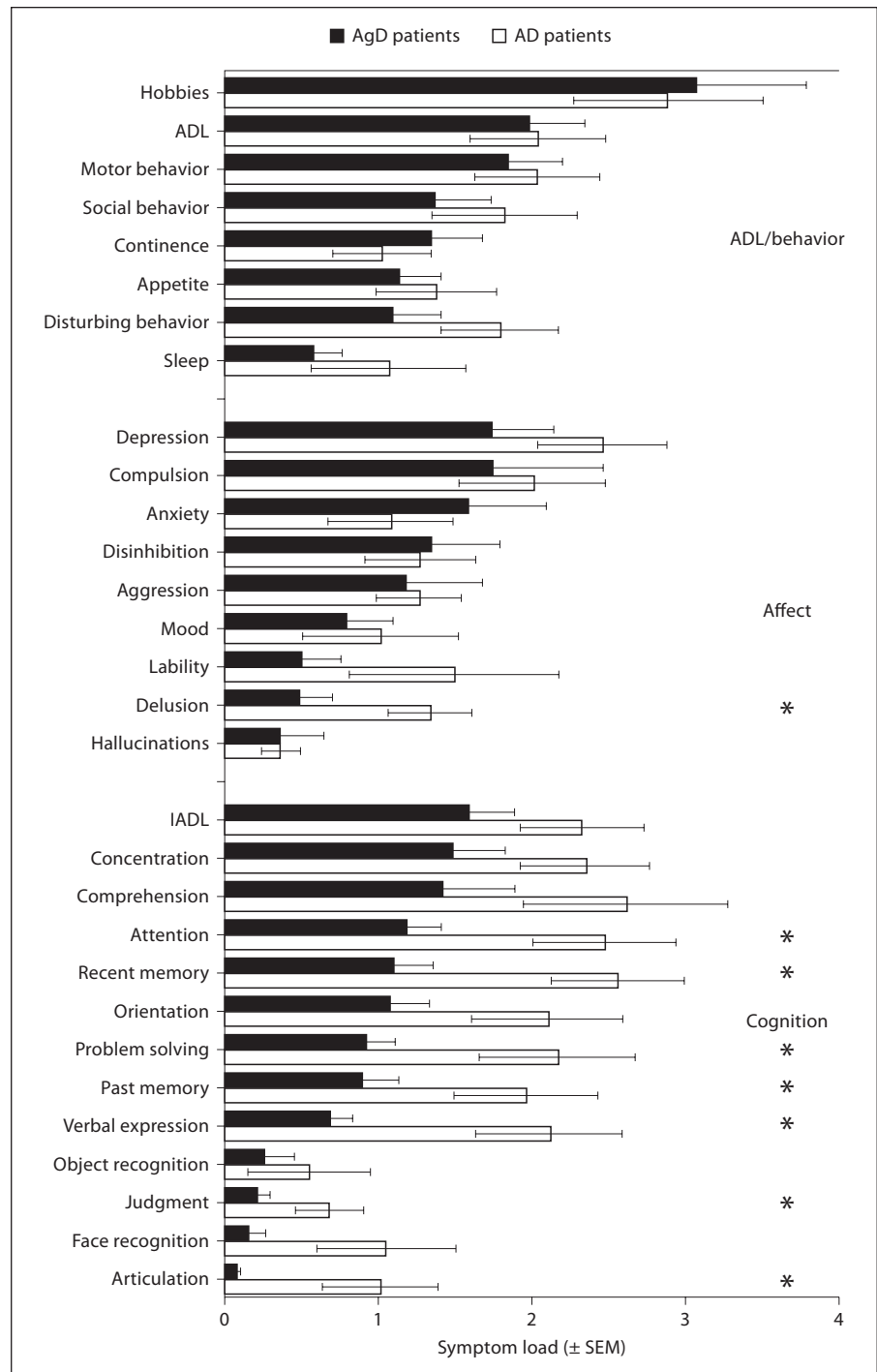
The clinical pattern of AgD in our study is consistent with the topographic distribution of its pathology. AgD is a progressive neurodegenerative disorder with an apparently stereotypical temporospatial spreading of pathological changes in limbic structures, including the ambient gyrus, amygdala, entorhinal cortex and regions of the hippocampal formation [19]. This pattern, as well as concomitant AD-type changes found in most AgD cases [4], might explain the substantial overlap in AgD and AD



**Fig. 1.** Reported symptom onset in patients with AgD and AD. IADL = Instrumental ADL; T = trend ( $p = 0.06$ ). \*  $p < 0.05$ .

ADL/behavioral and affective symptomatology. However, in contrast to AD, there is only mild neuronal loss in limbic structures and, importantly, neocortical involvement in AgD is scarce [4, 19], a pattern which may account for the relative sparing of cognitive functions early

in the course of AgD. Previous case studies of patients with AgD reported behavioral disturbances suggestive of frontotemporal dementia (such as inappropriate social conduct, egocentric, obsessive-compulsive, disinhibited behavior, dietary changes and apathy) [1, 8]. Some of



**Fig. 2.** Reported symptom load (symptom duration × extent) in patients with AgD and AD. IADL = Instrumental ADL. \*  $p < 0.05$ .

these reported cases [8] exhibited marked frontal and/or temporal lobe atrophy and widespread neocortical ArG, features which are not usually observed in AgD. However, in the present study, patients displayed neither frontotemporal dementia-like symptoms nor neuropathology. We therefore suggest that a rarer frontotemporal form

of AgD may exist alongside the more common limbic form of AgD. A number of caveats must be mentioned. This study relied on retrospective observations of informants. Retrospective studies work with ambiguous information. The sources may not be reliable and the answers could be influenced by the relationship between the

informant and the patient. Moreover, recollections of patients' histories dating back several years may be inaccurate. Clearly, prospective studies of the clinical-neuropathological characteristics of AgD are required to resolve many of these questions.

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