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M. Tolnay · M. Schwietert · A. U. Monsch
H. B. Staehelin · D. Langui · A. Probst

Argyrophilic grain disease: distribution of grains in patients with and without dementia

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Abstract In a previous study we reported on a late onset dementia which occurred in only half of the patients with argyrophilic grain disease (AgD) investigated. To find a correlation between the distribution of argyrophilic grains (ArG) and the occurrence of a late onset dementia, we examined the limbic area in 35 subjects who had ArG as the main neuropathological finding. A retrospective clinical analysis was performed by collecting information from hospital charts supplemented by standardized interviews based on DSM IV criteria for dementia. Sections from the rostral and caudal hippocampal regions, including the entorhinal/transentorhinal and parahippocampal cortex on both sides, were strained by the Gallays method. Nineteen subjects were diagnosed as demented according to these criteria; 16 were considered to have been cognitively normal. High numbers of ArG were observed in the anterior part of the CA1 subfield in all cases. However, the posterior half of CA1 was involved significantly more often and more severely in demented than in non-demented individuals ($P < 0.01$). Moreover, the distribution of ArG in the entorhinal/transentorhinal and parahippocampal cortex was more widespread in the group of demented patients ($P < 0.05$). These results show that the intellectual status of patients with AgD was related to the extension of ArG in the limbic area. We suggest that AgD is a progressive neurodegenerative disorder with early subclincial lesions in the anterior part of the hippocampal formation. To provide a more accurate clinicopathological correlation, the rostrocaudal extension of ArG in the limbic area should be evaluated in AgD cases.

M. Tolnay · M. Schwietert · D. Langui · A. Probst (✉)
Institute of Pathology, Division of Neuropathology,
University of Basel, Schönbeinstrasse 40,
CH-4003 Basel, Switzerland
Tel.: +41-61-265 2895; Fax: +41-61-265 3194

A. U. Monsch · H. B. Staehelin
Geriatric University Clinic, University of Basel,
CH-4003, Switzerland

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Introduction

Braak and Braak [3, 4] first reported a progressive late onset dementia, whose main morphological finding consisted of small argyrophilic neuropil grains (ArG) revealed by the Gallyas silver stain. Grains were most abundant in the CA1 subfield of the cornu ammonis, the pre-β layer of the entorhinal and transentorhinal cortices and in the adjacent temporal isocortex. The amygdala and the hypothalamic lateral tuberal nuclei were among the most affected subcortical structures [5].

ArG have not been encountered in glia or in neural cell perikarya, but recent investigation by Ikeda et al. [10] have shown the presence of grains in proximal dendrites and in spiny appendages of dendrites. Ultrastructurally, ArG have been found to consist of aggregates of 9- to 18-nm filaments [5, 11, 17] and of bundles of 25-nm smooth tubules [10, 13]. Paired helical filaments (PHF) have so far not been described in ArG.

The microtubule-associated protein tau encountered in ArG and in coiled bodies has been shown to share a number of abnormally phosphorylated sites with tau of neurofibrillary tangles (NFT) and neuropil threads (NTh) in Alzheimer's disease (AD) [10, 11, 13, 17, 18]. Moreover, we recently reported widespread hyperphosphorylation of tau protein in the somatodendritic domain of limbic neurons in argyrophilic grain disease (AgD) [17]. Unlike the situation in AD, hyperphosphorylated state of tau in AgD is obviously not associated with NFT formation in neuronal perikarya, even in presence of widespread ArG in the neuropil.

Although ArG constitute a well defined morphological change, easy to recognize with appropriate silver stain at postmortem examination, no reliable data are presently available on its prevalence in the elderly population. Braak and Braak [5] found ArG as the main histopathological feature in 28 out of 80 brains obtained at autopsy from demented subjects, thus suggesting a very high inci-

dence of grains among old demented patients. However, ArG constituted the most salient morphological change in only 10, while in 16 subjects ArG were associated with NFT, NTh and various numbers of neuritic plaques. Itagaki et al. [11] found AgD in only 1 case among 33 consecutive autopsies of old demented subjects without cerebrovascular pathology.

In a previous study of 301 consecutive autopsies of patients older than 65, we found 28 cases with AgD [17]. Among these 28 patients only 14 (50%) had presented progressive intellectual decline during the last year of their life. In most cases, ArG were associated with other morphological changes, among them NFT and senile plaques. However, changes of the Alzheimer type were not found to be more severe in demented patients, when compared with subjects without intellectual decline. In a recent study of 300 autopsied subjects older than 30 years, ArG were found in 17 cases, all aged over 68 [12]. Of these cases 6 had an additional specific diagnosis of a neurodegenerative disease [1 Pick's disease, 2 corticobasal degeneration, 2 progressive supranuclear palsy (PSP), 1 diffuse Lewy body disease], whereas the remaining 11 did not. However, among these 11 subjects with ArG, only 2 had presented dementia. These results indicate that ArG per se are not necessarily associated with an intellectual decline. Furthermore, intellectual impairment observed in some patients with ArG, did not seem to be accounted for by the presence or the severity of associated morphological changes.

As the presence or absence of an intellectual decline in subjects with ArG could be accounted for by the distribution and the density of ArG, we decided to investigate the relationship between these parameters and the intellectual status of 35 subjects with ArG found at autopsy.

Materials and methods

Brain material

Brains from 35 subjects with ArG as the main histopathological finding were investigated (for details see Table 1). Among these 35 patients, 28 were collected from 301 consecutive autopsies of patients older than 65 (cases 1–28 of Table 1). Seven additional cases (cases 29–35 of Table 1) with ArG were collected from non-consecutive autopsies.

As an inconstant finding, macroscopic examination revealed mild fronto-temporal lobe atrophy in a few cases. Old cerebral softenings, not larger than 3 cm in diameter (cases 1, 4, 7, 11, 19, 23–27 and 32 in Table 1) or deep lacunar infarcts (cases 11, 12, 20, 21, 25–27, 31, and 33) were found in 18 cases.

Brains were immersed in 4% neutral buffered formaldehyde solution pH 7.2 for 7–10 days, sliced in the coronal plane and then blocked for histopathological examination. For the present study, we used the anterior and posterior hippocampal regions on both sides of the brain. The anterior hippocampal regions included the head and body of the cornu ammonis, the dentate gyrus, the subiculum, the entorhinal/transentorhinal cortex and parts of the gyrus fusiformis near the rhinal sulcus. The posterior hippocampal region included the body and tail of the cornu ammonis, the dentate gyrus, the subiculum and the parahippocampal gyrus with adjacent temporobasal neocortex. Further regions included the frontal, fronto-orbital, rostral cingulate and occipital cortices, the striatum, the amygdala, the medial forebrain nuclei including the septal nuclei, the substantia nigra, the locus coeruleus and the cerebellum. Paraffin-embedded histological sections (4 μm) stained with hematoxylin and eosin, Holmes-Luxol (HL), periodic acid methenamine silver stain and the Gallyas silver technique [9] were used for diagnostic assessement and ArG distribution study.

Table 1 Cases with argyrophilic grain disease

Case	Age	Gender	Brain weight	Dementia	Braak stage	Other findings
1	93	f	1090 g	yes	3	v l.
2	84	f	1210 g	no	3	v l.
3	82	f	1070 g	no	1	v.l.
4	82	m	1075 g	no	2	v.l.
5	86	m	1335 g	yes	2	
6	77	m	1270 g	no	1	
7	78	f	1085 g	yes	1	v.l.
8	84	m	1280 g	yes	2	
9	70	m	1290 g	no	1	
10	82	m	1170 g	yes	3	
11	100	m	1190 g	yes	3	v.l.
12	85	f	960 g	yes	1	v.l.
13	75	f	1350 g	no	2	
14	85	m	1320 g	no	3	
15	79	f	1310 g	yes	1	
16	84	m	1410 g	no	2	
17	87	f	1070 g	yes	3	
18	85	m	1220 g	no	1	
19	67	m	1255 g	no	2	v.l.
20	92	m	1280 g	no	2	v.l.
21	84	m	1195 g	yes	3	v.l.
22	94	f	1085 g	yes	3	
23	81	f	1135 g	no	2	PD v.l.
24	88	f	1030 g	no	2	v.l.
25	77	m	1295 g	yes	3	v.l.
26	71	m	1410 g	yes	2	v.l.
27	89	f	1215 g	yes	3	v.l.
28	68	m	1320 g	no	2	
29	81	m	1235 g	no	1	
30	74	m	1255 g	yes	1	
31	91	f	1140 g	no	3	v.l.
32	82	m	1270 g	yes	1	v.l.
33	96	m	1250 g	yes	2	v.l.
34	86	f	1122 g	yes	2	
35	87	m	1250 g	yes	3	PD

Cases 1–28 were collected from consecutive, cases 29–35 from non consecutive autopsies (*v.l.* vascular lesions, *PD* idiopathic Parkinson's disease)

Clinical findings

Two of the authors (M. S., A. U. M.) – blind to the results of histological analyses – independently reviewed all available clinical informations and applied the criteria for dementia according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [1]. In addition, each patient's primary care physician was asked to fill out a questionnaire outlining the DSM-IV criteria for dementia. According to these criteria a patient was considered to have suffered from dementia when both, memory impairment and at least one of the following were present: aphasia, apraxia, agnosia, disturbance in executive functioning. These cognitive deficits must have caused significant impairment in social or

Table 2 Distribution and density of ArG in CA1-subfields, entorhinal and parahippocampal cortices in demented and non-demented patients (*ArG* argyrophilic grains, – absent, + few to moderate, ++ abundant, *l* left side, *r* right side, *ant* anterior, *post* posterior, *Enth.c.* entorhinal cortex, *Pa.hi.* parahippocampal cortex

Case	CA1 ant.l.	CA1 ant.r.	CA1 post.l.	CA1 post r.	Enth.c. l.	Enth.c. r.	Pa.hi. l.	Pa.hi. r.
Demented								
1	+	+	+	++	++	+	+	+
5	++	++	+	+	+	+	+	+
7	++	++	+	+	++	+	+	–
8	++	++	++	+	+	++	+	–
32	++	–	++	–	+	–	+	–
34	++	+	++	+	++	+	+	–
35	+	++	+	+	+	+	+	–
15	+	++	++	++	+	+	–	+
17	+	++	++	++	++	++	++	+
21	++	+	++	+	+	+	+	–
22	++	++	++	+	++	+	+	–
25	++	++	+	++	+	+	+	+
26	++	++	+	+	+	++	+	+
27	++	++	++	++	++	++	++	++
30	++	++	++	++	+	+	+	+
10	++	++	+	–	+	+	–	–
33	++	++	+	+	+	+	–	–
11	++	++	+	–	+	+	–	–
12	++	++	+	++	+	+	–	–
Non-demented								
3	++	++	+	+	++	+	+	–
14	++	++	+	+	++	++	++	++
18	++	–	+	–	+	–	+	–
20	++	++	+	+	+	++	+	–
2	++	+	+	+	+	+	–	–
16	++	+	+	–	+	–	–	–
31	++	++	+	+	+	+	–	–
24	+	+	++	–	–	–	+	–
28	++	–	+	+	–	–	–	–
23	++	++	–	–	+	–	+	–
4	+	++	–	–	+	–	–	–
6	+	++	–	–	–	++	–	–
13	++	+	–	–	+	+	–	–
19	++	–	–	–	+	+	–	–
9	++	–	–	–	–	–	–	–
29	+	+	–	–	–	–	–	–

occupational functioning. When a patient was described having functioned independently at home until shortly prior to death and/or, although hospitalized for other reasons, no cognitive disturbances were present, the patient was considered as cognitively normal.

Statistics

The densities of ArG in the cornu ammonis, entorhinal, transentorhinal and parahippocampal cortex were estimated semiquantitatively according to the following grading system: –, no grains; +, few to moderate; ++, abundant (Table 2). As no difference in the densities of grains was observed between the entorhinal and transentorhinal regions in any of the subjects of the cohort, the values obtained for these two areas were indicated as one unique value. Yates corrected χ^2 test or the student *t*test were used to compare the demented and non-demented groups.

Results

Clinical evaluation

Nineteen patients (8 females; 11 males; mean age 84.9 ± 17.5 years) were diagnosed as demented according to the DSM IV criteria. Sixteen patients (6 females, 10 males; mean age 80.8 ± 17.6 years) were considered to have been cognitively normal. Patients with dementia did not differ significantly from patients without dementia with respect to age [$t(33) = 1.65$; $P = 0.11$], or gender (Yates corrected χ^2 test < 1, not significant).

Distribution of ArG and coiled bodies

ArG were found in abundance within sector CA1 of the cornu ammonis, layer pre-β of the entorhinal/transentorhinal region, the parahippocampal cortex (for details concerning these regions see the following sections) and in the amygdaloid complex (Fig. 1). Grains were absent (22 cases) or only sparse in the granular and molecular layers of the dentate gyrus, in the sectors CA2-4 of the cornu ammonis, in the subiculum and the medial temporal isocortex. A few scatterd ArG were found in the frontoorbital cortex (2 cases), the striatum (1 case), the basal nucleus of Meynert (1 case), the septal nuclei (3 cases), the substantia nigra pars compacta (1 case) and the locus coeruleus (7 cases). ArG were specifically stained by the Gallyas method. They displayed an elongated spindle or comma-shaped body. Some grains showed spine-like protrusions and filiform appendages. Gallyas-positive coiled bodies [3, 4] were found within the white matter close to the cortical areas rich in ArG.

ArG were found in the limbic area of all cases, irrespective of the presence of a dementia. However, there

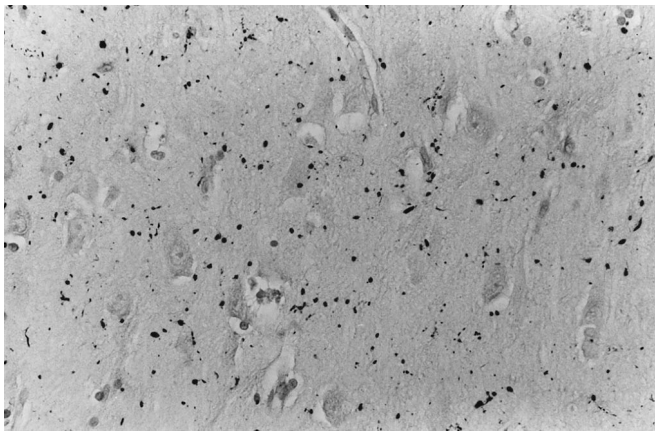

Fig. 1 Abundant diffuse argyrophilic grains in the neuropil of the anterior part of CA1. Gallyas stain, 200

were important differences in the total amount and in the distribution of ArG between demented and non-demented patients. The overall amount of ArG in structures of the limbic area was significantly higher in demented than in non-demented patients [$t(33) = 4.25$; $P < 0.0002$] (Table 2). This higher amount of ArG in demented patients was explained by higher incidence of grains in some limbic areas.

Distribution of ArG in demented and non demented subjects (Table 2)

CA1 subfield

ArG were present bilaterally in 18 of 19 demented subjects (94.7%), whereas both sides were affected in 12 out of 16 (75%) non-demented subjects. Abundant grains were found at least on one side in 18 (94.7%) of the demented subjects and in 14 (87.5%) of the non-demented. In contrast to the rostral half of the CA1 sector, a significant difference was found in the caudal half of CA1. Whereas all demented patients showed ArG (84.2% on both sides), the caudal part of CA1 was affected in only 9 (56,3%) of the non-demented patients (Yates corrected χ^2test = 10.39; $P < 0.01$]. Moreover, the densities of grains in the caudal cornu ammonis was higher in demented than in non demented subjects with ArG in this area. Thus, 12 (63.2%) of the demented subjects showed abundant grains (at least on one side), whereas high numbers of ArG were found in only 1 of the non-demented patients on one side (6.3%).

Entorhinal/transentorhinal and parahippocampal cortices

Demented patients showed more severe and more frequent involvement of the entorhinal/transentorhinal region than the non-demented. This cortical region was affected in all demented patients, and in 18 (94.7%) it was involved bilaterally. However, among cases with AgD without dementia, ArG were found in only 12 (75%) in this area (Yates corrected χ^2test = 5.36; $P < 0.05$). High densities of grains were found in 7 (36.8%) of the demented and in 4 (25%) of the non-demented subjects on at least one side.

In the more caudal parahippocampal cortex, as in the caudal half of sector CA1, grains were found more frequently and in a higher density in demented than in cognitively intact patients. Among demented subjects, ArG were found in 15 (78.9%), whereas in AgD cases without dementia the parahippocampal cortex was affected in only 6 (37.5%) cases (Yates corrected χ^2test = 6.21; $P < 0.05$). A high amount of ArG in this area was found in only 2 (10.5%) of the demented and in 1 (6.3%) of the non-demented AgD cases.

In summary, AgD cases with dementia showed more abundant ArG and a more widespread rostrocaudal extension of ArG in the limbic area than cases without dementia.

Additional neuropathological findings

Mild to moderate changes of the Alzheimer type were found in all AgD cases. They consisted of scattered NFT and NTh. The distribution of NFT corresponded to early Braak stages (Braak stage I) in 10 cases (28%), to Braak stage II in 13 cases (37%) and to Braak stage III in 12 cases (35%) (for details see Table 1) [6]. In only 19 cases (54.3%) were a few scattered senile plaques found in the hippocampal formation and the neocortex, whereas no plaques at all could be detected in 16 cases (45.7%). Braak stages did not significantly differ in patients with dementia and in those without dementia. Two cases with clinically known Parkinson's disease showed loss of pigmented cells and Lewy body inclusions in the substantia nigra (cases 23 and 35). None of our AgD cases showed a superficial cortical spongiosis which has been reported recently as an inconsistent finding in some AgD cases [12]. Furthermore, we were unable to find a subcortical gliosis [11, 18], or the presence of subcortical tangles in a distribution suggestive of PSP [13].

Discussion

The presence of a late onset dementia was the clinical hallmark of all previously reported AgD cases [4, 5, 10, 11, 13, 18]. However, as recently shown in a series of 301 consecutive autopsies of patients older than 65, ArG, despite being a main histopathological feature in 28 (9%), were associated with a late onset dementia in only 14 of these cases (50%) [17]. In a recent study by Martinez-Lage et al. [12], ArG were found as the only morphological change in 11 out of 300 unselected autopsies of individuals older than 30 years. All subjects with ArG were older than 68 years and intellectual decline was documented in only 2 subjects

The main finding in our AgD cases consisted of a significantly more widespread rostrocaudal extension of ArG change in the limbic area in subjects with documented intellectual decline than in cognitively normal subjects. Whereas no differences in distribution and density of ArG could been found in the rostral part of CA1, the caudal CA1 was significantly more often affected in AgD cases with dementia. In addition, ArG were significantly more widespread in the entorhinal/transentorhinal region and the parahippocampal cortex of demented patients. None of our AgD cases showed an exclusive involvement of the posterior hippocampal region without an involvement of the anterior region. This suggests that early changes in AgD might begin in the rostral hippocampus. At a later stage of the disease a more widespread distribution of the ArG change with an involvement of the caudal hippocampal formation would result in a late onset dementia. Presently the mechanisms responsible for this time related

distribution of ArG within the hippocampus and adjacent areas remain unknown.

The simultaneous occurrence of morphological features pertaining to different degenerative entities constitute a frequent finding. Masliah et al. [13] reported on five AgD cases which were all associated with subcortical tangles and threads in a distribution suggestive of PSP. In addition, Martinez-Lage et al. [12] found ArG in eight out of ten PSP cases and suggested ArG as a possible manifestation of PSP. Some ArG were also observed in cases of Pick's disease and corticobasal degeneration [10, 12]. However, none of our AgD cases demonstrated morphological features suggestive of PSP, cortico-basal degeneration or Pick's disease. We were also unable to find ArG in previously published cases of PSP, Pick's disease and frontal lobe degeneration [14–16]. Subcortical gliosis, as reported previously by Itagaki et al. [11] and Yamada et al. [18], was absent in all our AgD cases. In two AgD cases we found typical changes of idiopathic Parkinson's disease, an association already reported by some authors [5, 8, 10, 17].

ArG are often associated with changes of Alzheimer type. ArG have, therefore, been considered one manifestation of AD [7]. Braak and Braak [5] found ArG as the most salient histopathological feature in 28 of 80 old demented patients. Among these cases, 10 showed ArG as the only pathological finding, while 16 presented additional changes of the Alzheimer type with a distribution of NFT corresponding to Braak stages III and IV [6]. Our AgD cases showed mild changes of the Alzheimer type, consisting of scattered NFT and NTh. In only half of the cases were few senile plaques found in the hippocampus and the neocortex. The distribution of NFT was quite similar in demented and non-demented patients and corresponded to early Braak stages (65% entorhinal stage I and II, 35% limbic stage III). We therefore suggest that the mental deterioration observed in a subgroup of patients with AgD is caused by the progressive rostrocaudal involvement of the hippocampal formation in the course of the disease. As mentioned above, our findings suggest that early lesions of AgD might be located in the rostral part of CA1. This contrasts with AD, where early neurofibrillary lesions are typically located in the entorhinal/tranentorhinal cortex ("group 1 neurons", Braak stages I–II) later extending to limbic structures (Braak stages III-IV), with an only mild involvement of CA1, into the late isocortical stages (Braak stages V and VI) [3, 6].

Beside the frequent changes of the Alzheimer type in AgD cases, the hyperphosphorylated microtubule-associated protein tau in ArG and coiled bodies has been shown to share a number of phosphorylated sites with NFT and NTh of AD [10, 11, 13, 17, 17]. Furthermore, we recently demonstrated a widespread hyperphosphorylation of the tau protein in the somatodendritic domain of limbic neurons in AgD cases [17]. However, although the intraneuronal distribution of hyperphosphorylated tau looks similar to "stage 0 tangles" of Bancher [2] and "group 1 neurons" of Braak [3], which have been considered as possible precursor stages of neurofibrillary degeneration, hyperphosphorylation of tau in the somatodendritic domain in AgD, unlike in AD, is not associated to the formation of NFT, even in presence of widespread ArG in the cortical neuropil.

In conclusion, our findings suggest that AgD is, indeed, a distinct disease entity separated from other neurodegenerative disorders like AD, PSP, Pick's disease or corticobasal degeneration. Moreover, we suggest that AgD is a progressive neurodegenerative disorder with early subclinical lesions in the anterior part of the hippocampal formation. At later stages involvement of the more caudal parts of the hippocampal formation generally results in an intellectual decline. Rostrocaudal extension of ArG in the hippocampal formation has to be evaluated in AgD cases to provide more accurate clinicopathological correlation in each individual case.

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