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CASE REPORT

**K. Tsuchiya · K. Mitani · T. Arai · S. Yamada
T. Komiya · Y. Esaki · C. Haga · H. Yamanouchi
K. Ikeda**

Argyrophilic grain disease mimicking temporal Pick's disease: a clinical, radiological, and pathological study of an autopsy case with a clinical course of 15 years

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Abstract This report concerns an autopsy case of argyrophilic grain disease (AGD) mimicking temporal Pick's disease. The patient was a Japanese woman without hereditary burden who was 89 years old at the time of death. She developed memory impairment and began wandering at the age of 74, followed by prominent character changes about 6 years after disease onset. A neurological examination 5 months before her death revealed poor rapport, unconcern, severe dementia, and double incontinence, without aphasia or muscle rigidity. Serial neuroradiological examination revealed progressive enlargement of the bilateral inferior horns of the lateral ventricle, reflecting progressive atrophy of the medial temporal lobes. Macroscopically, neuropathological examination showed circumscribed atrophy of the bilateral amygdalae, hippocampi, parahippocampal gyri, and lateral occipitotemporal gyri. Histologically, there was neuronal loss in the areas mentioned above, the caudate nucleus, putamen, thalamus, substantia nigra, and locus ceruleus, with ballooned neurons in the cerebral cortex and amygdala. Numerous argyrophilic grains with coiled bodies were present not only in the limbic system, but also in the affected cerebrum. Rare neurofibrillary changes were present in the limbic areas, consistent with Braak stage II, with no senile plaques. Based on these findings and a review of the literature, we note that AGD is clinicopathologically similar not only to mesolimbocortical dementia, but also to atypical senile dementia of Alzheimer type. This report may contribute to the elucidation of the clinicopathological hallmarks of AGD.

Keywords Argyrophilic grains · Alzheimer's disease · Circumscribed atrophy · Mesolimbocortical dementia · Pick's disease

K. Tsuchiya (✉)
Department of Laboratory Medicine and Pathology,
Tokyo Metropolitan Matsuzawa Hospital,
2-1-1, Kamikitazawa, Setagaya-ku, Tokyo, 156-0057, Japan
Tel.: +81-3-33037211, Fax: +81-3-33045109

K. Tsuchiya · C. Haga · K. Ikeda
Department of Neuropathology, Tokyo Institute of Psychiatry, Tokyo, Japan

K. Mitani · T. Komiya · H. Yamanouchi
Department of Neurology,
Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

T. Arai · Y. Esaki
Department of Pathology, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

S. Yamada
Department of Neuropathology,
Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

Introduction

Argyrophilic grains (AG) were originally described as a novel neuropathological finding in patients with progressive late-onset dementia who lacked sufficient numbers of Alzheimer-type lesions to warrant the morphological diagnosis of Alzheimer's disease [1, 2, 3]. AG consist of minute, spindle- or comma-shaped argyrophilic structures in the neuropil, which are not only Gallyas stained and tau immunoreactive, but also distinct from neuropil threads and both flame-shaped and extracellular ghost tangles. Argyrophilic grain disease (AGD), also referred to as dementia with grains or argyrophilic grain dementia, has been considered to be a progressive disorder that may or may not be associated with dementia, with the grains being the only morphological substrates of cognitive decline [4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 20]. The clinical aspects of AGD have scarcely been mentioned, except for the study reported by Ikeda et al. [5, 6, 7]. The clinicopathological correlations of AGD remain to be elucidated [7, 9].

We report here a Japanese autopsy case of AGD with a clinical course of 15 years, in which clinical signs simulated those of temporal Pick's disease and neuroradiological examination revealed progressive atrophy of the bilateral medial temporal lobes [18]. Neuropathological examination revealed not only macroscopically prominent atro-

phy of the medial temporal lobes, but also neuronal loss and astrocytosis in the cerebral cortex, limbic system, striatum, thalamus, substantia nigra, and locus ceruleus. There were also ballooned neurons in the cerebral cortex and amygdala, as well as a massive appearance of argyrophilic grains and coiled bodies. Furthermore, we addressed the clinicopathological similarities among AGD, mesolimbocortical cortical dementia [19], originally reported by Torack and Morris [17], and senile dementia of Alzheimer type characterized by laminar neuronal loss exclusively in the hippocampus, parahippocampus and medial occipitotemporal cortex reported by Mizutani et al [12]. Our case verifies the diversity of clinicopathological features concerning AGD.

Case report

The patient was a Japanese woman who was 89 years old at the time of death. She had no family history of dementia or neurological disease. The patient presented with amnesia, disorientation, and aimless wandering at the age of 74. At the age of 79, she suffered a subarachnoid hemorrhage. Thereafter, she developed character changes, including violent, egocentric, stubborn behavior and apathy. The character changes became progressive. At the age of 82, she was admitted to a geriatric hospital because care at home

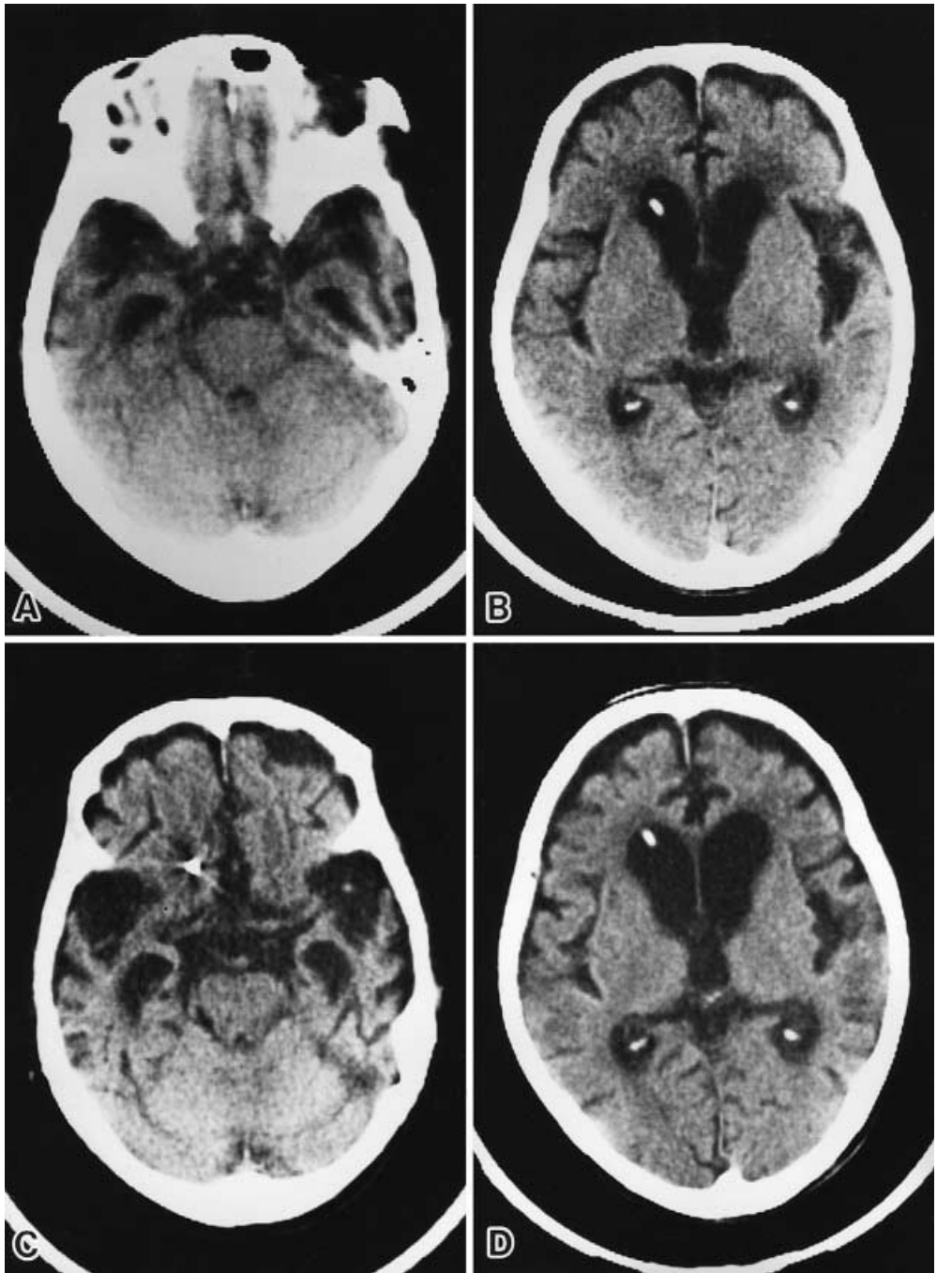


Fig. 1A–D Brain computed tomography showing progressive atrophy of the bilateral temporal lobes. **A**, **B** About 9 years after disease onset, **C**, **D** about 14 years after disease onset

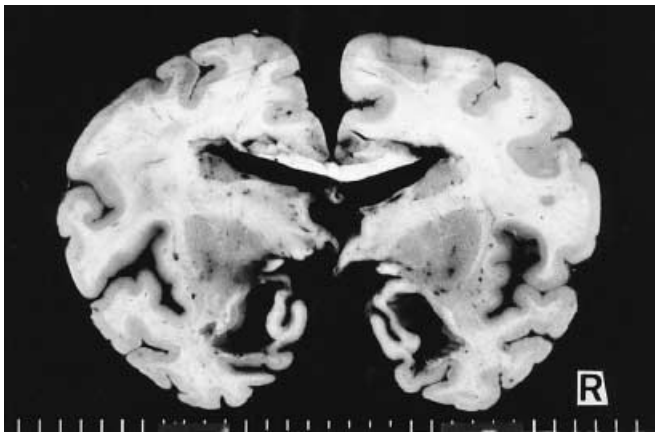


Fig. 2 Coronal section through the posterior part of the amygdala showing prominent atrophy of the bilateral amygdalae, hippocampi, parahippocampal gyri, and lateral occipitotemporal gyri (*R* right side of brain)

became impossible. At this time, she was bedridden. Neurological examination at the age of 88, 5 months before her death, showed poor rapport, unconcern, callous expression, severe dementia, agnosia, and double incontinence, without aphasia or muscle rigidity. She died of a subarachnoid hemorrhage due to a ruptured saccular aneurysm of the right posterior inferior cerebellar artery, about 15 years after the onset of the disease. She was clinically diagnosed as having temporal Pick's disease.

Neuroradiological findings

Brain computed tomography (CT) at age 83, about 9 years after disease onset, revealed obvious enlargement of the inferior horns of the lateral ventricles and the after-effects of a ventriculoperitoneal shunt due to a subarachnoid hemorrhage at age 79 (Fig. 1a, b). Brain CT at the age of 88 revealed prominent enlargement of the inferior horns of the lateral ventricles, reflecting progressive atrophy of the medial temporal lobes (Fig. 1c, d).

Neuropathological findings

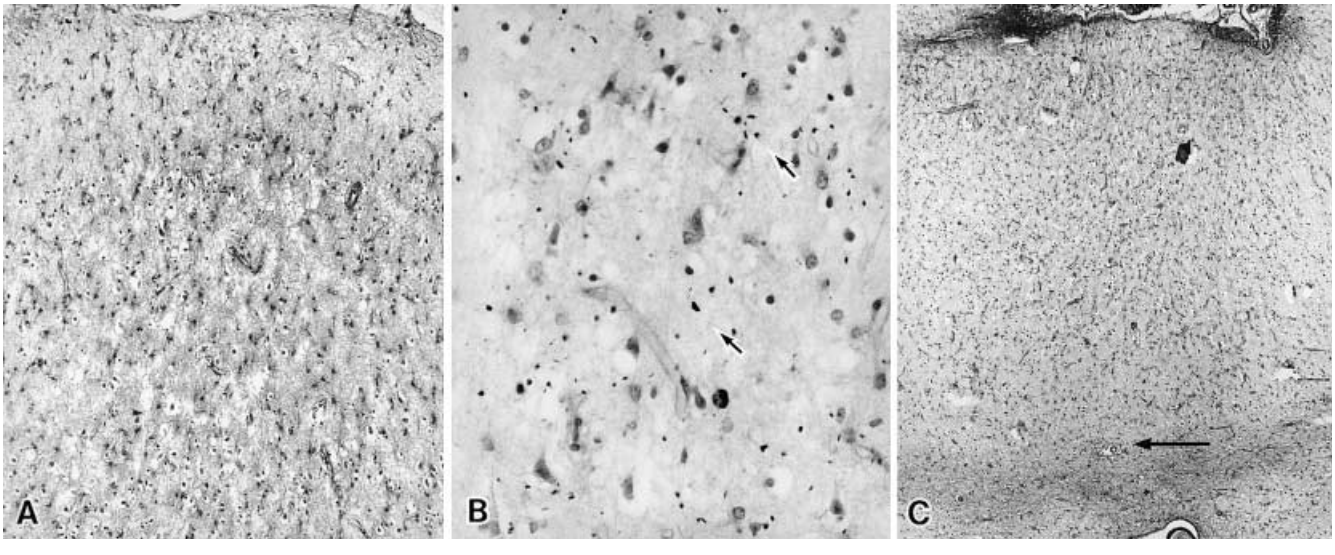
The weight of the brain was 1,250 g. Macroscopic examination showed circumscribed atrophy of the bilateral medial temporal lobes, including the amygdalae, hippocampi, parahippocampal gyri, and lateral occipitotemporal gyri, in addition to the recent widespread subarachnoid hemorrhage which caused her death (Fig. 2). Histological examination revealed obvious neuronal loss with astrocytosis and laminar spongiosis, predominantly seen in layer II in the cerebral cortex, including the orbital gyrus, rectal gyrus, oral and ventral portion of the insular gyrus, cingulate gyrus, parahippocampal gyrus, and lateral occipitotemporal gyrus (Fig. 3a). There was obvious fibrillary gliosis in the cerebral white matter subjacent to the involved cortex (Fig. 3c). The CA1 region and subiculum of the hippocampus, and amygdala, prominently in the basolateral group, showed prominent neuronal loss. Obvious neuronal loss was observed in the caudate nucleus, putamen, dorsomedial nucleus of the thalamus, substantia nigra, and locus ceruleus.

Widespread AG were found in the cerebral cortex, except for the occipital lobe, hippocampus, parahippocampus, amygdala, caudate nucleus, and putamen (Fig. 3b). Ballooned neurons were present in the superior frontal gyrus, cingulate gyrus, and amygdala (Fig. 4). Coiled bodies were found in the cerebral white matter subjacent to the involved cortex. A small number of neurofibrillary tangles (NFT) were present in the limbic areas, compatible with Braak stage II [3]. There were no senile plaques. There was no specific neuronal damage with NFT in the globus pallidus, subthalamic nucleus, substantia nigra, midbrain tegmentum, or dentate nucleus, suggesting the neuropathology of progressive supranuclear palsy.

Discussion

As mentioned in the introduction, the clinical aspects of AGD have been scarcely reported. According to Ikeda et al. [7], who conducted a detailed clinicopathological examination of three Japanese autopsy cases of AGD, emotional and personality changes with a mild degree of dementia were the clinical characteristics. In addition, they reported that Klüver-Bucy syndrome was not noted [7]. In

Fig. 3 Insular gyrus showing prominent neuronal loss (**A**), massive appearance of argyrophilic grains (*small arrow*, **B**), and subcortical gliosis (**C**). The demarcation between the cerebral cortex and cerebral white matter is represented by a *large arrow*. **A** H&E stain, **B** Gallyas stain, **C** Holzer stain; **A** ×50, **B** ×200, **C** ×20



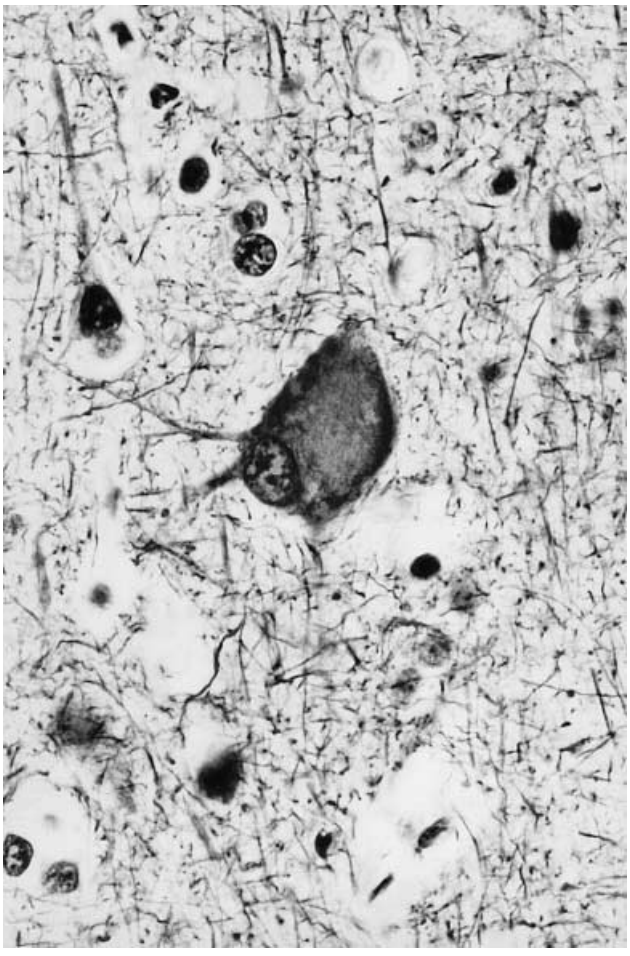


Fig. 4 Ballooned neuron in the first frontal gyrus. Bodian stain, ×860

1998, Braak and Braak [4] conducted a detailed pathological study on 48 cases of AGD, including 17 cases with dementia and only subtle concomitant Alzheimer-type pathology (Braak stages I–II), and reported that the clinical records of the 17 cases generally revealed an early onset of inappropriate social conduct and personality changes preceding memory failure and cognitive decline. Furthermore, they noted that in such patients, the emotional imbalance overshadowed the decline in intellectual capacities, and that the patients occasionally exhibited marked restless and psychotic episodes, but that, as time passed, dementia predominated and the patients soon became doubly incontinent. Based on a review of the literature concerning the clinical features of AGD, we speculate that in the early to middle stages of the disease, emotional and personality changes are the dominant clinical features of AGD, reflecting the prominent involvement of the limbic system.

It is generally believed that, macroscopically, the brains of patients with AGD may be unchanged or show mild diffuse and/or frontotemporal atrophy [9]. In 1997, Tolnay et al. [14], who examined widespread hyperphosphorylation of tau protein in the limbic neurons in 41 cases of AGD, found that gross examination of the brain in these patients revealed mild temporal lobe atrophy in only a few cases. Furthermore, in 1998, Braak and Braak [4] noted that upon gross examination, the brains of AGD cases appeared virtually unchanged or only mildly atrophic, and apparently did not differ from those of age-matched, mentally unimpaired controls. However, they noticed that in AGD the anteromedial portion of the temporal lobe bore the brunt of the lesions. On the basis of a literature review, we concluded that our case was an atypical case, showing macroscopically prominent atrophy of the medial temporal lobe not described previously.

The prominent neuropathological features in our case were not only the widespread occurrence of AG in the limbic system, frontotemporal cortex, and striatum, but also the presence of subcortical gliosis subjacent to the involved cortex and amygdala. There has been debate as to whether or not there is subcortical gliosis in AGD. In 1992, Yamada et al. [20], who reported detailed immunohistochemical and biochemical studies on two autopsy cases of AGD without significant Alzheimer-type pathology, including an autopsy case reported by Itagaki et al. [8], reported that in their cases there was slight to moderate subcortical gliosis. In contrast, Tolnay et al. [15], who examined the limbic area in 19 demented patients with AGD and 16 non-demented patients with AGD, reported that the distribution of AG in the entorhinal/transentorhinal and parahippocampal cortices was more widespread in the group of dementia patients. In addition, they reported that subcortical gliosis, as reported previously by Itagaki et al. and Yamada et al., was absent from all their AGD cases. We think that subcortical gliosis is due to the severity of cortical lesions, and that accumulation of cases with a long clinical course may elucidate this point.

One of the pathological hallmarks in our case was the presence of slight Alzheimer-type changes: the neurofibrillary changes were consistent with stage II of Braaks' classification, with the absence of senile plaques. Therefore, it seems unlikely that Alzheimer-type lesions caused clinical signs in our case. Although pathologically AGD constitutes a well-defined disease entity, its nosological status is still unclear because most of reported AGD cases are associated with Alzheimer-type changes [16]. Our case strongly supports the speculation by Tolnay et al. [16] that AGD is a clinical and pathological entity, independent of Alzheimer's disease.

Mesolimbocortical dementia is a rare clinicopathological disorder [17, 19]. Torack and Morris [17] reported the clinical and pathological findings of a woman, 64 years old at death, who developed character changes, including irritability and hypersexuality at the age of 57, followed by progressive dementia and parkinsonism. A neuropathological examination revealed neuronal loss with gliosis not only in the limbic system, including the amygdala, subiculum, parahippocampal gyrus, orbital cortex, and cingulate cortex, but also in the caudate nucleus, putamen, and substantia nigra, with an absence of NFT and senile plaques. In 1990, Verity et al. [19] reported two patients with mesolimbocortical dementia, who were 78 and

68 years old at onset, respectively. Both cases were characterized by late-onset slowly progressive personality changes and progressive intellectual deterioration without parkinsonism. A neuropathological examination showed neuronal loss with gliosis, not only in the limbic system, including the amygdala, hippocampus, subiculum, and parahippocampal gyrus, but also in the caudate nucleus, thalamus, and substantia nigra, without NFT. Mizutani et al. [12] reported seven cases of senile dementia of Alzheimer type (SDAT) with unusual clinicopathological findings, of which the main clinical features were character changes, while cranial CT showed marked dilatation of the oral portion of the inferior horn of the lateral ventricle in the early stage. They noted that in their cases, neuronal loss with gliosis was exclusively confined to the CA1 region of the hippocampus, parahippocampal gyrus, and lateral occipitotemporal gyrus, with NFT and senile plaques being less marked than those usually found in SDAT. Furthermore, they described that in four of the seven cases, the substantia nigra showed moderate loss of pigmented neurons with Lewy bodies in one case, and that in six cases the locus ceruleus revealed moderate to severe loss of pigmented neurons. Based on a review of the literature on mesolimbocortical dementia and atypical senile dementia reported by Mizutani et al., we speculate that the mesolimbocortical dementia and atypical senile dementia they reported were clinicopathologically similar to our case, particularly in regard to the distribution pattern of neuronal loss with astrocytosis in the central nervous system.

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