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ORIGINAL COMMUNICATION

Prominent psychiatric symptoms in patients with Parkinson's disease and concomitant argyrophilic grain disease

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Abstract In Parkinson's disease (PD), cognitive decline and psychiatric symptoms may occur and very often co-exist, eventually leading to PD-dementia. We report three patients with PD who presented striking psychiatric manifestations along with mild cognitive decline not progressing to dementia across the course of disease and in which postmortem neuropathological study revealed, besides alpha-synuclein inmunoreactive Lewy-body pathology, concomitant four-repeat tau positive argyrophilic grain pathology. We consider that argyrophilic grains might have modulated the clinical presentation of PD in these patients, being the main substrate of their prominent psychiatric symptoms in the absence of definite dementia.

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Introduction

Argyrophilic grain disease (AgD) is a sporadic neurodegenerative disorder associated with old age that may account for 5 % of all dementia cases or a greater percentage if only aged individuals are considered [1, 2]. Neuropathologically, it is characterized by the presence of argyrophilic grains in neuronal processes and coiled bodies in oligodendrocytes, primarily located in limbic structures, especially the hippocampus, the entorhinal and transentorhinal cortices and the amygdala, where frequent ballooned neurons can also be detected [3, 4]. Argyrophilic grains contain hyperphosphorylated tau protein, with a predominance of four repeat (4R) tau isoforms [5]. A mild form of dementia with prominent mood and behavioural disturbance, as well as personality changes, aggressiveness and psychosis, has been proposed as a distinct clinical picture of AgD [6, 7]. Argyrophilic grains have been described in association with several pathologies, including Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy, Creutzfeldt–Jakob disease, senile dementia with tangles, progressive supranuclear palsy, corticobasal degeneration, Pick's disease and limbic TDP-43 pathology, and can also be encountered even in cognitively normal subjects [1, 8–10]. When co-occurring with other neurodegenerative diseases, AgD clinical features might be masked.

Here we report the unusual features of three patients with PD, later confirmed as PD and AgD, and which, in hindsight, might have raised the suspicion of the presence of underlying argyrophilic grain disease.

Materials and methods

Subjects and clinical information

We retrospectively reviewed the medical records of brain donors with PD from the Neurological Tissue Bank from the Biobanc-Hospital Clinic-IDIBAPS (NTB-IDIBAPS) in whom neuropathologic examination revealed the presence of AgD, in addition to PD-related pathology. To put these findings in perspective, we also reviewed the clinico-pathological associations of all cases with AgD from the brain bank, as well as the medical records of neuropathologically confirmed PD cases without AgD followed at the Movement Disorders Unit of our hospital, paying special attention to psychiatric manifestations.

Neuropathological examination

Neuropathologic studies were performed after obtaining the written informed consent for the use of brain tissue for diagnostic and research purposes. For neuropathological work-up, one half-brain was sliced in 0.5-cm-thick sections, immediately frozen and kept at −80 °C. The other half-brain was fixed in 10 % buffered formaldehyde solution for 4 weeks. At least 25 brain areas were selected for histopathological evaluation according to our standardized protocol and included frontal, temporal, parietal and occipital cortices, anterior cingulate, anterior and posterior basal ganglia, anterior, medial and posterior thalamic nuclei, hippocampus, amygdala, midbrain, pons, medulla oblongata, olfactory bulb, cerebellar vermis and dentate nucleus, and cervical, thoracic and lumbar spinal cord.

Five-micrometer-thick sections were obtained from each brain area and were stained with hematoxylin-eosin (HE) and by immunohistochemistry using the following monoclonal (mc) and polyclonal (pc) antibodies: anti-bA4-amyloid (DAKO, Glostrup, Denmark, mc, clone 6F/3D, dilution 1:400), anti-phosphorylated tau (Thermo Scientific, Rockford, IL, USA; mc, clone AT8, dilution 1:200), ubiquitin (DAKO, pc, dilution 1:400), alpha-synuclein (Novocastra, Newcastle, UK, mc, clone KM51, dilution 1:500), TDP-43 (Abnova, Taipei, Taiwan, mc, clone 2E2-D3, dilution 1:500), anti-RD3 (Millipore, Billerica, MA, USA, mc, clone 8E6/C11, dilution 1:1000), anti-RD4 (Millipore, mc, clone 1E1/A6, dilution 1:50), anti-alpha-internexin (Invitrogen, Camarillo, CA, USA, mc, clone 2E3, dilution 1:800), and anti-alpha-B-crystallin (Novocastra, mc, clone G2JF, dilution 1:100). Staging of Parkinson's disease-related pathology was performed on alpha-synuclein stained sections according to Braak's classification as stages 1–6 and staging of argyrophilic grains was performed on AT8 and RD4-tau stained sections according to Saito et al. [11, 12] as stage I, II or III.

Table 1 Summary of demographic and clinical features of PD patients with ($n = 3$) and without ($n = 23$) AgD

	Patient 1	Patient 2	Patient 3	PD with AgD (mean or %)	PD without AgD (mean or %)
Delusions	Yes	Yes	Yes	100 %	48 %
Visual hallucinations	Yes	Yes	Yes	100 %	65 %
Auditory hallucinations	No	Yes	No	33 %	9 %
Behaviour disorder	Yes	Yes	Yes	100 %	44 %
Aggressiveness/irritability	Yes	No	Yes	67 %	30 %
Depression	Yes	Yes	Yes	100 %	48 %
Suicidal ideation/suicide attempt	Yes	No	Yes	67 %	4 %
Anxiety	Yes	Yes	Yes	100 %	40 %
Cognitive impairment	Mild amnestic	Mild disexecutive	No	NA	NA
Dementia	No	No	No	0 %	65 %
Response to antipsychotic drugs	Partial	Good	Good	NA	NA
Time from onset of parkinsonism to depression (years)	2	7	2	3.7	3.6
Time from onset of parkinsonism to psychotic symptoms (years)	15	7	11	11	12.1
Time from first psychotic symptom to dementia	NA	NA	NA	NA	1.8 years
Total disease duration (years)	20	22	13	18.3	13.7
Age at death	71	69	83	74.3 years	76.8 years

PD Parkinson's disease, *AgD* argyrophilic grain disease, *NA* not applicable

Results

We identified four patients with PD and concomitant AgD from a total of 60 neuropathologically confirmed PD cases. Three out of these four cases, as well as 23 PD cases without AgD, had been followed during several years at the Movement Disorders Unit of our hospital and therefore had detailed clinical information available (Table 1). On the other hand, we identified 34 cases with AgD among 1,400 brains of the brain bank cohort (2.4 %) with a mean age of 78 years (range 58–98 years) and with the following age distribution: <60 years: 3 %, 61–70 years: 15 %, 71–80 years: 41 % and >80: 41 %. Except for two that were considered "pure" forms ($n = 2/34$; 6 %), the others were associated with different neurodegenerative diseases: e.g. AD ($n = 9/34$; 26 %), tauopathies ($n = 7/34$; 20 %), PD ($n = 4/34$; 12 %), DLB ($n = 4/34$; 12 %), CJD ($n = 4/34$; 12 %), vascular pathology ($n = 2/34$; 6 %) and FTLD-TDP ($n = 2/34$; 6 %).

Patient 1

This 54-year-old woman was first visited because of rigidity and tremor in her left limbs having started 3 years before. She had also experienced depressive symptoms during the previous year. She was treated with levodopa and several dopamine agonists in different combinations, initially with good response. At the age of 61 years she tried to commit suicide. Depressive symptoms persisted, despite treatment with several antidepressants. At the age of 66, while staying in a nursing home because of worsening of her parkinsonian symptoms, she presented episodes of anxiety, irritability, visual hallucinations (she saw her late husband) and abnormal behaviour (e.g., escaping from the medical centre, shouting and dancing in inappropriate situations and compulsively shopping).

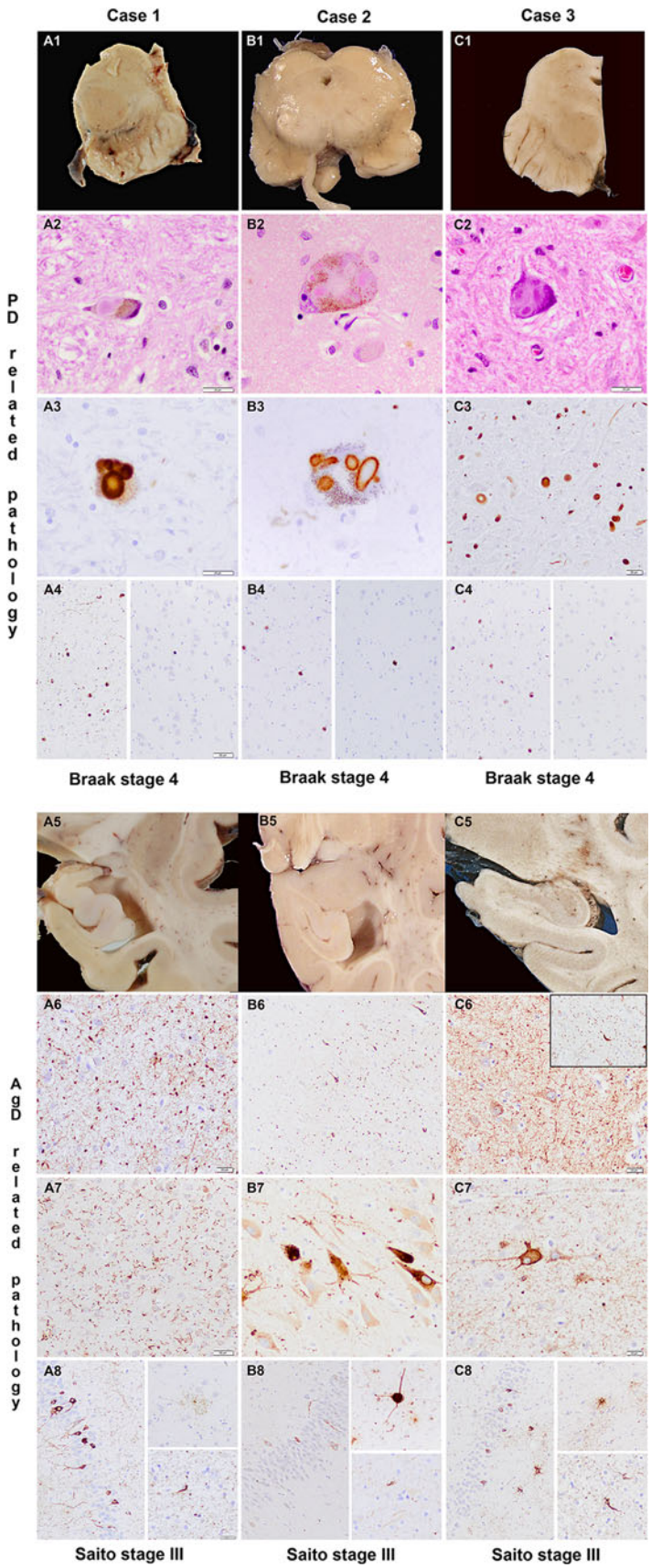
She was treated with quetiapine, with initial good response, and the following months developed a paranoid delusion towards her family with dramatic worsening of her anxiety, including panic attacks and occasional aggressiveness. None of these episodes was preceded by any medication changes, neither occurred during a delirium caused by any medical condition. She died at the age of 71 years due to a respiratory infection. She scored 29/30 in a Mini Mental State Exam 14 years after the onset of motor symptoms, and the last 3 years of her life, she experienced mild memory impairment, without other cognitive deficits, but no signs of dementia were noticed during the entire follow-up period.

Neuropathologic study

Unfixed brain weight was 1.130 g. Moderate, temporally accentuated brain atrophy was observed macroscopically with widening of sulci. There was a moderate pallor of substantia nigra and locus coeruleus (Fig. 1a1). Histologically, alpha-synuclein immunoreactive Lewy-body pathology (Lewy-bodies, Lewy neurites, diffuse and granular cytoplasmic staining) involving intermediolateral column of spinal cord, pigmented and non-pigmented brain stem nuclei, basal forebrain nuclei, amygdala, ento- and transentorhinal cortex, and only few in frontal cortex were observed, corresponding to a Braak stage 4 of Parkinson's disease related pathology (Fig. 1a2–a4). In addition, abundant AT8 positive grains immunoreactive for four-repeat tau isoforms and negative for three-repeat tau isoforms (Fig. 1a6–a7), were observed in amygdala, entorhinal and transentorhinal cortex and in CA1 sector of the hippocampus, cingulum and insula, with abundant pretangles bush-like and ramified astrocytes and oligodendroglial coiled bodies (Fig. 1a8), as well as some ballooned cells amygdala, corresponding to stage III of argyrophilic grain pathology according to Saito et al. [11]. In addition to these findings, we found moderate Alzheimer-type pathology with moderate diffuse and mature beta-amyloid deposits and an amyloid phase 4 according to Thal et al. with mild amyloid angiopathy, moderate neuritic plaques (CERAD age-related plaque score B) and neurofibrillary pathology confined to the limbic system (Braak stage III), corresponding to an a3, b2, c2 score according to the current NIA/AA guidelines. [13].

Patient 2

A 54-year-old woman was referred to our hospital because of an asymmetric tremoric-akinetic syndrome that had started 7 years before. She reported having experienced anxiety since several years before the onset of motor symptoms. One month after her first visit, she was admitted to a Psychiatry Department because of major depression with psychotic features, which included ideation of ruin. She had been treated with stable doses of levodopa and dopamine agonists the last months before admission. Psychiatric symptoms improved with thioridazine. Two years later, following an increase in the dose of dopamine agonists, she presented delusional ideas, which disappeared within a week of down titration of the antiparkinsonian medication and starting treatment with fluvoxamine and risperidone. However, the latter was removed because of motor impairment, which led to worsening of her depressive symptoms followed by the appearance of abnormal behaviour, and delusional ideation, including catastrophic and guilt thoughts, auditory hallucinations, agoraphobia, anxiety and restlessness. She was successfully treated with clozapine and imipramine, allowing for clozapine withdrawal 1 year later. Ten years after this episode, and following an intraduodenal levodopa-gel test, she suddenly


Case 1
Case 2
Case 3
A1
B1
C1
A2
B2
C2
A3
B3
C3
A4
B4
C4
PD related pathology
Braak stage 4
Braak stage 4
Braak stage 4
A5
B5
C5
A6
B6
C6
A7
B7
C7
A8
B8
C8
AgD related pathology
Saito stage III
Saito stage III
Saito stage III

◀ **Fig. 1** Representative gross and histopathological images of the three patients. First column (**a1–a8**) represents patient 1, second column (**b1–b8**) represents patient 2 and third column (**c1–c8**) represents patient 3. **a1–a4**, **b1–b4** and **c1–c4** correspond to Parkinson's disease related pathology while **a5–a8**, **b5–b8** and **c5–c8** correspond to argyrophilic grain pathology. **a1**, **b1** and **c1**: macroscopic aspect of substantia nigra at the level of the third cranial nerve of the three patients showing marked pallor in case 2 (**b1**) and 3 (**c1**) and moderate pallor in case 1 (**a1**). **a2**, **b2** and **c2**: frequent eosinophilic intraneuronal cytoplasmic inclusions in form of Lewy bodies were detected in H&E stained sections in pigmented neurons of substantia nigra and locus coeruleus, which were strongly immunoreactive for alpha-synuclein (**a3**, **b3**, **c3**). **a4**, **b4**, **c4**: alpha-synuclein immunoreactive Lewy-bodies and Lewy neurites were detected in amygdala (*left panel*) in all three cases and were abundant in case 1 (**a4**), and moderate in case 2 (**b4**) and 3 (**c4**). In contrast, only very isolated and tiny alpha-synuclein aggregates were detected in frontal cortex (*right panel* of **a4**, **b4** and **c4**). **a5–c8**: concomitantly, mild atrophy of anterior hippocampus (**a5**, case 1), amygdala (**b5**, case 2) and better preserved posterior hippocampus (**c5**, case 3) was seen. **a6–a8**, **b6–b8** and **c6–c8**: abundant tau (AT8) immunoreactive grains, neuropil threads and pretangles (**b7**) were detected in the limbic system in all cases, mainly in amygdala, entorrhinal cortex, and CA1 sector of the hippocampus. Grains were strongly immunoreactive for four-repeat tau isoforms (**a7**, **b6** and **c6** inset). Moderate amount of ring-like cytoplasmic immunoreactivity of granule cells of dentate gyrus was observed (**a8**, **b8** and **c8**). In addition, some ballooned neurons immunoreactive for alpha-B-crystallin and AT8 (**c7** and **b8** *upper right*) were detected in amygdala. AT8 positive oligodendroglial coiled bodies (**a8**, **b8** and **c8** *lower right*) as well as bush-like astrocytes (**a8** and **c8**, *upper right*) were observed. Scale bars: 20 μm for **a2–c2**, **b3–c3**; **a6**, **c6**, **b7**, **c7**; **a8–c8**: *right figures* 50 μm for **a4–c4**, **a7**, **b6**; **a8–c8** *left figures*

showed anxious and depressive symptoms, emotional lability, confusion and visual hallucinations. The disproportionate fear to this test the days before and the subsequent predominance of anxiety over other psychiatric manifestations led not to consider this episode as an intraduodenal levodopa side effect. Moreover, the anti-parkinsonian treatment had been adjusted in a way that the equivalent daily levodopa dose was inferior to her drug regime before admission. She was treated with quetiapine, which significantly ameliorated her symptoms and did not exhibit any other major psychiatric manifestations. A neuropsychological test performed at age 67, revealed a mild disexecutive disorder, with a score of 27/30 in a Mini Mental State Exam, but no clinical signs of dementia were noticed throughout the follow-up. She died at the age of 69 due to a respiratory infection.

Neuropathologic study:

Unfixed brain weight was 1.195 g. Macroscopically, moderate diffuse atrophy with widening of sulci was observed along with severe pallor of substantia nigra and locus coeruleus (Fig. 1b1). Histologically there was severe loss of pigmented neurons of brainstem nuclei (substantia nigra, locus coeruleus, dorsal nucleus of the vagal nerve) with frequent Lewy-bodies and pale bodies (Fig. 1b2). Immunohistochemistry showed abundant alpha-synuclein immunoreactive LB and Lewy neurites in the aforementioned nuclei and in raphe, basal nucleus of Meynert, amygdala, entorhinal cortex, cingulum with mild involvement of insula and orbitofrontal region, without neocortical involvement (Fig. 1b3–b4). There were also LB and LN in intermediolateral column of spinal cord and olfactory bulb. This corresponded to a Braak stage 4 of PD-related pathology. In addition, AT8 and four-repeat tau immunoreactive grains (Fig. 1b6), threads, pretangles (Fig. 1b7), coiled bodies and ramified astrocytes were detected in entorhinal, transentorhinal cortices, hippocampus including rings in granule cells of dentate gyrus (Fig. 1b8), as well as in amygdala, cingulum, caudal part of the insula and orbitofrontal region, corresponding to a stage III of Saito et al. [11], with abundant ballooned cells in amygdala (Fig. 1b8, right upper panel). No beta-amyloid deposits or TDP-43 protein aggregates were detected.

Patient 3

A 74-year-old woman was referred because of a bradykinetic-tremolous syndrome that had started 4 years before. She also had experienced anxiety episodes during more than 30 years, as well as depression with suicide ideation the last 2 years. Seven years after first assessment, she developed delusions and aggressiveness, which were successfully treated with olanzapine. Two years later, she was admitted to the Psychiatry Department of our hospital due to anxiety and well-formed visual hallucinations (people she had known in the past). Upon admission, she was still under olanzapine with no other recent medication changes that might have accounted for the psychiatric symptoms. She died at the age of 83 years, having remained non-demented upon last clinical assessment.

Neuropathologic study:

Unfixed brain weight was 1.200 g. No gross brain atrophy was observed, but a severe pallor of substantia nigra and locus coeruleus (Fig. 1c1). Histologically, alpha-synuclein immunoreactive Lewy-body pathology (Lewy-bodies, Lewy neurites, diffuse and granular cytoplasmic staining) involving intermediolateral column of spinal cord, pigmented and non-pigmented brain stem nuclei, basal forebrain nuclei, and amygdala was observed, corresponding to a Braak stage 4 of Parkinson's disease-related pathology (Fig. 1c2–c4). In addition, abundant AT8 positive grains immunoreactive for four-repeat tau isoforms and negative for three-repeat tau isoforms, were detected in amygdala, entorhinal and transentorhinal cortex and in CA1 sector of

the hippocampus, with abundant pretangles (Fig. 1c6–c8), corresponding to stage III of Saito et al. [11]. No beta-amyloid deposits were detected.

In contrast to the three PD patients with AgD, 82 % of PD patients without AgD who were also followed at our Unit ($n = 23$) developed dementia in less than 2 years since the appearance of the first psychotic symptom (64 % in less than 1 year). Clinical features of both groups of subjects are summarized in Table 1.

Discussion

Three cases of pathologically confirmed Parkinson's disease with concomitant argyrophilic grain disease, who presented striking psychiatric manifestations, chiefly depression, irritability, aggressiveness, anxiety, hallucinations, delusions and abnormal behaviour but did not progress to dementia are reported.

The neuropsychiatric symptoms featured by these cases are common in the clinical spectrum of PD, especially in advanced stages of the disease and in demented patients [14, 15]. A point-prevalence of 15–30 % of psychotic symptoms, such as hallucinations and delusions, has been reported in PD patients in cross-sectional studies, as well as in 60 % of patients in a community-based longitudinal study with 12-years follow-up [16–18], which is in accordance with our results. Antiparkinsonian drugs can cause psychotic symptoms, especially in patients with dementia, advanced age, premorbid psychiatric illness, exposure to high dose of anti-PD drugs or multiple drugs in combination [19]. However, most of the psychiatric symptoms reported in our patients could not be explained by the use of these medications, neither by any other intercurrent medical condition. Other main factors associated with neuropsychiatric symptoms in PD patients are cognitive impairment, disease severity and duration [15–17]. Indeed, visual hallucinations have been pointed as a significant predictor of the development of dementia in patients with PD, and it has been shown that up to 75 % of patients who present visual hallucinations can develop dementia during the next 2 years [20, 21]. It is noteworthy that any of our patients developed dementia, despite the long disease duration and advanced stage of the disease, as well as the presence of psychotic symptoms (including visual hallucinations) in all of them.

Depression and anxiety are also common symptoms in PD, and can predate motor symptoms [15, 22]. All of our patients presented these symptoms but, interestingly, depression was accompanied by suicidal ideation in two of them and psychotic ideation, with feelings of ruin and guilt, in the other one. However, despite the elevated prevalence of depression and anxiety in PD, feelings of guilt or worthlessness, suicidal ideation or suicidal attempts are not common in PD [23, 24].

All patients presented different degrees of abnormal behaviour at some point of the disease course. These were not recurrent or progressive, but isolated episodes that appeared in the context of other prominent psychiatric symptoms, such as psychosis, depression or anxiety, thus not fulfilling the clinical criteria for frontotemporal dementia (FTD). Brain areas considered to be part of the anatomical substrate of behavioural alterations, such as anterior cingulate, frontoinsular and orbitofrontal regions, were variably affected by AgD and/or Lewy-body pathology. Moreover, Lewy-body pathology and AgD were especially abundant in amygdala in all three patients, which might have contributed to the appearance of behavioural and psychiatric symptoms.

Accordingly, we consider the clinical picture of the cases herein reported do not fit with the usual psychiatric profile of PD patients. Even though we cannot exclude that both the use of antiparkinsonian drugs and PD intrinsic brain changes might have contributed, to some extent, to the constellation of symptoms previously described, we hypothesize that a significant part of these symptoms were somehow shaped by the concomitant presence of AgD. This would be in keeping with the clinical profile proposed for AgD, consisting on salient psychiatric symptoms and mild amnestic cognitive decline, which is biologically plausible, since limbic structures, which have a critical role in emotion and memory processing, are the areas with a greater concentration of neuropathological changes in AgD. Although these areas are also especially vulnerable to Lewy-body pathology in PD, which may also explain part of these symptoms, prominent psychiatric manifestations as those described in our three patients with concomitant AgD are usually not observed in patients with PD in the absence of obvious cognitive decline [25]. Moreover, in our three patients, AgD pathology clearly exceeded alpha-synuclein pathology in these areas, more specifically in the amygdala. A synergistic interaction between AgD and PD-related pathology in limbic structures could, however, trigger the appearance of neuropsychiatric symptoms. At least, this has been hypothesized in patients with PD and dementia, in whom cognitive decline would be enhanced by the association of Lewy-body and Alzheimer-type pathologies [26, 27]. Regarding the coexistence of AgD and PD, previously reported percentages range between 4 and 25 % [4, 10, 28].

The limited number of cases analyzed in our study as well as its retrospective nature compels us to be cautious about these conclusions. In addition, a definite clinical picture of AgD has not been yet defined and, despite the accumulated evidence allowing us to regard AgD as a distinct anatomo-clinical entity, even the existence of AgD

as a disease has been challenged by some investigators who suggest that argyrophilic grains could represent a transient phase of neurofibrillary degeneration, on the basis of the presence of argyrophilic grains in the brains of cognitively normal subjects in their cohort, and the fact that they are commonly found in association with other neurodegenerative diseases, particularly AD [10].

It has been suggested that AgD might lower the dementia threshold in patients with other concomitant neurodegenerative diseases [29]. We postulate that AgD might also modulate the clinical picture in PD and that perhaps the presence of prominent neuropsychiatric features in PD in the absence of significant cognitive decline could raise the suspicion of associated AgD. A better definition of the clinical pattern of patients with AgD may allow us to recognize characteristic features of this disease, even in the context of other neurodegenerative diseases. This is important, given that a deep knowledge of the phenotype of AgD patients is a mandatory step prior to the development of biomarkers that might help us to identify potential candidates for future specific disease modifying treatments, the same way it is being done with other neurodegenerative disease, such as AD and PD [30].

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Conflicts of interest None.

Ethical standard This study was performed under the auspices of the ethics committee of Hospital Clínic de Barcelona.

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