ORIGINAL ARTICLE

Argyrophilic grain disease in individuals younger than 75 years: clinical variability in an under-recognized limbic tauopathy

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Background and purpose: Argyrophilic grain disease (AGD) is a limbic-predominant 4R-tauopathy. AGD is thought to be an age-related disorder and is frequently detected as a concomitant pathology with other neurodegenerative conditions. There is a paucity of data on the clinical phenotype of pure AGD. In elderly patients, however, AGD pathology frequently associates with cognitive decline, personality changes, urine incontinence and cachexia. In this study, clinicopathological findings were analysed in individuals younger than 75.

Methods: Patients were identified retrospectively based on neuropathological examinations during 2006–2017 and selected when AGD was the primary and dominant pathological finding. Clinical data were obtained retrospectively through medical records.

Results: In all, 55 patients (2% of all examinations performed during that period) with AGD were identified. In seven cases (13%) AGD was the primary neuropathological diagnosis without significant concomitant pathologies. Two patients were female, median age at the time of death was 64 years (range 51–74) and the median duration of disease was 3 months (range 0.5–36). The most frequent symptoms were progressive cognitive decline, urinary incontinence, seizures and psychiatric symptoms. Brain magnetic resonance imaging revealed mild temporal atrophy.

Conclusions: Argyrophilic grain disease is a rarely recognized limbic tauopathy in younger individuals. Widening the clinicopathological spectrum of tauopathies may allow identification of further patients who could benefit from tau-based therapeutic strategies.

Introduction

Argyrophilic grain disease (AGD) is a neuropathological term encompassing a limbic four-repeat (4R) tauopathy characterized by accumulation of argyrophilic grains in dendrites associated with neuronal, astroglial and oligodendroglial tau pathology in elderly individuals [1]. Due to its heterogeneous presentation [2–4] and frequent overlap with other neurodegenerative diseases [5,6], clinically it is practically unrecognized. Its frequency increases with age and is found in more than one-third of post-mortem examinations performed on people aged 100 years or older [7], frequently in combination with other neuropathological findings, and in more than one-third of cognitively normal elderly [8]. This prompts the

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question whether it is indeed a distinct neurological disease entity or a byproduct of aging processes. However, on neuropathological examination, AGD displays a typical and specific pattern of spatial and temporal distribution of changes [9]. It localizes to the medial temporal lobe with a preference for the limbic system and affects the amygdala, the hippocampus, the ambient gyrus, the accumbens nucleus and lastly the neocortex and brainstem [10]. This involvement is believed to follow a pattern along which the disease can be staged [11,12]. Macroscopically, it might present with atrophy of the ambient gyrus or without visible changes [13].

It is different from most other tauopathies in that the tau deposits are not acetylated, leading some to hypothesize that AGD could eventually be protective against other forms of more aggressive tauopathies [14]. Moreover, there is a predominance of 'pretangle' rather than fibrillary tangle neuronal pathology. On a functional level, AGD shows preserved axonal connections – in contrast to Alzheimer's disease (AD) related dementia – with disturbance in the dendritic network, suggesting a distinct form of neurodegeneration [15].

Clinically, AGD lacks a uniform definition. It is associated with slowly progressive cognitive decline and can also present with prominent psychiatric symptoms at a relatively late onset, perhaps reflecting the anatomical distribution of lesions [16,17]. Urinary incontinence [18], alcohol abuse and catatonia [19] are also reported. Generally, the old age and frequent concurrence with other neurodegenerative findings [20,21] impair clear definitions and the clinical and neuropathological findings in younger patients have not been systematically described to date. Another disorder with limbic predominance of pathology, limbic-predominant age-related TDP-43 encephalopathy (LATE), usually presents as an amnestic disorder [22].

Here AGD cases in patients younger than 75 years identified through a retrospective analysis of all cases sent in for postmortem analysis to a large, university-affiliated tertiary centre from 2006 to 2017 are presented.

Methods

Patient identification and selection

All postmortem examinations of brain tissue performed at the Division of Neuropathology and Neurochemistry (Obersteiner Institute), Department of Neurology of the Medical University of Vienna, from 2006 until 2017 were retrospectively screened. The institute serves as the national reference centre for the surveillance of Creutzfeldt–Jakob disease (CJD). Patients were retrieved from the neuropathological records database of the institute (by R.W.) and the diagnosis was reconfirmed by an experienced neuropathologist (G.G.K.).

Patients were flagged for further analysis when AGD was (i) the primary and (ii) the dominant pathological finding on examination. Patients were then included when the age at the time of death was 75 years or less. The cut-off was chosen to exclude patients in whom frequent cerebrovascular and/or other neurodegenerative pathologies were to be expected [23] whilst allowing cases to be captured that, despite a somewhat advanced age, could show isolated AGD and represent a biologically younger phenotype.

Patients were excluded when another pathological finding was better suited to explain the neurological condition or when another condition was severely restraining the pathological examination's ability to ascertain a cause of the symptoms (e.g. hypoxic encephalopathy after successful resuscitation). Our study was performed in the framework of the Surveillance for Human Prion and Neurodegenerative Diseases and conforms to the provisions of the Declaration of Helsinki (as revised in Brazil 2013) and was performed in the framework of a study ('Molecular neuropathologic investigation of neurodegenerative diseases') approved by the Institutional Review Board of the Medical University of Vienna (EK #1454/2018 and EK #1636/2019).

Clinical information

Available patient records were retrieved either retrospectively via electronic healthcare records when available or were submitted by the treating institutions. Information was retrieved for the admission during which the death occurred and for 5 years leading up to the death. Records were then systematically analysed. Duration of disease was extracted from the records either when it was explicitly mentioned or by referring to the time of first mention of neurological or psychiatric (excluding prior depression) symptoms. The clinical suspicion/reason for referral and diagnostic findings from magnetic resonance imaging (MRI) and electroencephalography (EEG) were reduced to clinically relevant/abnormal findings and presented in descriptive phrases. Results of cerebrospinal fluid (CSF) findings were evaluated whenever available.

Symptoms were clustered in categories when they occurred at least once in the identified patients or when there was prior evidence in the literature connecting this cluster to AGD [19]. Symptoms were then

dichotomized into occurring or not occurring. History of substance abuse was recorded when it was explicitly noted in the patients' records.

Neuropathological methods

Formalin fixed, paraffin-embedded tissue blocks (2.5 × 2.0 cm) were evaluated. Postmortem delay was below 24 h for all (range 10–24 h). In addition to haematoxylin and eosin, Luxol Fast Red, Gallyas and Bielschowsky silver staining, the following monoclonal antibodies were used for immunohistochemistry: anti-PrP (prion protein; 12F10: aa.146–160; 1:2000; Cayman Chemicals, Ann Arbor, MI, USA), anti-tau AT8 (pS202/pT205; 1:200; Pierce Biotechnology, Rockford, IL, USA), anti-phospho-TDP-43 (pS409/410; 1:2000; Cosmo Bio, Tokyo, Japan), anti-4R tau (RD4; 1:200; Upstate, Charlottesville, VA, USA) and anti-3R tau (RD3; 1:2000; Upstate), anti-α-synuclein (1:2000; clone 5G4; Roboscreen, Leipzig, Germany), anti-A-beta (1:50; clone 6F/3D; Dako, Glostrup, Denmark), anti-p62 (1:1000; BD Transduction, Lexington, KY, USA), anti-ubiquitin (1:50 000; Millipore, Temecula, CA, USA) and polyclonal anti-FUS (1:1000; Sigma, St Louis, MO, USA). The Dako EnVision© detection kit, peroxidase/DAB, rabbit/mouse (Dako, Glostrup, Denmark) was used for visualization of antibody reactions. First, anti-PrP immunostaining was performed using an established pretreatment that included 10 min autoclaving at 121°C, followed by 5 min concentrated formic acid followed by 5 min proteinase K treatment (5 μg/ml, in Tris) at 37°C. Following clearly negative results further immunostaining and detailed evaluation were undertaken. Neuropathological alterations were semi-quantitatively (none, mild, moderate, severe) evaluated in all examined anatomical regions.

Determination of biomarker proteins in cerebrospinal fluid

Concentrations of amyloid-β (1–42), total tau protein and phosphorylated tau were measured by enzyme-linked immunosorbent assay (ELISA) using INNOTEST® β-AMYLOID (1–42), INNOTEST® hTAU Ag and INNOTEST® PHOSPHO-TAU (181P) assays (Fujirebio Europe N.V., Gent, Belgium) and following the recommendations of the supplier. For quantification of 14-3-3 protein, the CircuLex 14-3-3 Gamma ELISA Kit (CycLex Co., Nagano, Japan) was used as described in the corresponding manual. To detect the misfolded pathological form of prion protein, real-time quaking-induced conversion (RT-QuIC) assays were utilized [24].

Statistical methods

The description of the quantitative demographic traits is presented as median, minimum and maximum (range). Statistical analyses were performed using R version 3.6.0 [R Core Team (2019), R Foundation for Statistical Computing, Vienna, Austria].

Results

During the period 2006–2017, 2787 neuropathological examinations were performed at the department. Apart from 20–40 faetal brains per year, this includes a wide variety of adult-onset neurological conditions with systematic sampling and stainings for a range of diagnostic antibodies (see the review [25]). Fifty-five patients (2%) in whom AGD was noted as a primary or secondary finding in the pathological workup were identified. Of these, seven (8% of all AGD cases) patients fulfilled the inclusion criterion of age <75 years at the time of death and no exclusion criteria, and were subsequently analysed in this clinicopathological study.

Patients were at a median age of 64 years [range (min) 51–(max) 74] at the time of death. Two patients were female (28%). The duration of disease was recorded as a median of 3 months (range 0.5–36). Two patients died within 2 weeks of admission to hospital. One homeless patient without next of kin presented with status epilepticus with known epilepsy and alcohol abuse and died without regaining consciousness; thus a thorough history could not be obtained. The second patient was admitted for rapid cognitive decline and confusion, had a history of severe cardiac disease and died due to rapid cardiac decompensation. Although they died of causes unrelated to AGD these cases were included since they showed progressive neurological symptoms and AGD was an unexpected finding on neuropathology.

The initial clinical suspicion noted on the request for neuropathological workup pertained to altered mentation in four cases (57%): two patients presented with primary symptoms of cognitive changes/memory problems, and two presented with rapidly progressive dementia and cognitive decline (i.e. suspicious for CJD). The remaining reasons for referral to a neuropathological workup were (i) unexplained and refractory status epilepticus; (ii) sudden behavioural changes, and (iii) refractory major depression in one case each. A number of antemortem diagnostic examinations were performed: MRI was available in four cases, EEG in six cases and cerebrospinal fluid analysis in four cases. MRI showed generalized and mesiotemporal atrophy in two cases, and the EEG

was abnormal in four cases (see Table 1 for more details). CSF showed elevated tau levels in two cases. 14-3-3 protein was also detectable in these same cases; however, RT-QuIC for disease-associated prion protein was negative. In a further two cases total tau was only mildly increased or normal but with phosphorylated tau above the normal range. Amyloid-β levels were >500 pg/ml (institutional lower limit of normal) for all patients assessed.

Clinical symptoms in the majority of patients were cognitive changes/dementia, epileptic seizures including status epilepticus, psychotic symptoms and urinary incontinence. A history of alcohol abuse was explicitly noted in three cases. For a comprehensive overview of the clinical characteristics see Table 1. The cause of death was pneumonia in four cases, cardiac failure in two and hypoxic brain damage following successful resuscitation for cardiac arrest of unknown cause in one case.

Neuropathological workup identified AGD pathology at a Saito stage II in five (71%) and stage III in two cases (nos. 1 and 6). An overview of the neuropathological findings is given in Table 2. Atrophy was noted on macroscopic evaluation in all cases and localized to the frontal and temporal regions with variable involvement of the hippocampi, the amygdala and the hypothalamus. Anterior hippocampal atrophy was noted in five cases (71%). Immunohistochemistry was performed and revealed primary AGD with argyrophilic and tau-positive grains, pretangles, oligodendroglial coiled bodies and astrocytic processes; representative histological images are given in Fig. 1. Concomitant pathological findings (not shown in the figure) included signs of alcoholic encephalopathy (i.e. chromatolytic neurons as described also in pellagra encephalopathy) in one or metabolic encephalopathy (i.e. accumulation of Alzheimer type II glial cells) in two cases and TAR DNA binding protein 43 (TDP-43) depositions compatible with the LATE neuropathological change stage 1 [22] in two cases without hippocampal sclerosis. Neurofibrillary tangles were confined to the entorhinal stage (II) in all but

Table 1 Clinical presentation of patients younger than 75 years with unexpected postmortem diagnosis of argyrophilic grain disease

	Case number						
	1	2	3	4	5	6	7
Sex	M	F	M	M	M	M	F
Age (years)	51	64	61	69	63	72	74
Duration (months)	36	3	3	0.5	>6	0.5	6
Referral diagnosis	CJD	Major depression	Cognitive changes	Cognitive changes	Behavioural change	Status epilepticus	CJD
Cause of death	Pneumonia	Pneumonia	Pneumonia	Cardiac failure	Hypoxic brain damage	Pneumonia	Cardiac failure
Diagnostic							
MRI	n.a.	n.a.	n.a.	Generalized atrophy, especially HC	Frontal + HC atrophy	Mild generalized atrophy	Leukoencephalopathy
EEG	Slow waves, bilateral spikes	Normal	Normal	n.a.	Slow waves, spikes frontal	Periodic epileptic discharges	Triphasic waves
Symptoms							
Dementia	✓	–	✓	✓	✓	–	–
Seizures	✓	–	–	–	✓	✓	✓
Cerebellar	✓	–	✓	–	–	–	–
Extrapyramidal	–	–	–	✓	–	–	–
Depression	–	✓	✓	–	–	–	✓
Personality	–	–	–	–	✓	–	–
Psychosis	–	✓	–	✓	✓	–	✓
Catatonia	–	–	–	–	–	–	–
Incontinence	✓	✓	✓	–	✓	–	✓
Other autonomic	–	–	–	–	–	–	–
Hx alcohol abuse	✓	–	✓	–	–	–	✓

CJD, Creutzfeldt–Jakob disease; EEG, electroencephalogram; HC, hippocampus; Hx, history of; MRI, magnetic resonance imaging; n.a., not available.

one case where a Braak neurofibrillary stage of III was noted (case 6). Amyloid-β plaques were found only in one case (Thal stage 3); thus all other cases were interpreted as primary-age-related tauopathy (PART). Apart from the typical AGD-related tau-positive granular/fuzzy astrocytes (GFAs) in the amygdala, further components of aging-related tau astrogliopathy [26], reflected by GFAs in one case in the cortex and subpial and white matter thorn-shaped astrocytes in four cases in the hippocampus, altogether representing distinct responses to different pathogenic events were noted [27] (Table 3). Lewy-related pathology was absent. Single microvascular lesions were noted in two cases, localizing to the thalamus and the putamen, respectively.

Discussion

The clinicopathological findings in younger patients with AGD defined by an age of death below 75 years are reported here. AGD was found unexpectedly in cases with a fulminant course of disease and showed male preponderance in this cohort, contrasting with older patients where more than 60% of cases were reported in females [28]. The clinical presentation was defined by cognitive decline, including memory impairment, seizures, psychotic episodes and urinary incontinence in the absence of other signs of autonomic dysfunction. Whilst no single unifying clinical symptom was found, all cases identified in our sample presented with at least two of the four mentioned symptoms. On antemortem workup, imaging was remarkable for signs of neurodegeneration with hippocampal accentuation in two out of four available MRI scans. Hippocampal atrophy is often found in elderly patients with AGD and can be appreciated both on MRI and on postmortem evaluation [29]. Recent studies suggest atrophy in the anterior temporal lobe in AGD cases [30], a feature that was observed on macroscopic evaluation of the cases.

Conventionally, AGD is described as a disease that increases with age and is frequently found in patients with long-standing memory complaints, but it is also found in cognitively normal patients upon postmortem examination [1,14]. Whilst it was initially believed to be clinically indistinguishable from AD, it has since been shown that AGD is actually associated with higher rates of mild cognitive impairment and lower rates of overt dementia, pointing towards a slower progression and in line with its pathological changes being mostly confined to medial temporal structures [31]. This slow and relatively isolated neurodegeneration described usually in the elderly contrasts with our findings. The unifying attribute of the cases identified here is that the neuropathological diagnosis was unexpected. Owing to a fast rate of clinical decline, most patients were *a priori* investigated for other causes or due to the startling clinical course. This appears to separate the phenotype in younger individuals described here from the more common senile form leading to under-appreciation of these cases. This was amplified by the fact that some of the patients identified here were in a poor socioeconomic status, including chronic alcohol abuse, which contributed to the complexity of clinical symptoms such as cerebellar ataxia or even the fulminant disease course. In contrast to AD, however, CSF amyloid-β levels were found to be within normal ranges in those patients who underwent testing, suggesting that biomarkers could help to distinguish the two entities antemortem.

Another rare neurological disease with abrupt onset dementia and rapid progression towards death is CJD. Indeed, four of the cases studied here presented with primary symptoms suggestive of CJD. On further workup, two patients who presented with epileptic seizures had positive CSF tests for 14-3-3 protein and elevated total tau levels; however, pathological prion protein could not be detected with the RT-QuIC assay in any of these cases. Apart from neuronal loss in the limbic system, our systematic neuropathological examination did not find any lesions as morphological substrates for the elevated 14-3-3 and total tau levels. Regarding the epileptic seizures, apart from the systemic metabolic disturbances, it is theorized that the severe tau pathology in neurons and particularly their dendrites (i.e. grains) led to neuronal network dysfunction in medial temporal lobe structures contributing to the seizure activity. It is concluded that the epileptic seizures might have contributed to the tau alterations of the CSF examination. Whilst AGD has been found as a comorbid pathology in CJD cases [32,33], the presentation of AGD as a CJD mimic has not been reported before. In this context, it is important to note that our institute serves as the national reference centre for prion diseases in both Austria and Hungary and suspicion of CJD mandates neuropathological workup in times where autopsy rates are declining rapidly [34]. Hence it is conceivable that our institute is exposed to significantly more cases of AGD in younger individuals than other neuropathological units. On the other hand, the number of unidentified AGD cases might be high due to the lack of systematic neuropathology examinations, including those of the homeless and patients with chronic alcohol abuse. A history of alcohol abuse was noted in three cases, in contrast with a study reporting that alcohol abuse appears to be somewhat less frequent in a larger group of late-onset AGD cases [28]. The

Table 2 Autopsy findings in patients younger than 75 years with unexpected postmortem diagnosis of argyrophilic grain disease

	Case number						
	1	2	3	4	5	6	7
Sex	M	F	M	M	M	M	F
Age (years)	51	64	61	69	63	72	74
Duration (months)	36	3	3	0.5	>6	0.5	6
Referral diagnosis	CJD	Major depression	Cognitive changes	Cognitive changes	Behavioural change	Status epilepticus	CJD
Autopsy findings							
AGD Saito stage	III	II	II	II	II	III	II
Secondary	None	None	Alcoholic encephalopathy	LATE-NC	Metabolic encephalopathy; LATE-NC	ARTAG, metabolic encephalopathy	None
Atrophy	Mild FT, Ant. HC	Ant. HC	Ant. HC	Ant. HC, Amy.	Mild F, Ant. HC, Amy.	F, HT	F
Braak NFT stage	II	II	II	II	II	III	II
Thal phase	0	0	0	3	0	0	0
ABC score	A0B1C0	A0B1C0	A0B1C0	A2B1C2	A0B1C0	A0B2C0	A0B1C0
TDP-43 (LATE-NC)	–	–	–	Stage 1	Stage 1	–	–
Lewy pathology	–	–	–	–	–	–	–
Vascular lesion	–	–	–	–	Gliotic lesion thalamus	–	Lacunar infarct: putamen
CSF							
Tau (<450 pg/ml)	2343	n.a.	n.a.	578	2405	n.a.	448
p-tau (<61 pg/ml)	26	n.a.	n.a.	**68**	28	n.a.	**78**
Aβ (>500 pg/ml)	561	n.a.	n.a.	1020	531	n.a.	604
14-3-3	pos.	n.a.	n.a.	n.a.	pos.	n.a.	neg.

Aβ, amyloid-β; AGD, argyrophilic grain disease; Amy., amygdala; Ant., anterior; ARTAG, aging-related tau astrogliopathy; CJD, Creutzfeldt–Jakob disease; CSF, cerebrospinal fluid; F, frontal; FT, frontotemporal; HC, hippocampus; HT, hypothalamus; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathological changes; NFT, neurofibrillary tangles; p-tau, phosphorylated tau; TDP-43, TAR DNA binding protein 43.

amygdala and the limbic system have been established as important neuronal circuits in the development of substance abuse and addiction [35]. AGD is known to preferentially affect these structures [36], and indeed they were found to be the most affected regions in those patients with a history of alcohol abuse in our study. Notably, the limbic striatum containing the accumbens nucleus was also affected in most cases. It is tempting to theorize that AGD at a younger age manifests with psychiatric conditions eventually leading to substance abuse, and this in turn contributes to progressive neuropsychiatric symptoms. Damage to the limbic striatum has previously been directly linked to increased alcohol intake in rodents [37]. However, tau deposition in the limbic system, including the amygdala and the limbic striatum, was not limited to the cases with definitive alcohol abuse in our study and alcohol abuse has been shown to increase the rate of tau accumulation in a cellular model [38], pointing towards an exacerbating effect of alcohol abuse in the development of AGD. Frontotemporal lobar degeneration (FTLD) often presents with changes in personality and behaviour, including reduced inhibition and increased substance abuse [39]. Argyrophilic grains have been found in a subgroup of cases where a mutation in the tau gene is believed to shift the ratio

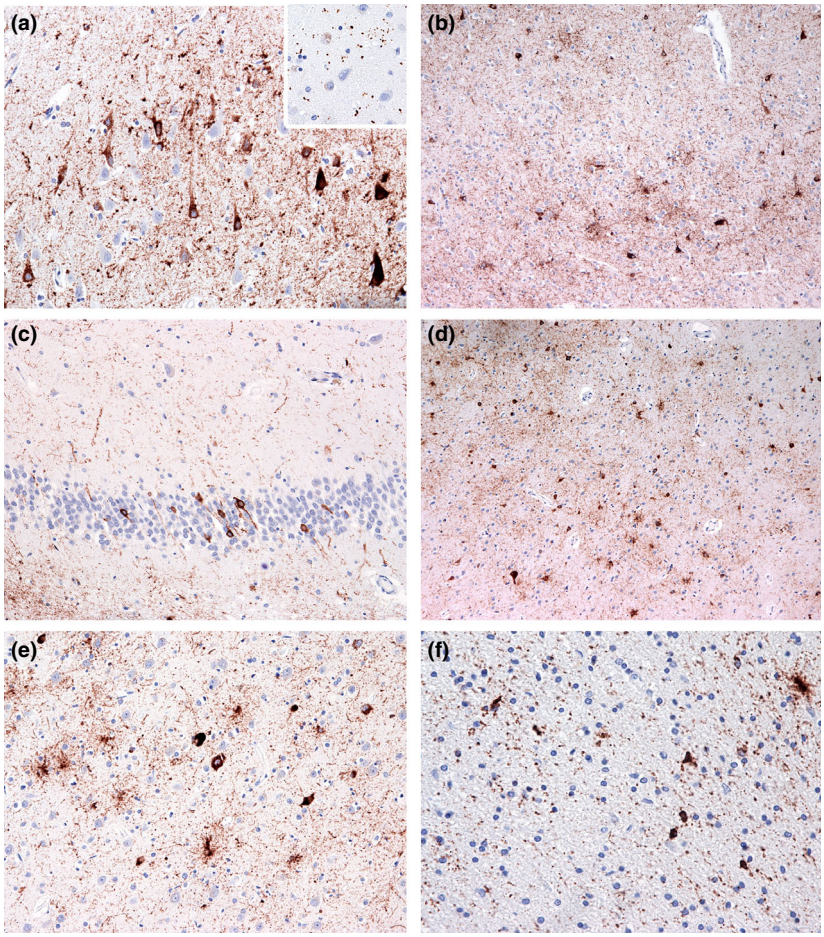

Figure 1 Representative images of immunostaining for phospho-tau (AT8). Pretangles and grains in the hippocampus CA1 subregion (right upper inset demonstrates grains in immunostaining for p62) (a). Pretangles and granular/fuzzy astrocytes in the temporal cortex (b), nucleus accumbens (d) and amygdala (e) and pretangles in the granular layer of the dentate gyrus (c). Oligodendroglial coiled bodies in the white matter of the hippocampus (f).

four-repeat/three-repeat tau isoform (FTLD-tau) as well as in cases with corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) [40]. Indeed, some FTLD-*MAPT*, CBD, PSP and AGD share the fact that 4R-tau is the predominant neuropathological finding. Intriguingly, there are reports of dominantly psychiatric phenotypes in cases of pure AGD [17,41,42] leading to the concept that AGD might be on the FTLD spectrum. The age of onset in these psychiatric cases, however, was considerably higher than in our patients and, whilst psychotic symptoms were present in four out of seven cases, they were not the primary clinical finding. It seems that the phenotype in the population described here would clearly extend the FTLD spectrum, pointing perhaps towards two distinct disease patterns: early-onset versus late-onset AGD.

Another potential differential diagnosis for amyloid-negative cognitive decline is the recently established LATE, a TDP-43 proteinopathy that localizes predominantly to limbic structures [22]. In contrast to the population studied here, however, it presents with memory loss similar to AD and affects primarily elderly patients. Additionally, the presence of productive psychiatric symptoms as seen in our sample of early-onset AGD cases has not been reported. Conversely, agitation and aggression, two symptoms typical for AD patients, were found in some LATE patients [43] but not in our population. Importantly, the earliest stage of LATE was detected in two cases, which is also unusual in this age group. There, the relatively restricted TDP-43 proteinopathy in the amygdala and the lack of further characteristic findings argue against an early form of FTLD-TDP.

At the current time, AGD is diagnosed strictly postmortem since the lack of a clearly distinguishable phenotype has strongly impaired the development of biomarkers. Recent advances in *in vivo* imaging of tau depositions via positron emission tomography have led to very promising improvements in spatial resolution and sensitivity of this technique, so much so that other 4R-tauopathies such as CBD could be identified on imaging [44]. One could envision a diagnostic algorithm in which the finding of a tauopathy in imaging could prompt further analysis of CSF tau. Here, AGD differs from most other tauopathies in that it is

Table 3 Detailed subtyping and localization of tau pathology in patients younger than 75 years with unexpected postmortem diagnosis of argyrophilic grain disease

Number	NFT	Pretangle	Threads	Grain	GFA	TSA	Coiled body	Total tau load
Case 1								
Cortical	0	1	1	2	0	0	1	5
Hippocampus	2	2	2	3	0	0	2	11
Dentate gyrus	0	2	0	0	0	0	0	2
Entorhinal Cx	2	2	3	2	0	0	2	11
Amygdala	2	3	2	3	2	0	2	14
Motor striatum	0	0	0	0	0	0	0	0
Limbic striatum	0	2	1	1	0	0	0	4
Thalamus	0	0	0	0	0	0	0	0
Brainstem	0	1	1	0	0	0	0	2
Case 2								
Cortical	0	1	1	0	0	0	1	3
Hippocampus	2	3	2	3	0	0	3	13
Dentate gyrus	0	2	0	0	0	0	0	2
Entorhinal Cx	2	3	3	2	0	0	2	12
Amygdala	2	3	2	3	2	0	3	15
Motor striatum	0	0	0	0	0	0	0	0
Limbic striatum	0	1	1	0	0	0	0	2
Thalamus	0	0	0	0	0	0	0	0
Brainstem	0	1	1	0	0	0	0	2
Case 3								
Cortical	0	1	1	0	0	0	1	3
Hippocampus	2	3	2	3	0	0	3	13
Dentate gyrus	0	2	0	0	0	0	0	2
Entorhinal Cx	2	3	3	2	0	0	2	12
Amygdala	2	3	2	3	2	0	3	15
Motor striatum	0	0	0	0	0	0	0	0
Limbic striatum	0	2	1	1	0	0	0	4
Thalamus	0	0	0	0	0	0	0	0
Brainstem	0	1	1	0	0	0	0	2
Case 4								
Cortical	0	0	0	0	0	0	0	0
Hippocampus	1	2	2	1	1	1	0	8
Dentate gyrus	0	1	0	0	0	0	0	1
Entorhinal Cx	2	3	3	2	0	0	0	10
Amygdala	1	2	2	1	1	0	0	7
Motor striatum	0	0	0	0	0	0	0	0
Limbic striatum	0	0	0	0	0	0	0	0
Thalamus	0	0	0	0	0	0	0	0
Brainstem	0	1	1	0	0	0	0	2
Case 5								
Cortical	0	0	0	0	0	0	0	0
Hippocampus	1	3	2	3	1	0	2	12
Dentate gyrus	0	2	0	0	0	0	0	2
Entorhinal Cx	2	3	3	2	0	0	1	11
Amygdala	1	3	2	3	3	0	3	15
Motor striatum	0	1	0	0	0	0	0	1
Limbic striatum	0	3	2	1	0	0	3	9
Thalamus	0	0	0	0	0	0	0	0
Brainstem	0	0	1	0	0	0	0	1
Case 6								
Cortical	1	3	3	1	3	2	2	16
Hippocampus	3	3	3	3	2	1	2	17
Dentate gyrus	0	3	0	0	0	0	0	3
Entorhinal Cx	3	3	3	3	1	0	2	15
Amygdala	1	3	3	3	3	3	3	19
Motor striatum	1	1	0	0	0	0	0	2
Limbic striatum	1	3	3	2	2	0	2	13

(continued)

Table 3 *(Continued)*

Number	NFT	Pretangle	Threads	Grain	GFA	TSA	Coiled body	Total tau load
Thalamus	0	1	0	0	2	0	0	3
Brainstem	0	2	2	0	2	2	0	8
Case 7								
Cortical	0	0	0	0	0	0	0	0
Hippocampus	1	3	2	3	1	0	2	12
Dentate gyrus	0	2	0	0	0	0	0	2
Entorhinal Cx	2	3	3	2	0	0	1	11
Amygdala	1	3	2	3	1	0	2	12
Motor striatum	0	0	0	0	0	0	0	0
Limbic striatum	0	3	2	1	0	0	2	8
Thalamus	0	0	0	0	0	0	0	0
Brainstem	0	1	1	0	0	0	0	2

Cortical indicates anterior cingulate and inferior temporal gyrus: other cortical regions did not show tau pathology. Hippocampus includes cornu ammonis and subiculum subregions. Cx, cortex; GFA, granular/fuzzy astrocytes (grey matter); NFT, neurofibrillary tangles; TSA, thorn-shaped astrocyte (subpial and white matter). Scoring: 0, none; 1, mild; 2, moderate; 3, severe.

not only dominated by the 4R isoform but also shows an uncommon lack of acetylation [14]. This could be targeted for biomarker development to allow the antemortem diagnosis of this disease. This might also have therapeutic value since tau has become a target for drug development and both vaccinations as well as intravenous antibodies for treatment of neurodegenerative disease are becoming available [45]. A progressive and aggressive disease affecting young patients, such as the one presented here, could be an ideal candidate for phase II trials.

Limitations

This work is limited by its single centre design with regard to the neuropathological workup. However, the patients included were treated at different centres and across different regions and nations (Austria and Hungary). The study is also limited by a potential selection bias in that the neuropathological site also serves as a reference site for CJD cases. Thus, all clinically suspected cases of CJD must be sent to our centre for confirmation or rejection of this diagnosis and, as such, the generalizability of our findings to other neuropathological settings might be limited. On the other hand, as it is shown that early-onset AGD might be associated with chronic alcoholism and metabolic disturbances leading to rapid deterioration and thus clinically mimic CJD, a reference centre might be an ideal setting to screen for this very rare pathology.

Additionally, the study is limited by its retrospective design in such a way that clinical data could only be extracted from available documentation and further investigation was not possible. Finally, the contribution of further pathologies such as PART and LATE on the clinical phenotype cannot be characterized.

Conclusion

The clinicopathological spectrum of primary tauopathies is expanded by showing that AGD is present in relatively young patients. It is theorized that AGD in younger individuals without significant other neurodegenerative conditions might be associated with premorbid psychiatric conditions leading to chronic alcoholism, eventually nutritional deficiencies and metabolic disturbances. Altogether these might evolve into rapidly progressive cognitive decline, urinary incontinence, psychiatric symptoms, seizures and various additional neurological symptoms. The combination of these features, eventually combined with atrophy in the anterior part of the hippocampal formation, amygdala, and gyrus ambiens, detectable with MRI, and CSF results not suggestive of AD pathogenesis in young patients should thus raise clinical suspicion and prompt postmortem workup. With *in vivo* diagnostic methods for primary tauopathies improving at a rapid pace, AGD might be a potential candidate for tau-based therapy strategies. Finally, both AGD (tau) and LATE (TDP-43) alone or in combination can be considered in amyloid-negative cognitive decline and additional symptoms found in our cohort might be helpful to identify these cases clinically. With this study, the aim was to raise awareness of AGD in younger individuals to initiate further observations on this emerging entity.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Consent

Consent for this analysis was waived by the Institutional Review Board due to its retrospective nature and postmortem setting.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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