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Tau-positive grains are constant in centenarians' hippocampus

Chi-Tuan Pham [a,b], Rohan de Silva [c], Stéphane Haïk [a,b], Marc Verny [d,e], Annick Sachet [f], Bernard Forette [g], Andrew Lees [c], Jean-Jacques Hauw [a,b], Charles Duyckaerts [a,b,e,*]

[a] *Laboratoire de Neuropathologie Raymond Escourolle, Hôpital de la Pitié-Salpétrière, APHP, 75651 Paris Cedex 13, France*
[b] *Centre de Recherche de l'Institut du Cerveau et de la Moelle (CRICM), Paris, France*
[c] *Reta Lila Weston Institute of Neurological Studies, University College London, London W1T 4JF, United Kingdom*
[d] *Centre de Gériatrie Marguerite Bottard, Hôpital de la Pitié-Salpêtrière, APHP, 75651 Paris Cedex 13, France*
[e] *UPMC Paris Universitas, Paris, France*
[f] *Hôpital Charles Foix, APHP, Ivry-sur-Seine, 94205 Cedex 5, France*
[g] *Service de Médecine Interne–Gériatrie, Hôpital Sainte-Perine, APHP, 75781 Paris Cedex 16, France*

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Abstract

The influence of age on the prevalence of argyrophilic grain disease has been analyzed in the hippocampus from 29 centenarians. Argyrophilic grains were detected in 12 cases with Gallyas silver method, in 24 cases with anti-exon 10 (RD4) immunohistochemistry, in all the cases with a phospho-independent anti-tau (piTau) antibody and with a monoclonal antibody against Ser202 of the tau protein (AT8), suggesting a maturation of the grains. Ballooned neurons were found in the hippocampus of 12 cases in which grains were, on average, more abundant. Coiled bodies were found in 26, 15 and 13 cases respectively with piTau antibody, RD4 and Gallyas method. Cases with coiled bodies had a higher density of grains. The mean density of grains did not differ in the patients with or without dementia. The prevalence of tau-positive grains has been underestimated in the very old population. As neurofibrillary tangles, they appear to be a constant accompaniment of age but, contrarily to neurofibrillary tangles, do not seem to be strongly associated with dementia.

Keywords: Dementia; Argyrophilic grain disease; Coiled bodies; Tau; Tauopathy; Aging; Centenarians; RD4; Gallyas

1. Introduction

The "grains" of argyrophilic grain disease (AGD) (Braak and Braak, 1987) are ovoid structures, a few μm in size, scattered in the neuropil. They were initially revealed by Gallyas silver technique – hence the term "argyrophilic". Argyrophilic grains are also selectively labeled by antibodies directed against tau protein and AGD is therefore listed among the tauopathies (Tolnay et al., 2003). As shown here, some grains are tau positive and Gallyas negative. The term "grains", not further qualified, will therefore be used rather than "argyrophilic grains". Grains are commonly associated with a diffuse tau labeling of the cell body of the neurons ("pretangle"), with coiled bodies (Braak and Braak, 1989) (i.e. accumulation of tau protein in the cell body of the oligodendrocytes) and with ballooned neurons (BNs), immunostained by an antibody directed against the small heat shock protein αB-crystallin. Grains are found in the hippocampus and amygdala while BNs are commonly located in the amygdala (Tolnay and Probst, 1998).

Antibodies directed against exon 10 of the tau protein, such as RD4 (de Silva et al., 2003), detect the accumulation of 4R tau in grains. Grains, by contrast, are not immunostained by the RD3 antibody which recognizes an epitope, located between exon 9 and 11, that is not present in 4R tau. AGD thus belongs to the 4R subgroup of tauopathies

* Corresponding author at: Laboratoire de Neuropathologie Raymond Escourolle, Hôpital de la Pitié-Salpêtrière, 47-83, boulevard de l'Hôpital, 75651 Paris Cedex 13, France. Tel.: +33 1 42161891; fax: +33 1 42161899.
E-mail address: charles.duyckaerts@psl.aphp.fr (C. Duyckaerts).

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Table 1
Patients.

Cases #	Age	Gender	Cause of death	Brain weight (g)	Dementia status	Braak stages	CERAD-plaque score STG	Grains	Ballooned neurons	Coiled bodies	Tau-positive astrocytes
1	100	F	Pneumopathy	960	d	V	3	15	+	+++	+
2	100	F	n/a	970	nd	IV	2	20	+	+++	–
3	100	F	n/a	980	d	V	1	10	+	+	–
4	100	F	Colon cancer	1028	nd	III	1	9	–	+++	–
5	100	F	n/a	1050	nd	IV	3	16	–	++	–
6	100	F	Pneumopathy	1060	d	IV	1	13	–	+	–
7	100	F	Pulmonary embolism	1130	nd	V	3	15	–	++	+++
8	100	F	Sudden death	1170	d	III	2	16	+	+	–
9	100	F	Myocardial infarction	1200	nd	III	1	16	–	++	–
10	100	F	Pneumopathy/pulmonary oedema	1200	d	III	2	7	–	–	–
11	101	F	Myocardial infarction	995	nd	III	1	10	–	+	–
12	101	F	Pulmonary embolism	1000	d	V	1	13	–	++	+++
13	101	F	n/a	1060	nd	III	0	8	–	–	–
14	101	F	Pneumopathy/pulmonary embolism	1070	nd	IV	0	14	+	+++	–
15	101	F	Myocardial infarction	1120	d	IV	2	16	–	++	–
16	101	F	n/a	1130	nd	VI	3	11	+	++	–
17	101	M	Sudden death	1140	nd	III	0	13	–	+	–
18	101	M	n/a	1150	nd	IV	2	9	–	++	–
19	102	F	n/a	900	d	V	2	20	+	+++	+++
20	102	F	n/a	940	d	VI	1	18	–	+++	–
21	102	F	n/a	950	d	VI	2	21	+	++	+++
22	102	F	Pneumopathy/myocardial infarction	1190	nd	III	1	15	–	+	–
23	103	F	Pulmonary embolism	930	nd	V	3	17	+	+++	+++
24	103	M	Heart failure	1100	d	VI	3	19	–	++	++
25	104	F	Stroke	1050	d	VI	0*	11	+	+	–
26	106	M	Pneumopathy	1280	nd	V	1	16	+	+++	–
27	107	F	Pneumopathy/undernutrition	1100	nd	V	3	18	–	+	–
28	109	F	n/a	730	d	V	3	15	–	+	–
29	110	F	Septic shock	980	nd	III	1	9	+	–	–

n/a: not available; g: grams; d: considered as demented; nd: considered as non-demented; Braak stages: neurofibrillary stage (Braak and Braak, 1991). CERAD: 0 = none; 1 = sparse; 2 = moderate; 3 = frequent (Mirra et al., 1991). STG: superior temporal gyrus. Grains, coiled bodies, tau-positive astrocytes: alterations identified after piTau immunohistochemistry. Grains: sum of semi-quantitative evaluation (+, ++; +++) in the CA4, CA3, CA2, and CA1 subfields, in the subiculum and in area TF-TH. Ballooned neurons: identified after αB-crystallin immunohistochemistry.

* : This case was a "tangle predominant form" i.e. numerous tangles without amyloid plaques in the isocortex.