Published in final edited form as:

Acta Neuropathol. 2020 October ; 140(4): 591–593. doi:10.1007/s00401-020-02192-0.

Thorn-shaped astrocytes in the depth of cortical sulci in Western Pacific ALS/Parkinsonism-Dementia complex

Gabor G. Kovacs^{1,2,3,4}, John L. Robinson¹, Daniel P. Perl⁵, Virginia M.-Y. Lee¹, John Q. Trojanowski¹

¹Center for Neurodegenerative Disease Research (CNDR), Institute On Aging and Department of Pathology and Laboratory Medicine, University of Pennsylvania, 3600 Spruce Street, 3 Maloney Building, Philadelphia, PA 19104-4283, USA

²Tanz Centre for Research in Neurodegenerative Disease (CRND), University of Toronto, Krembil Discovery Tower, 60 Leonard Ave, Toronto, ON M5T 0S8, Canada

³Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

⁴Laboratory Medicine Program, University Health Network, Toronto, ON, Canada

⁵Department of Pathology, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814, USA

Guam amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS/PDC) is a progressive neurodegenerative disorder characterized by diverse neuronal and glial tau pathologies [6]. With the aim to evaluate aging-related tau astroglialopathy (ARTAG) we examined the collection at the CNDR, University of Pennsylvania, consisting of blocks of the frontal parietal, temporal, and occipital cortices in 33, the hippocampus in 13, and the spinal cord samples in 30 additional cases. Formalin fixed, paraffin-embedded tissue blocks were evaluated using anti-tau antibodies PHF-1 (Ser396/Ser404, 1:2000; Gift of Peter Davies) and AT8 (phospho-epitope Ser202/Thr205; Pierce Biotechnology, Rockford, IL, USA).

In addition to neuronal and oligodendroglial tau pathology, we observed astrocytic tau pathology reminiscent of granular/fuzzy astrocytes (GFAs) as in gray matter ARTAG [3] (Fig. 1a, b). Furthermore, thorn-shaped astrocytes (TSAs) in subpial location (Fig. 1c) and in the white (Fig. 1d) with gray matter GFAs (Fig. 1e) were also observed.

Twenty-one out of 33 cases (63%; 2 controls, 14 PDC and 5 without clinical classification; median age 69 years, range 55–93 years) showed subpial TSAs diffusely along the cortical surface in one or more cortical regions. Fourteen of the 21 cases (66%) showed white matter TSAs in the same area. Subpial TSAs were variably seen in the frontal ($n = 14$ out of 23 where region was available for examination; 60.8%), temporal (12/26; 46%), parietal (7/17; 41.1%), and occipital cortices (1/11; 9%). One case (73-year-old female patient with PDC) showed diffuse subpial TSAs in all four cortical regions (out of 8 where all regions were

[✉]Gabor G. Kovacs, gabor.kovacs@uhnresearch.ca, John Q. Trojanowski, trojanow@upenn.edu.

available). Three PDC showed involvement of the frontal, temporal, and parietal cortices, and 2 each (PDC) of frontal and temporal and parietal and temporal cortices together. Accumulation of TSAs in the depth of the sulci (Fig. 1e, f) were seen in 5 out of 12 cases (41%) in the temporal, 1/14 (7%) in the frontal and 1/7 (14%) in parietal cortex. Out of these, in the frontal and temporal cortices in a 69-year-old individual, and in the temporal cortex two additional cases (one of them 80-year-old female and a 75-year-old male) showed additional patchy accumulation of astrocytic tau inclusions in the gray matter in the depth of the sulci. However, there was a lack of perivascular neuronal tau pathology in the depth of the sulci (Fig. 1g, h).

In the spinal cord 5 out of 30 (16%) patients (all PDC, age-range 63–81) showed subpial and white matter TSAs as reported also in cervical spondylotic myelopathy [5]. Four PDC cases showed gray matter astrocytic tau pathology associated with relatively preserved anterior horn neurons (Fig. 1i), as previously reported [3]. Twelve hippocampus (92%) samples showed subpial and white matter TSAs, including two in the gray matter and one with TSAs in the the dentate gyrus (Fig. 1j).

In summary, pathology described also in ARTAG [3] is seen in cortical regions, spinal cord, and hippocampus in Guam ALS/PDC. A particular aspect is the accumulation of TSAs in the depth of cortical sulci. Especially for the temporal cortex, this is approximately 20 times more frequent than reported in a European aging cohort [1]. TSAs in the depth of cortical sulci are seen also in the frame of chronic traumatic encephalopathy (CTE), a condition related to repeated mild traumatic brain injury [4]. Interestingly, the laminar predilection of cortical neurofibrillary tangles in Guam ALS/PDC is reminiscent of that in CTE [2, 4]. Therefore, it is important to emphasize the lack of perivascular accentuation of neuronal tau at the depth of the sulci where we noted the TSAs. Thus, verbatim application of current definition of CTE pathology [4] does not allow us to consider CTE as a neuropathological diagnostic entity in our cohort. Since our study lacked standardized questionnaire on head injury, we cannot exclude that some form of traumatic brain injury contributed to this pathology. The presence of subpial TSAs in the depth of cortical sulci in CTE and Guam PDC, and less frequently in aging brains [1], might suggest common mechanisms. Description of disease conditions with tau pathologies in the depth of cortical sulci might help to further crystallize specific constellations of neuropathological lesions of CTE.

Acknowledgements

Grants: P30 AG010124 and U19 AG062418 for JQT and VML; grant P30 AG 014382 for DPP, Rossy Foundation, “Rossy PSP Program”, Edmond J. Safra Foundation, and Bishop Karl Golser Award for GJK. The opinions expressed herein are those of the authors and are not necessarily representative of those of the Uniformed Services University, the United States Department of Defense or the United States Army, Navy, or Air Force.

References

1. Forrest SL, Kril JJ, Wagner S, Honigschnabl S, Reiner A, Fischer P et al. (2019) Chronic traumatic encephalopathy (CTE) is absent from a european community-based aging cohort while cortical aging-related tau astroglipathy (ARTAG) is highly prevalent. *J Neuropathol Exp Neurol* 78:398–405. 10.1093/jnen/nlz017 [PubMed: 30939193]

2. Hof PR, Perl DP, Loerzel AJ, Morrison JH (1991) Neurofibrillary tangle distribution in the cerebral cortex of parkinsonism-dementia cases from Guam: differences with Alzheimer's disease. *Brain Res* 564:306–313. 10.1016/0006-8993(91)91467-f [PubMed: 1810629]
3. Kovacs GG, Robinson JL, Xie SX, Lee EB, Grossman M, Wolk DA et al. (2017) Evaluating the patterns of aging-related tau astrogliopathy unravels novel insights into brain aging and neurodegenerative diseases. *J Neuropathol Exp Neurol* 76:270–288. 10.1093/jnen/nlx007 [PubMed: 28340083]
4. McKee AC, Cairns NJ, Dickson DW, Folkerth RD, Keene CD, Litvan I et al. (2016) The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol* 131:75–86. 10.1007/s00401-015-1515-z [PubMed: 26667418]
5. Shimizu H, Kakita A, Takahashi H (2008) Spinal cord tau pathology in cervical spondylotic myelopathy. *Acta Neuropathol* 115:185–192. 10.1007/s00401-007-0321-7 [PubMed: 18040698]
6. Trojanowski JQ, Ishihara T, Higuchi M, Yoshiyama Y, Hong M, Zhang B et al. (2002) Amyotrophic lateral sclerosis/parkinsonism dementia complex: transgenic mice provide insights into mechanisms underlying a common tauopathy in an ethnic minority on Guam. *Exp Neurol* 176:1–11. 10.1006/exnr.2002.7940 [PubMed: 12093078]

Fig. 1.

GFAs in PDC (**a**, **b**; arrows). Subpial TSAs in the frontal cortex (**c**) showing focal accumulations at the surface (arrow). TSAs accumulate in the white matter (**d**). Subpial TSAs in the depth of sulci (**e–h**), associated occasionally with gray matter GFAs (**e**: arrows; **g**: box enlarged in **h**), without perivascular neuronal tangles. TSAs surrounding well-preserved motor neurons of the cervical spinal cord (**i**) and in the dentate gyrus (**j**). Scale bar in “**a**” represents 15 μ m for **a**, **b**; 25 μ m for **i**, **j**; 100 μ m for **e–g**; 30 μ m for **c**; 50 μ m for **h**; and 250 μ m for **d**