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CORRESPONDENCE

Purkinje cell axonal torpedoes are unrelated to advanced aging and likely reflect cerebellar injury

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Torpedoes, swellings of the proximal Purkinje cell axon, are thought to represent a cellular response to injury [3]. They may occur in a variety of cerebellar disorders [7]. Most recently, their numbers were noted to be six-times higher in essential tremor (ET) than control brains [4]. Torpedoes are also often viewed as a cumulative phenomenon associated with advanced aging [3, 4], yet there are surprisingly few supporting data. We quantified torpedoes in normal human cerebella spanning a considerable age range to assess whether torpedoes are a cumulative phenomenon of aging. These data help place the relative abundance of torpedoes in ET in context.

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Control brains at the New York Brain Bank, Columbia University Medical Center (CUMC) had been controls in the Alzheimer's Disease Research Center or non-neurologic patients at CUMC. Each had a complete neuropathologic assessment [4] including Braak AD stage [2] and CERAD [5] for Alzheimer's tangle and plaque pathologies.

As documented [4], a standard 3 × 20 × 25-mm parasagittal tissue block was harvested from each neocerebellum ($N = 48$) and immersion-fixed in 10% buffered formalin. Paraffin sections (7-μm thick) were stained with Luxol fast blue counterstained with Hematoxylin and Eosin (LH&E) [4]. Torpedoes (Fig. 1) in one entire LH&E section were counted blinded to age. Purkinje cells in five randomly-selected 100× LH&E stained fields of the standard cerebellar section were counted and the mean reported. In 32 brains, a second set of sections from the same blocks were used as replicate data.

Non-parametric tests (Spearman's r, Mann–Whitney test, Kruskal–Wallis test) were used. Because of zero values (0 torpedoes), in linear regression analyses, $\log_{10}$(torpedoes +1) was the dependent variable and age, the independent variable.

Age at death ranged from 6 to 93 years. Mean ± SD (median, range) number of torpedoes = 1.8 ± 2.1 (1, 0–11) (Table 1).

Number of torpedoes was correlated with age at death ($r = 0.35$, $P = 0.02$, Table 1), but not when the brains in the youngest age quartile (≤36 years) were excluded (i.e., in brains with age of death ranging from 37–93 years, $r = -0.03$, $P = 0.85$). While (mean ± SD, median) number of torpedoes was low in brains in the youngest quartile (quartile 1, ≤36 years, 0.5 ± 0.9, 0), it did not differ among brains in the remaining 3 quartiles: quartile 2 (37–63 years) 1.9 ± 1.6, 1.5; quartile 3 (64–80 years)

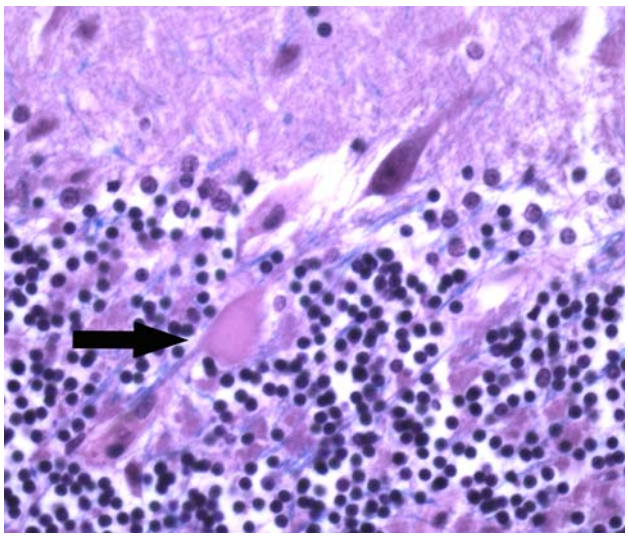

Fig. 1 Control cerebellar tissue showing a torpedo (*arrow*). LH&E ×400 magnification

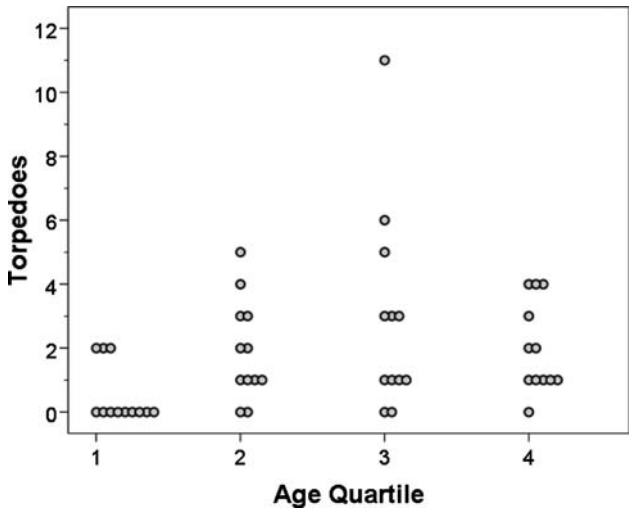

Fig. 2 Number of torpedoes (*Y* axis) by age at death quartile (*X* axis)

2.9 ± 3.2, 2; quartile 4 (≥81 years) 2.0 ± 1.4, 1.5 (for comparison of quartiles 2–4, $P = 0.88$) (Fig. 2).

In a linear regression analysis, log-transformed number of torpedoes was associated with age (beta 0.004, $P = 0.01$) but not in a fully adjusted model including gender, race, postmortem interval (PMI), brain weight, number of Purkinje cells, CERAD plaque score and Braak stage(beta for age −0.003, $P = 0.71$). In unadjusted and adjusted models restricted to age quartiles 2–4, beta = −0.001, $P = 0.70$ and beta = −0.003 and $P = 0.69$, respectively.

The results of replicate analyses on 32 brains were similar to our primary analyses. The number of torpedoes was lowest in the youngest age quartile (0.2 ± 0.4, 0) but was similar in the remaining three age quartiles (quartile 2: 1.8 ± 1.9, 2; quartile 3: 3.2 ± 2.3, 3.5; quartile 4: 2.7 ± 2.4, 2.5) (for comparison of quartiles 2–4, $P = 0.82$).

We examined control brains spanning a wide age range. Torpedoes were rare in the first four decades of life, but thereafter, there was no aging-associated increase. Torpedoes have been commented on as rare incidental findings in normal human control brains, although it has

Table 1 Clinical characteristics/postmortem features (48 controls)

	Clinical/postmortem features	Torpedoes on LH&E	Correlation (*r*) between clinical/postmortem feature and torpedoes
Age at death (years)	58.7 ± 25.1		0.35, $P = 0.02$
Gender			
Women	20 (41.7)	2.5 ± 2.5 (2)	
Men	28 (58.3)	1.4 ± 1.6 (1)	
		$P = 0.05$	
Cause of death			
Cardio-pulmonary	19 (39.6)	2.5 ± 2.7 (2)	
Cancer	9 (18.8)	1.1 ± 1.6 (1)	
Other	11 (22.9)	1.5 ± 1.6 (1)	
Unknown	9 (18.8)	1.6 ± 1.3 (1)	
		$P = 0.31$	
PMI (h)	7.2 ± 7.1		0.13, $P = 0.51$
Brain weight (g)	1,298 ± 152		−0.20, $P = 0.22$
Torpedoes	1.8 ± 2.1		
Purkinje cells	9.2 ± 2.5		−0.13, $P = 0.40$
CERAD plaque score	0.2 ± 0.5		0.14, $P = 0.35$
Braak stage	0.5 ± 1.0		0.03, $P = 0.82$

Mean ± SD (median) or counts (%)

not been demonstrated that they are more abundant as a function of advanced age. One study [3] examined 32 axons in 3 normal individuals (ages 64, 70, 86). The 86 year old had two torpedoes. In a study of two normal mouse strains (age 8 days–32 months) [1], <0.1% of Purkinje cells had torpedoes at 6 months; this increased linearly to 13.7% by age 32 months [1]. However, in a study of other normal mice strains, torpedoes were absent, suggesting that torpedoes are not a "simple aging phenomena" [6]. The lack of an association here between these lesions and advanced aging suggests that the abundance of these lesions in ET is a marker of cerebellar injury and not merely representative of accelerated aging.

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Conflict of interest statement The authors report no conflicts of interest.

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