Neuropathology of Essential Tremor

Jellinger KA*
Institute of Clinical Neurobiology, Vienna, Austria

Abstract

Whereas the underlying pathology of essential tremor (ET) has been elusive until recently, controlled postmortem studies demonstrated various structural changes in the ET cerebellum, including loss of axonal swellings ("torpedoes"), and abnormal synaptic connections. Although these changes were not seen in all studies, these and modern neurophysiological studies indicated the involvement of the cerebellum in this neurodegenerative disease.

Keywords: Essential tremor; Cerebellar pathology; Purkinje cell loss

Introduction

Essential tremor (ET), the most common pathological tremor in humans, is a frequent, chronic progressive neurological disease that clearly involves the cerebellar system and the cerebello-frontal network, although its neuropathology, in particular, cerebellar pathology, is still a matter of controversy [1-11]. Whereas limited previous clinicopathological studies of ET patients have been elusive, more recent controlled postmortem studies demonstrated a considerable number of structural changes in the ET cerebellum, involving Purkinje cell and neighboring neuronal populations [9,10,12,13]. Purkinje cell loss has been documented in some, although not all studies [8,10,14-17]. Here, there are conflicting data resulting in considerable controversy over the issue of Purkinje cell loss and related changes of cerebellar structures as well as abnormal climbing fiber-Purkinje cell connections, loss of dendritic spines and the occurrence of Purkinje cell axonal swellings ("torpedoes") in ET, whereas no changes in parallel counts and density were seen in ET [9,11,13,17-20]. Three recent clinicopathological studies of ET patients reported deviating results concerning cerebellar pathology. One study comparing 32 ET (mean age 86 ± 6.1 years) patients and 16 age-matched controls using free-floating parasagittal 100 µm thick sections stained for calbindin, without random unbiased stereological methods, demonstrated an 18% reduction of Purkinje cell linear density and its inverse association with torpedo count; another study from the same group comparing 50 ET cases and 25 age-matched controls using a random sampling approach at 217 sites to quantify Purkinje cells along this cell layer reported significant loss of Purkinje cells and greater distances between single Purkinje cell bodies, supporting the neurodegenerative hypothesis of ET [18,21]. Another study comparing 56 ET patients (including 10 with asymptomatic Lewy bodies) and 2 with progressive supranuclear palsy (PSP) (mean age 89 ± 5.6 years) using 5 µm thick paraffin sections with routine and immunohistochemical methods demonstrated no changes in Purkinje cell linear density, while in an earlier study, the same group reported some cerebellar pathology in 7/11 ET patients (superior vermis atrophy, proliferation of Bergman glia) without mentioning Purkinje cell loss or occurrence of torpedoes [16,22]. These data were in line with other studies of ET patients suggesting that neither lower brainstem Lewy bodies nor cerebellar Purkinje cell loss represent the neuropathological basis of ET [17]. The reasons for these deviating data are not clear and cannot be explained by differences in techniques and lack of standardized studies [11]. Recent postmortem studies of ET and Parkinson disease (PD) brains showed accumulation of insoluble amyloid β-42 in ET cerebellum but not in PD, but whether this anomaly plays a role in ET symptoms warrants further investigation [23].

The pathophysiology of ET remains not fully understood, since standard neuropathological studies reported no consistent changes and some reported neurodegenerative changes in some ET cases: Lower brainstem Lewy bodies were seen in 24% but were not different from those in controls, loss of cerebellar Purkinje cells in 76%, whereas reduction of Purkinje cells could not be replicated by others [3,15-17,24,25]. There are no consistent data on the dentate nucleus in ET; cell reduction was observed in 6 to 12.5% [15,22]. No changes in substantia nigra were reported in ET, and neuromelanin-sensitive MRI techniques can discriminate ET from early-stage tremor-dominant PD [26]. Brain biochemistry of ET brains revealed no changes in striatal tyrosin-hydroxylase nor in locus ceruleus dopamine β-hydroxylase activities discriminating ET from early PD [27]. Recent voxel-based MRI morphometry in ET patients exhibited less gray matter in cerebellar lobule VIII and less connectivity between cerebellar cortex and dentate nuclei as well as interrelated changes in the supplementary motor area, indicating dysfunctions in the cerebello-frontal network as a direct consequence of cerebellar defects, while others reported disturbed cerebello-dentato-thalamic activity and cerebello-cortical connectivity, supporting previous evidence of functional cerebellar changes in ET [3,4].

In conclusion, despite deviating neuropathological findings in ET patients, recent studies strongly suggest both morphological and functional changes in the cerebellum and related systems, but further prospective clinico-pathological studies in ET subjects and controls using standardized methods will be necessary in order to clarify the morphological and pathophysiological basis of ET.

References


*Corresponding author: Kurt A Jellinger, Institute of Clinical Neurobiology, Vienna, Austria, Tel: 436641325237; E-mail: kurt.jellinger@univie.ac.at
Received January 13, 2016; Accepted January 22, 2016; Published January 29, 2016
Citation: Jellinger KA (2016) Neuropathology of Essential Tremor. J Mult Scler (Foster City) 3:165. doi:10.4172/2376-0389.1000165
Copyright: © 2016 Jellinger KA. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.