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MINI - REVIEW

Neuropathological Findings in Essential Tremor

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Abstract.

In this paper we are mainly describing some recent and relevant neuropathological findings in essential tremor, considering its pathiphysiological importance, by mainly reffering to Purkinje cells' pathology and also on the Lewy bodies in the brainstem.

Keywords: Essential Tremor, Purkinje cells' pathology, Lewy bodies in the brainstem.

Introduction

Essential tremor (ET) is a chronic progressive, neurological syndrome of heterogenous clinical phenotypes, clinically characterized by involuntary tremor on hands or arms and progressively on head, jaw, and voice (1-4), while some patients manifest more extensive and complex deficits (5-10).

The pathophysiology of essential tremor is not clearly defined. Many studies on familial cases of essential tremor have proposed a genetic predisposition, provoked by certain DNA mutations (11-14). Postmortem neuropathology studies have revealed certain alterations at the histological and cellular level, in brain tissues of affected patients. Various neuropathological findings have been reported in ET. It is unclear which findings are well established, since not all of them reflect large series of patients. However, according to recent meta-analyses of the neuropathological evidence on ET, these could be categorized under two main groups; the first regarding Purkinje cell changes and the second the presence of Lewy bodies in the brainstem. Further sub-categorization is possible, in these main groups (15).

Apart from these main hypotheses, some studies have investigated the role of the dentate nucleus in the pathogenesis of ET. Severe neuronal loss and atrophy, microglial clusters, and reduction in the number of efferent fibers,16 along with reduced GABAA and GABAB receptors, have been reported.17

However, in the majority of studies, not enough evidence to support this correlation was found.

1. Purkinje cells' pathology

The main and probably the most important evidence refer to alterations in number, location or transformations in structure of the Purkinje cells. Purkinje cells are the main inhibitory neurons in the cerebellar cortex and the main cerebellar output; therefore, their decrement or changes in their structure could be linked to hyperactivity of the cerebellum and consequently to tremor (18).

The first theory supports a change in number of Purkinje cells. A decrease in Purkinje cell density and greater distances between single Purkinje cell bodies have been extensively described by pathological and morphometric studies; 19,20,21,22,23 however, other studies describe no significant difference in the number of Purkinje cells between essential tremor patients and normal controls (24,25,26).

Other studies have demonstrated Purkinje cells' heterotopia as a disease-associated feature of ET (27, 28, and 29). Heterotopic Purkinje cells are those whose cell body is mis-localized in the molecular layer. These are viewed as markers of neurodegeneration. Kuo et al reported three times higher numbers of heterotopic Purkinje cells, and an inverse relationship between these numbers and total numbers of Purkinje cells, in a comparative study between ET brains and normal controls (28).

Certain morphological changes on Purkinje cell dendritic arborizations have been revealed with Golgi's silver staining method, including a significant loss of dendritic branches, with a decrease in total dendritic length, branch length, and maximum branch order, leading to a significantly lower density of the dendritic field of Purkinje cells and a reduction in the number of dendritic spines (30). Furthermore, focal dendritic swellings of Purkinje cells correlate well with the presence of ET, according to some researchers (21, 31).

Purkinje cell axonal abnormalities have also been related to ET. Abnormal ovoid swellings of the proximal portion of the axon, namely axonal torpedoes have been described in essential tremor brains (32, 33). Axonal torpedoes are non-specific for essential tremor since they can be present in spinocerebellar ataxias, and other neurodegenerative conditions, and to a less extent in normal controls (70% less frequent), and they contain an accumulation of hyperphosphorylated neurofilaments and disrupted organelles (34, 11). Among the axonal changes, an increased number of arciform axons that gradually curve back toward the Purkinje cell layer, an increase in the number of axon recurrent collaterals, an increase in axonal branching, and an increase in terminal axonal sprouting have been observed in essential tremor cerebella.12 The axonal alterations and changes in their primary orientation are thought to inhibit

anterograde and retrograde axonal transport, leading to cell strangulation, dysfunction and finally to cell death and loss of Purkinje cells.

Basket cells, which normally form a complex basket-shaped structure around the Purkinje cell body, exhibit a dense and tangled appearance of their axonal plexuses in essential tremor cases (13).

Besides cell morphology alterations, abnormalities in climbing fiber-Purkinje cell synaptic connections have also been documented in essential tremor. Olivocerebellar climbing fibers are the main glutaminergic input to Purkinje cells. In essential tremor, qualitative and morphological changes of the climbing fiber-Purkinje cell synapses have been reported.

Changes at the expression of membrane glutamate transporters that have been described in essential tremor, which are of critical importance for the recycling of glutamate, can be linked to a failure of glutamate reuptake by astrocytes, accumulation in the synaptic cleft, and over-stimulation of glutamate receptors, leading to over-excitation of glutaminergic olivocerebellar climbing fibers. The aforementioned changes could be related to aberrant Purkinje to Purkinje cell and Purkinje to other cell types interactions and alterations on the normal cerebellar circuitry and output (12). With the use of immunohistochemistry, Lin et al. reported a decreased climbing fiber-Purkinje cell synaptic density, and an increased number of climbing fibers extending to the outer portion of the molecular layer, in ET brains. Furthermore, they documented more climbing fiber-Purkinje cell synapses on the thin Purkinje cell spiny branchlets, instead of the proximal Purkinje cell dendrites in the inner portion of the molecular layer, as well as a positive inverse association between the increased climbing fiber-Purkinje cell synapse on the thin branchlets and the clinical tremor severity. (35).

Essential tremor has also been linked to genetic polymorphisms in solute carrier family 1, member 2, known as SLC1A2, (11-13) which encodes a major glutamate transporter in the adult brain, the excitatory amino acid transporter type 2 (EAAT2) (14). Western blot analysis studies have shown decreased levels of EAAT2 in essential tremor cases compared with normal controls, suggesting an astrocytic involvement in the pathophysiology and an increased vulnerability of Purkinje cells to excitotoxic damage in essential tremor.36

In addition to that, increased Bergman astrogliosis and cerebellar cortical sclerosis have also been demonstrated in essential tremor cases (37).

2. Lewy bodies in the brainstem

Lewy bodies are found in the locus coeruleus of about one in four essential tremor cases, and it has been proposed that they are incidental (38) and/or related to normal aging or emerging Parkinson's disease or Lewy body dementia (39). Lewy bodies pathology in Parkinson's disease begins in the dorsal vagal nucleus and spreads to the locus coeruleus in Braak stage II-III; however, in essential

tremor cases they are solely found in the locus coeruleus (40-42). The locus coeruleus is the main norepinephrine center of the central nervous system, and one of the main inputs to the Purkinje cells, and of high importance for the modulation of responses to climbing fibers and to normal function and inhibitory output of Purkinje cells (43, 42, 16); therefore, Lewy body pathology of the locus coeruleus pathology is also thought be linked to the pathophysiology of essential tremor.

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