An Old Problem Not Yet Resolved: The Association of Several Neurodegenerative Disorders

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In this issue of Neuroepidemiology there appears an interesting review about the co-occurrence of essential tremor (ET) and other neurodegenerative diseases (NDD) [1]. The uncertain NDD nosology and the indecision of many neurologists whether to include ET in it make some introductory comments necessary.

The concept of NDD has its roots in the 19th century with the pessimistic theory of degeneration: several mental disorders such as feeble-mindedness, epilepsy and madness were associated with each other and with moral depravation (crime, poverty). Genetic inheritance and ‘poisoned blood’ (syphilis, alcoholism) were responsible for these disorders. The degenerated person would transmit the degeneration by inheritance until the disappearance of part (or systems) of the nervous system (NS) and disappeared after the First World War with the epidemiological evidence of co-occurrence of ET, PD and AD [1]. The relationship between ET and PD is a subject with a long history [8]. In this review, a clear and consistent relationship in case-control and population-based surveys measured by scientific tools (significant odds and relative risks) was demonstrated [1].

The concept of neurodegeneration (that begins with the Wallerian degeneration of nerves) continued with the progressive neuronal death without clear cause [4]. Neuron degeneration was also called ‘abiotrophy’ by Gowers and ‘apoptosis’ in the 1970s [2, 4]. These historical facts and the absence of a scientific explanation for many neurological illnesses in which neurodegeneration is present explain the reluctance of many neurologists to apply this denomination [5, 6]. Nevertheless, this concept has persisted in describing the cellular changes of progressive neuronal death that appear in aging and in NDD. Several journals, Neurodegeneration, Molecular Neurodegeneration and Neurodegenerative Diseases, demonstrate its continued use. But the nosology of NDD continues to be controversial; the current textbooks of neurology do not include this denomination [5], with some exceptions [5–7], and the largest book on NDD does not define these illnesses [8].

The most accepted definition for NDD enumerated a group of diseases united only by the gradually progressive disintegration of part (or systems) of the nervous system (NS) [9]. Some definitions include symmetrical NS affection and unknown or complex etiology [5, 6] and another, NS accumulation of proteins without clear inflammation [7], or with neuronal cytoskeletal damage [10]. Alzheimer’s disease (AD), Parkinson’s disease (PD) and amyotrophic lateral sclerosis [10] are the main NDD. Classical authors included ET as an NDD [6, 8]. The pathological findings of ET cerebellar neuronal degeneration [11] with aggregates of proteins in ‘torpedo’ neurons and its high prevalence [12] encourage this inclusion.

Two characteristics of the NDD require comment: its clear association with human aging and the relationship among several NDD. Population aging (that facilitates the NDD increase) is a characteristic of human beings, and it is rare in nonhuman primates and other animals [13]. Cellular protein homeostasis is a time-dependent mechanism that is related both to aging and to neurodegenerative processes [14]. The degeneration hypothesis included the relationship of several degenerations. Although history completely changed its former significance, it is a fact that NDD are related. AD and PD are clearly associated [14, 15] as well as other NDD [1, 15, 16]. Why? We are in the field of proven facts without clear explanations.

In this complex scenario, the aforementioned review analyses the epidemiological evidence of co-occurrence of ET, PD and AD [1]. The relationship between ET and PD is a subject with a long history [8]. In this review, a clear and consistent relationship in case-control and population-based surveys measured by scientific tools (significant odds and relative risks) was demonstrated [1]. Perhaps there are not enough studies to completely end the discussion, but the consistency of the results and the biological plausibility of the association are very strong. ET and PD had a clear co-occurrence (in the same family, in the same brain) [17].

With fewer neuroepidemiological studies available, the association of ET and AD [1] is presented. This relationship is really a story of the last decade. Only two population-based surveys have investigated this subject [1]. At the moment, it is clear that ET is associated with several mild cognitive dysfunctions (mainly executive dysfunction), mild cognitive impairment, and with an increased risk of dementia (AD type) [18]. Does ET really predispose to suffering cognitive impairment and AD? This fascinating subject, in some way analogous to the association of cerebrovascular lesions and sporadic AD [19], needs more data. Future cohort studies with clinical, genetic and pathological examinations will probably verify these preliminary findings. The long-distance race of research into the ET-AD connection has begun.

Disclosure Statement
There are no conflicts of interest.

References
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