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LETTER TO THE EDITOR

Sudden unexpected death in Parkinson's disease: why do neuroscientists still ignore this condition?

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Although translational studies dramatically increased our understanding of the pathophysiology of Parkinson's disease (PD) over the last 200 years since its first description, PD is the second most common age-related neurodegenerative disorder after Alzheimer's disease and entails a major burden in disability, comorbidities, stigma, costs, and even mortality [1, 2]. With this in mind, the results presented in the interesting article recently published by Xue and colleagues [3], which discussed the 100 most cited articles on PD to point out the most impressive advances, developments, and discoveries in this field during the last century, evoked the following questions and considerations with regard to mortality in PD.

Why were neuroscientists in the last century not interested in the mortality of PD? Which are the mortality rates in PD? Can individuals with PD die prematurely? Are there cases of sudden death in PD?

Firstly, it is extremely important to emphasize that sudden cardiac death (SCD) is a complex disorder and a serious health problem since more than seven million lives per year are lost due to SCD worldwide [4]. Specifically, prospective studies utilizing multiple sources from the Americas, Europe, and Asia demonstrated that SCD rates range from 50 to 100 per 100,000 in the general population [5]. With respect to PD, mortality can be considered a "hot topic" representing an extensive field for neuroscience. Recently, our research group attempted to quantify mortality in PD in a research effort particularly since the "Decade of the Brain" declaration and to confirm its impact [2]. Briefly, a total of almost 97,000 articles associated exclusively with PD and 1650 scientific papers related to mortality in PD were found [2], demonstrating that only 2% of the published research articles since the "Decade of the Brain" declaration referred to mortality [2].

Concerning the articles about mortality in PD, some interesting data are attracting attention. For example, results from several well-conducted studies have shown that mortality in PD individuals is higher as compared to the general population [2, 6]. Moreover, a detailed study has demonstrated that mortality in PD is not increased in the first 5 years after disease onset, but increases thereafter, with a relative risk of 3.5 after 10 years [1, 6]. In all these cases, the leading causes of death in PD are pneumonia, cerebrovascular disease, and cardiovascular disease [2, 6]. Importantly, some studies published in recent years found that an increasing number of PD patients died suddenly and unexplained, referred as "Sudden Unexpected Death in Parkinson's Disease" (SUDPAR) [2, 7]. Considering that SUDPAR is a rare phenomenon, difficult to diagnose, and only rarely reported, it is a phenomenon that attracted the interest of the neuroscientific community since the late 1970s [7]. In a general context, SUDPAR is underinvestigated and not fully clarified. Nevertheless, an important retrospective study carried out in Japan a few years ago reviewed the clinical data and causes of death among 16 persons with PD who underwent post-mortem examinations [8]. In this study, 4 of 16 PD patients died suddenly without identifying a satisfactory cause of death, even after autopsy investigations. The authors concluded that a significant number of individuals with PD die of sudden death [8]. Currently, there is no general definition of SUDPAR available. In a didactic or even simplistic way, SUDPAR could be defined as an unexpected death in a patient with PD without any satisfactory explanation of death as determined by autopsy studies and review of the history [2, 7]. The true incidence of SUDPAR, however, is unknown and risk factors are not completely understood [2, 7]. Considering these facts, it has been speculated that duration of PD, gender, severity of motor involvement, sleep disorders, concomitant cardiac and pulmonary disease, and drug treatment, particularly polypharmacy, could be possible risk

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factors that may trigger sudden fatal events in PD patients [2, 7]. The possible pathophysiological mechanisms involve cardiac abnormalities, pulmonary disease, cerebral disease, or autonomic dysfunction, because ~60% of PD patients have cardiovascular disturbances, all have cerebral disease, and because of the frequent autonomic dysfunction in PD [2, 7]. While the specific risk factors and mechanisms of SUDPAR are not fully understood, prevention of SUDPAR is crucial [2, 7]. In doing so, we fully agree with the conclusions of Xue and colleagues [3] that despite the great progress made in research in PD, there is an urgent need to define appropriate topics for research as well as to design future studies.

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