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Letter to the Editor

Reply to the Letter to the Editor: Stefani A, "Is it too early to Underrate Genetic onto PD Pathogenesis? Reflections on History"

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We thank Dr. Stefani for sharing his comments [1] on our recent publication in which we argued that environmental factors take a principal role in the development of Parkinson's disease (PD), based on two perspectives from the field of genetics [2].

You draw attention to the fact that PD – or at least several parkinson-like signs – may have occurred before the description by James Parkinson in 1817. Indeed, some descriptions of what could have been PD are described sporadically in older literature, and we certainly acknowledge the likelihood of its existence before 1817, but we reiterate that it was definitely a rare disease prior to the 19th century. Whether the historical descriptions of these affected individuals referred to genetic cases or not remains unknown. One could speculate that specific de novo monogenetic forms of PD were around at the time, but which subsequently disappeared because of natural selection. Alternatively, as dr. Stefani points out, the parkinsonian signs in these historical cases could have been caused by natural organic compounds, for example because of an unusual appetite for plants containing toxins (for example, rotenone, a well-known pesticide, is derived from the plant deguelia utilis – although it is not known to be eaten). Nonetheless, the prevalence we encounter nowadays is beyond compare, and so is the rapid worldwide growth in the prevalence of PD, which would be difficult to reconcile with merely a largely unchanged genetic risk profile. If we specifically consider young-onset PD (which is commonly seen in persons with a genetic form of PD, its phenotype, especially in absence of treatment, is so remarkable that we would have expected more than the rare descriptions that exist in the older literature. Even in older times when overall survival was much lower than today, many individuals would have lived long enough to develop PD. Indeed, a sizeable subgroup of persons with PD develop the disease before the age of 65, and a certain percentage of them even under the age of 40 [3].

You also discuss the roles of age and sensitivity of the diagnosis. It is absolutely true that age is a major risk factor for developing PD, so the lower life expectancy in earlier times will certainly have reduced the risk of developing PD. It should be noted, however, that this lower life expectancy was partly driven by a high infancy mortality. Men that survived beyond the age of 15, and certainly those in wealthier parts of society, had an average life expectancy of around 60 over 2000 years ago [4]. Whether the association of PD risk with older age is an argument for genetics or for environmental factors can be reasoned both ways. We acknowledge that ageing could mean more time for a genetically driven subopti-

mal cellular process to become clinically apparent. Similarly, ageing could mean an increasing duration of exposure to environmental factors during the life course of an individual. As we have pointed out recently in this journal [5], one persuasive argument that argues for the latter explanation is the striking similarity between the age-related incidence of lung cancer and PD – both show a remarkably comparable increase in incidence with advancing age, but we widely acknowledge that in case of lung cancer, it is not ageing itself that causes the malignancy, but rather an accumulation of pack years that built up over time. Similarly, ageing would imply that people have had more time to be exposed to a cumulative number of environmental neurotoxins.

Another common explanation for the growth of PD is that our knowledge and awareness of the disease have increased, and that our ability to diagnose PD has improved. We feel that these factors do not play a major role. Our diagnostic skills and tools for other neurological disorders, such as multiple sclerosis, have increased considerably over time, thanks to the advent of for example advanced neuroimaging and analyses of the cerebral spinal fluid. However, the small growth of multiple sclerosis over the years is not comparable to the enormous growth of PD, even though this condition is diagnosed based on clinical grounds, without need for much ancillary testing, as it was done centuries ago [5]. Moreover, regardless of any improvements in diagnostic skills, it is difficult to imagine that later stages of PD (which invariably arise due to the progressive course of the disease) would have been missed even by a non-trained eye, and certainly without the availability of any symptomatic treatment. This would be especially true for persons with young-onset PD.

We do not mean to argue that genetics are not of importance, and we suspect that the etiology for the majority of persons with PD depends on an interaction between a genetic predisposition followed by exposure to environmental neurotoxins. A person's genotype likely determines his or her resilience against – or susceptibility to – environmental factors, which makes genetics highly relevant. In that regard, we refer readers to an excellent review paper published recently in this journal, and which highlights the importance of genetic factors in the etiology of PD [6]. We believe that these genetic factors, at least several of which appear to be very old, have become increasingly relevant in the last centuries following the advent of man-driven changes in environmental factors. The rapid growth of PD indicates that this gene-environment interaction is ongoing, and it calls for action.

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