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COMMENTARY

Is Alzheimer's disease a single illness or multiple illnesses?

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From the very first case of Alzheimer's disease described by Alois Alzheimer in 1901, there has been an appreciation for the heterogeneity of its symptoms. Alzheimer himself recognized that there were "variants" of the primary dementing illness that he described, including the early realization that not all persons diagnosed with the condition had plaques and tangles (Hippius and Neundörfer, 2003). Research in the subsequent decades has helped crystallize the concept of Alzheimer's disease as a pathological entity characterized by neurocognitive decline primarily in short-term memory, accompanied by other losses in cognitive function, and with multifactorial neurobiological underpinnings (Butterfield and Halliwell, 2019; Paroni *et al.*, 2019; Wang *et al.*, 2022). While it is acknowledged that there is no single risk factor or pathological process that can explain causation of Alzheimer's disease, a growing body of literature makes the case for why this may not be a single condition at all, but instead potentially a set of distinct neuropathological entities all of which have certain cognitive symptoms in common (Klinedinst *et al.*, 2020; Veitch *et al.*, 2019).

While such a conceptualization has not been formally proposed and is not reflected in the current diagnostic criteria for Alzheimer's disease, current models require updating to reflect the range of known risk factors and neuropathological correlates. There have even been calls for a single unifying theory of Alzheimer's disease that may explain the interactivity between these various factors (Khachaturian, 2000; Nehls, 2016). However, advances in our understanding of the neuropathology, genetics, and gene–environment interactions that may underlie Alzheimer's disease have not been sufficiently connected to real-world clinical outcomes. There is a significant gap in the literature around how clinical trajectories of Alzheimer's disease may differ based on an individual's unique combination of risk factors and neuropathology.

The paper in this issue of International Psychogeriatrics coauthored by Carl Cohen, Barry Reisberg, and Robert Yaffee represents a step in filling this gap. The authors' work demonstrates how trajectories of clinical outcomes vary. The authors follow 414 participants to study Alzheimer's Disease progression over the course of 5 years. They identified eight distinct trajectories of clinical outcome that they classify as five main categories with three subgroups. These include (in order of prevalence) fast decliners (32.6%), slow decliners (30.7%), zig-zag stable (i.e. persons whose outcomes showed variance over 5 years but stability compared to baseline at 5 years) (15.9%), stable (15.9%), and improvers (4.8%). The authors further describe three subcategories among the decliners including zig-zag decline (improve or decline then return to baseline), late decline (no change for many years, then decline), and curvilinear or "double zig-zag."

Most categories are self-explanatory, but the authors' finding of "zig-zag" trajectories bears closer consideration. In the simplest terms, it means that the course of illness is not linear, there are ups and downs in cognitive function. For some participants, this meant that their cognitive function improved after a brief initial decline; for others, it meant that it improved initially but then declined to baseline; and for some, it meant that after initial improvement or decline, their cognitive function was identical to baseline at the end of the monitoring period. The authors do note that some of these participants may have been misdiagnosed based on current diagnostic criteria, most notably the "improvers" and "stable" participants. Cohen and colleagues also outline risk and protective factors for quick and slow progression of Alzheimer's. Interestingly, they found that women with low baseline mini-mental status exam (MMSE) scores and taking cognitive-enhancing drugs were at the highest risk for a quick decline and short duration of illness.

Cohen and colleagues' approach is supported by high positive predictive value. However, this work still represents early-stage research into understanding the various clinical trajectories of Alzheimer's disease and identifying their determinants. This work opens up numerous avenues for consequential future research. Specific predictors of various cognitive trajectories will need to be identified. While this work does not delve into whether the various trajectories were accompanied by particular behavior symptoms, the ability to characterize and ultimately predict cognitive outcomes may also pave the way for better understanding of relationship between the cognitive and behavioral components of Alzheimer's disease. Advances in technology have meant that it is possible to quantify both cognition and behavior with a high degree of precision (Au-Yeung *et al.*, 2022; Germine *et al.*, 2021). The authors' finding that some persons experienced an improvement in cognitive status over time directly calls into question fundamental assumptions about Alzheimer's disease being accompanied by progressive decline and merits replication.

The work presented by Cohen and colleagues may help bridge the translational gap between neuropathological phenotypes, behavioral and cognitive phenotypes, and real-world clinical outcomes. Once the research advances to the point where predictive markers of outcomes are identified, fundamental shifts in our understanding of Alzheimer's disease are all but certain. This includes making a determination on whether this can even be considered a single entity or multiple entities that happen to have some common clinical features.

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