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Letter to the Editor

Not Only can Frailty Contribute to Cognitive Decline, but Conversely, Cognitive Impairment can also Promote Frailty

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Letter to the Editor

We read with interest the article by Gilles *et al.* regarding a prospective study that investigated whether frailty and biomarkers for cerebral disease (cerebral MRI, DaTSCAN, p-Tau181, NFL, GFAP) correlate with the severity of cognitive impairment over time in 168 patients with Alzheimer's disease, vascular dementia, or Lewy body dementia ^[1]. The study revealed that both frailty and cerebral pathologies influence cognitive function. However, only frailty was associated with neuropsychiatric symptoms such as apathy ^[1]. Increasing cerebral pathology correlated with progressive cognitive decline ^[1]. While the study is noteworthy, a few points warrant discussion.

A first point is that only symptoms of a neurological disorder served as an exclusion criterion. Symptoms are subjective in nature and do not necessarily indicate the absence of a prior neurological condition in a patient's medical history. Patients may have a history of traumatic brain injury, epilepsy, stroke, headache, cerebral hemorrhage, meningitis, encephalitis, multiple sclerosis, or malignancies without necessarily exhibiting symptoms of these conditions at the time of the study. Was a history of neurological disease a general exclusion criterion, or did this apply only if patients exhibited symptoms at the time of assessment?

A second point concerns the fact that the use of antipsychotics was an exclusion criterion, whereas the use of other medications affecting brain function apparently was not ^[1]. Since anticonvulsants, antidepressants, sedatives, cardiac medications, antihistamines, GLP-1 receptor agonists, and adrenergic stimulants can also affect cognitive functions and intellectual performance ^[2], it would have been necessary to exclude, as a general rule, all patients who regularly took medications affecting brain function.

A third point is that the frailty index has several disadvantages ^[3]. The main disadvantage lies in the wide range of score variation, which depends on the number of health deficits used to construct it. Furthermore, the index loses accuracy if health domains such as cognition or physical mobility are not taken into account. In groups of very ill or very elderly individuals, the index may reach its maximum value or cluster at the upper end of the scale, making it difficult to distinguish between different degrees of severe decline.

A fourth point is that the "vascular lesions" observed on MRI were not precisely defined ^[1]. A distinction should have been made regarding whether acute or chronic vascular lesions were being referred to and, in the case of chronic lesions, how they were defined. If chronic vascular lesions were defined solely based on T2 hyperintensities, classifying them as vascular lesions could be misleading. T2 hyperintensities can also result from aging processes, migraines, past infections, autoimmune diseases, hypoxia, intoxication, liver disease, vitamin deficiencies, neurofibromatosis, or low-grade astrocytomas ^[4]. Were these conditions actually ruled out as causes for the T2 hyperintensities?

A fifth point is that the absence of such a large amount of data is inexplicable ^[1]. If the study truly employed a prospective design, there should be no or very few missing data. What is the reason for the high proportion of missing data? Missing data call the results into question and make their interpretation doubtful. Participants with missing data should have been excluded from the analysis.

Overall, physical frailty increases the likelihood of a loss of memory and cognitive abilities. Conversely, poor brain function weakens the body and makes it more vulnerable. If one area deteriorates, it drags the other down with it in a recurring downward spiral.

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