A New Hypothesis (Concept) of Diagnosing Alzheimer’s Disease

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The diagnosis of dementia has proven problematic due to different criteria. Even neuropathological changes are arbitrarily defined. A mathematical model is proposed that may standardize diagnosis of dementia, and Alzheimer’s disease was used as an example. The model suggests that there are cognitive decline curves that represent the rate of natural attrition for neurons in the cerebral cortex. In normal aging, each individual will lose neurons along one curve. Individuals with higher brain reserve will start off at a higher percentile. An accelerated loss of neurons (dementia) is depicted as a deviation from the natural cognitive decline curve. This model may differentiate age-related cognitive decline from dementia or preclinical dementia. Furthermore, it may allow dementia to be diagnosed earlier, hence earlier treatment. Comparison of data may be easier and more valid if the diagnosis of dementia is standardized under this model. Advantages and challenges of this concept are further discussed.

**HYPOTHESIS**

With all of the above background information as baseline, I propose that there are cognitive decline curves that represent the rate of natural attrition for neurons in the cerebral cortex (Figure 1).

Under normal aging circumstances, each individual will lose neurons at a rate depicted along one curve. People with higher brain reserve will decline along a higher curve (percentile). In AD, however, instead of losing neurons at the usual rate, the individual is losing neurons at an accelerated rate. In other words, instead of declining along the natural curve, the individual’s decline has deviated to a steeper slope. The gradient of the slope is dictated by the intensity of the disease process (Figure 1). In events such as stroke or head injury, the person may sustain certain neuronal loss, which would shift the person’s decline to a lower curve (a new curve of natural attrition). Hence, the dementing process can be redefined as cognitive decline not following the...
natural attrition curve of decline, but as an accelerated process of cognitive decline that has dropped to a steeper/diseased curve. The rate of decline (or gradient of the curve) is determined by the intensity of the disease process. In this hypothesis, there is an assumption that cognitive function parallels the number of functioning neurons (or the rate at which neurons are dying parallels cognitive decline) (Figure 2). This idea is similar to the growth charts of children, except it is exactly the reverse process (reverse growth chart).

Therefore, instead of defining what is normal and what is not by comparing the cognitive performance of the concerned individuals with others, this new hypothesis redefines dementia as a “process of accelerated neuronal loss precipitated and driven by a disease process.” This new concept may explain why well-educated people can still perform quite well in cognitive tests and not be diagnosed as having dementia until they reach a late stage (because they have started off at a higher percentile curve), and their rate of decline may not reach the standard of dementia from the old definitions (e.g., Diagnostic and Statistical Manual or International Classification of Diseases) even though clearly they have the disease process. This will also explain the paradox of pathological evidence of dementia in post-mortem findings not echoed by clinical evidence in some well-educated individuals with high brain reserve.

Evidence Supporting the New Hypothesis

There is some evidence from longitudinal studies that supports the above model. Kemper and colleagues (23) have shown that cognitive functions involving linguistic abilities decline over time in healthy older adults as well as in those with dementia. However, AD accelerates the decline, regardless of age. Hall and colleagues (24) have demonstrated the use of Bayesian and profile likelihood methods to simultaneously estimate different change points in the longitudinal course of two different measurements of cognitive function in subjects who developed AD. Importantly, their analyses have shown that accelerated memory decline begins 7 to 8 years before the clinical diagnosis of AD, and speeded tasks begin 2 years before the diagnosis.

Njegovan and colleagues (25), in a longitudinal study of a large cohort of elders, have demonstrated that progressive cognitive decline is associated with a hierarchical pattern of loss of functional tasks. They believe that clear cognitive thresholds at which development of functional dependency (clinical dementia) occurs and its time could be estimated. This finding adds further weight to the hypothesis.

Challenges: Curvilinear Relationship of Cognitive and Behavioral Decline

In spite of some researchers’ beliefs that both cognitive impairment and behavioral problems increase throughout the course of AD (26,27), recent evidence (28,29) has shown that some behavioral problems may not parallel the decline of cognitive function. A recent longitudinal study of behavioral problems during AD indicated that curvilinear associations between dementia severity and certain behavioral problems (e.g., emotional and impulsive behaviors) exist (29). Some problem areas actually show improvements as AD progresses through severe stages (29). Therefore, although problems with activities of daily living continue to decline as AD progresses, the same cannot be said about some behavioral problems. The improvement in some behavioral problems may be related to the dying of those neurons controlling unwanted behaviors. Hence, emotional and impulsive behaviors may reduce in frequency and severity as the patient becomes more apathetic.

Advantages of This New Concept

With this new method of diagnosis, well-educated people with high brain reserve who have dementing process may be picked up earlier. This may prove to be an advantage in view of treatment currently available for AD.

Age-related cognitive decline may be differentiated easier and earlier from dementia or preclinical dementia.

This new concept may help to standardize the different diagnostic criteria being used amongst different researchers working in this field. This will have the advantage of more valid comparison of data for research purposes. The confirmation of the presence or absence of disease may not rely so
much on neuropathological findings, and this may enhance the accuracy of a lot of studies that currently rely on clinical diagnostic criteria alone. Not having to go through neuropathological examinations will also speed up the logistics of studies.

CHALLENGES

A large number of cases may need to be included and followed up with time to plot such curves of decline, and the logistics may be challenging. We also need to decide which neuropsychological battery of tests to use.

The hypothesis may require postmortem (neuropathological) studies for validation. Although not everyone will require postmortem studies, a subset of cases of both demented and non-demented individuals may be required to test its validity.

CONCLUSION

This hypothesis suggests that cognitive decline may be depicted mathematically by means of curves of decline. A deviation from the original percentile curve means there is accelerated neuronal loss and may be interpreted as dementia in progress. The hypothesis may be confirmed (or refuted) by following a large cohort with time and measuring their cognitive function as the cohort ages. Additional validation in the form of postmortem examination of brains may be required. Such a concept may standardize different diagnostic criteria for dementia and may make comparison of data more valid. It may also explain why some people may have neuropathological markers (high densities of plaques and tangles) of AD but function as nondemented individuals clinically. It will help to identify early AD cases as well as help to explain the brain reserve idea. Overall, it is an important hypothesis for us to explore further.

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