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.

Dementia is a common neurodegenerative disease affecting mainly older people. Alzheimer’s disease (AD) is the most common form of dementia, and its incidence doubles every 4.4 years from age 60 to 65 years upward (0.08% per year for 60–65 years, rising to 6.48% per year in the 85+ group) (1). The diagnostic criteria of dementia have undergone a lot of changes and updates through the years (e.g., 2,3) as new evidence from research necessitates the changes. According to the strictness of the criteria, the estimation of frequency of dementia in a population or the diagnosis of dementia can vary considerably (4). Because there is no reliable biological marker, the golden test for dementia (e.g., AD) is by autopsy and the finding of its characteristic neuropathological changes. This is, however, not possible or practical in everyday clinical practice. Even the pathological appearances of plaques and tangles can be found in normal aging, and the diagnosis of AD is therefore arbitrarily defined (e.g., by using a certain density of plaques present as a cut off [5] or density of neocortical neurofibrillary tangles as reference [6]).

Recently, the relationship between mild cognitive impairment, preclinical AD, and cognitive decline associated with aging has become a topic of contention. Whether they actually are entirely separate entities or whether they overlap or represent continuum of the dementing process is still being debated. This article attempts to redefine dementia in a mathematical model, using AD as an example. This hypothetical model would need to be studied in a large community population to test its validity.

**Basis for Hypothetical Model**

It is known that plaques and tangles are associated with neuronal loss in the cortex, which in turn is associated with AD. Aging causes natural attrition of neurons, and the rate of neuronal loss is probably accelerated in AD. The rate rises exponentially as suggested by epidemiological data (1,7–9). However, many investigators have found the correlation between brain pathology and brain function is imperfect. For instance, significant negative correlations have been reported between amyloid plaque density or neurofibrillary tangle counts and cognitive performance (10,11). Furthermore, the pathological features of AD may evolve over many years prior to clinical disease onset (12,13). Hence the hypothesis of brain reserve model, which suggests that people with high brain reserve (e.g., better education [14]) may have a higher cognitive performance, and therefore it takes longer to decline to the level of dementia than for people with low brain reserve (15). There is also some evidence (although not universally agreed upon) that brain pathology such as head injuries (16) and vascular diseases (17–19) may lower the brain reserve in AD.

Some aspects of cognition decline little (if at all) with age (20). However, age-related declines occur for the learning of new information (21) and in cerebral processing resources needed to encode and retrieve information (22).

**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.

Njegovon 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 demening 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 nondemented 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 dementing disease 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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References