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Insular Alzheimer disease pathology and the psychometric correlates of mortality

ABSTRACT

Right hemisphere dysfunction is associated with mortality in Alzheimer's disease (AD) and other neurologic conditions. These associations may be mediated by insular pathology, as insular lesions result in demonstrable changes in cardiovascular and autonomic control. AD affects the insulae at a preclinical stage, and insular AD pathology may be present in up to 40% of nondemented septuagenarians and octogenarians. This pathology can affect in vivo cardiac conduction and thereby dispose to cardiac arrhythmias and sudden death. Thus, AD pathology should be considered as a possible explanation for autonomic morbidity and mortality in nondemented elderly persons.

Only a few brain structures have been implicated in the autonomic control of blood pressure and heart rate. Among them are heteromodal association areas in the cortex, especially the insular cortex. Insular infarction has been associated with both cardiac arrhythmias and mortality. However, stroke may not be the only insular pathology with the potential to disrupt autonomic function. Alzheimer disease (AD) is associated with both insular pathology and autonomic dysfunction.

This article presents the hypothesis that autonomic dysfunction reflects subclinical stages of AD pathology affecting the insular cortex and discusses the resulting clinical implications.

AUTONOMIC DYSFUNCTION AS A PRODUCT OF SUBCLINICAL ALZHEIMER DISEASE

Braak and Braak have demonstrated a hierarchical progression of AD pathology that includes the insular cortex.[1] This may explain why AD has effects on blood pressure and central autonomic cardioregulatory functions. However, AD reaches the insular cortex at a "preclinical" stage in the Braak and Braak sequence (before "dementia" can be diagnosed). Thus, AD pathology should also be considered as a possible explanation for autonomic morbidity and mortality in *nondemented* elderly persons.[2]

Suggestive evidence

The following observations support this possibility:

- Clinical AD is associated with a wide range of dysautonomic phenomena. These can already be demonstrated at the initial diagnosis, which suggests a preclinical onset.
- Only a limited set of brain regions are capable of affecting autonomic control. The insulae are affected at a preclinical stage in the sequence of Braak and Braak (ie, stage III of VI).
- Neurofibrillary tangle (NFT) counts inside the insulae moderate the association between the heart rate–corrected QT interval (QTc) and survival. This has been demonstrated by my colleagues and I in collaboration with the Honolulu-Asia Aging Study, which is examining the association between insular pathology at autopsy and the slope of premorbid change in the QTc.

Implications of AD-mediated autonomic dysfunction

AD-mediated autonomic dysfunction could have important clinical implications:

- The prevalence of preclinical AD is likely to be higher than the number of demented cases. Many apparently well elderly persons may be affected solely on the basis of subclinical AD pathology.
- Autonomic functions have widespread effects; many cardiac and noncardiac "age-related" changes may actually be related to AD.
- Pharmacologic therapies for AD are known to delay the progression of symptoms and to reduce mortality; these medications may also impact AD-related autonomic problems.
- Conversely, the association between other medications and cardiac arrhythmias/sudden death may be mediated via effects on insular function.

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ALZHEIMER DISEASE DISRUPTS AUTONOMIC CONTROL

AD has been associated with a wide variety of dysautonomic phenomena, including increased pupillary dilation, altered skin conductivity, blunted autonomic response to noxious stimuli, diminished heart rate variability, depressed baroreflex sensitivity, and orthostasis. Autonomic instability has yet to be sought in mild cognitive impairment or even earlier preclinical stages of AD. However, nondemented subjects with mild cognitive impairment and early AD do experience more frequent falls and more gait and balance problems than do age-matched controls.

INSULAR CORTEX: A LIKELY TARGET

The insulae have been specifically implicated in the cortical control of autonomic function.[3] The vulnerability of the insular cortex to AD is easy to understand. NFTs appear to spread retrogradely along cortico-cortical and cortico-subcortical connections.[4] The insulae are mesiotemporal structures with direct connections to the hippocampus and entorhinal cortex.

Insular lesions result in changes in cardiovascular and autonomic control that are readily detectable by a variety of measures and procedures, including blood pressure, tilt table, balance platform, and electrocardiogram. The electrocardiographic effects of insular pathology include diminished heart rate variability, determined in either the time domain or the frequency domain. Diminished heart rate variability has been associated with increased mortality in cardiovascular disease and type 2 diabetes. It is important to note, however, that the effects of diminished heart rate variability are statistically *independent* of disease severity in these disorders, and that they can be demonstrated in the absence of clinically significant cardiovascular disease.[5]

HOLTER MONITOR EVIDENCE

Autopsy studies suggest that as many as 40% of nondemented septuagenarians and octogenarians may have AD pathology that is sufficiently advanced to affect the insular cortex.[1] This might explain the high prevalence of supraventricular arrhythmias and longitudinal decreases in heart rate variability among well elderly persons who are free of cardiovascular disease. In fact, unexplained supraventricular arrhythmias are quite common among such individuals. Both tachyarrhythmias and bradyarrhythmias are common on 24-hour Holter monitor recordings among subjects older than 80 years, and most are unexplained. In a study of the causes of syncope in a large (N = 711) sample of octogenarians, Lipsitz et al confirmed a cardiac etiology in only 21% of cases, whereas 31% of cases were unexplained.[6]

MORTALITY IN ALZHEIMER DISEASE IS ASSOCIATED WITH RIGHT HEMISPHERE DYSFUNCTION

AD pathology is widely thought to be symmetrically distributed. However, this may not be true of the preclinical "limbic" stages of AD.[7] Since insular effects on autonomic function are highly lateralized, the side of the brain affected by NFTs may be relevant to effects on cardiac rhythm and, hence, mortality risk.

Interestingly, mortality in AD is specifically associated with right hemisphere metabolic changes by electroencephalography, single-photon emission computed tomography, and positron emission tomography. Mortality can also be specifically associated with tests of constructional praxis. Claus and colleagues found that only the praxis subscore of the Cambridge Cognitive Examination (CAMCOG) was significantly related to survival in patients with early AD ($P < .001$).[8] Its predictive power was based on only two items: copying ability for a spiral and for a three-dimensional house. The effect was independent of age, sex, education, dementia severity, total CAMCOG score, and symptom duration. Similarly, Swan et al found a significant association between performance on the digit symbol substitution test and 5-year mortality among 1,118 subjects (with a mean age of 70.6 years) in the Western Collaborative Group Study.[9] In Cox regression analyses, the relative risk for all-cause mortality was 1.44 (95% confidence interval, 1.12 to 1.86) after adjustment for age, education, blood pressure, cancer, cardiovascular/cerebrovascular disease, and smoking.[9]

RIGHT HEMISPHERE DYSFUNCTION AFFECTS MORTALITY IN OTHER CONDITIONS

The effect of right hemisphere dysfunction on mortality is not limited to AD; it can also be demonstrated in other disorders, including epilepsy, head injury, and stroke.

We have been studying the cognitive correlates of mortality among well elderly septuagenarians and octogenarians living in a single comprehensive care retirement community (CCRC). Once again, visuospatial measures have been found to be selectively associated with mortality.[10] Clock drawing appears to be the cognitive predictor most strongly correlated

with mortality,[10] a finding that has been independently replicated in a second CCRC cohort.[11] This effect is independent of other cognitive domains, notably executive function.[10]

We recently examined the effect of insular NFTs on the association between QTc at examination 4 (circa 1991) of the Honolulu-Asia Aging Study and 12-year survival. Cases were dichotomized into those without and those with left or right insular NFT lesions (models 1, 2, 3, and 4 in **Table 1**). Each model was adjusted for age at exam 4. In the default models (1 and 2, with NFTs absent), neither age nor QTc at exam 4 was associated with survival; in contrast, in the presence of insular NFTs (models 3 and 4), age predicted survival **(Table 1)**. QTc trended toward significance in the presence of right insular pathology (model 4; $P = .067$) but not in the presence of left insular pathology (model 3). QTc was inversely related to survival in the presence of insular NFTs, suggesting that the effect of insular lesions on survival may be mediated through prolonged QT intervals.

TABLE 1
Insular neuropathology moderates associations of age and QTc with survival in the Honolulu-Asia Aging Study

	Estimate (days)*	SE	CR	*P*
No neurofibrillary tangles				
1. Left insula (n = 77)				
ΔtD ← QTc	3.50	2.09	1.13	.26
ΔtD ← Age	−18.11	16.27	−1.11	.27
2. Right insula (n = 73)				
ΔtD ← QTc	3.74	2.95	1.27	.21
ΔtD ← Age	−21.43	17.69	−1.21	.23
Neurofibrillary tangles present				
3. Left insula (n = 61)				
ΔtD ← QTc	−4.66	3.13	−1.49	.14
ΔtD ← Age	−48.82	18.88	−2.59	.01
4. Right insula (n = 65)				
ΔtD ← QTc	−5.96	3.26	−1.83	.067
ΔtD ← Age	−42.86	16.43	−2.61	< .01

* Estimated effect of each unit change in the predictor on mean survival in days.
QTc = corrected QT interval; SE = standard error; CR = critical range; ΔtD = time to death

SUMMARY

Right hemisphere dysfunction is associated with mortality in AD and other conditions. These associations may be mediated by insular pathology. AD affects the insulae at a preclinical stage, and insular AD pathology may affect as many as 40% of nondemented septuagenarians and octogenarians. This pathology can be shown to affect in vivo cardiac conduction, and may dispose elderly persons to cardiac arrhythmias and sudden death. If so, then AD must be considered a potential cause of cardiac arrhythmia, sudden death, and other autonomic disturbances in nondemented older adults.

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