Semantic dementia versus Alzheimer's disease: A matter of semantics?

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The last two decades have yielded remarkable advances in the understanding of neurodegenerative dementing illnesses. Although AD remains by far the most common cause, there is increasing evidence that other disorders account for perhaps 30% of the dementias. Among them, the frontotemporal dementias (FTD) represent an etiologically diverse group of disorders that share the pathologic feature of primary degeneration (cortical microvacuolation, neuronal loss, and gliosis) of frontal and anterior temporal lobes in the absence of the hallmark lesions of AD.[1] The prototype FTD is Pick's disease. The clinical profiles of Pick's disease and other FTD generally include progressive nonfluent aphasia, socially disruptive behaviors, or both depending on which brain regions carry the brunt of the pathologic involvement. The early and prominent disturbances in language (aspontaneity, agrammatism) and behavior (disinhibition, impaired social conduct, apathy) combined with relative preservation of declarative (episodic) memory distinguishes these disorders from AD. Atypical presentations of AD can occur, however, and may include both nonfluent aphasia[2] and frontal lobe features.[3]

The clinical overlap of FTD with atypical AD hampers differential diagnosis and is further complicated by the considerable heterogeneity and nonuniform nomenclature of FTD. Some investigators stress features common to all FTD disorders and use the term Pick complex to highlight similarities.[4] Others find identifiable FTD subtypes: frontotemporal dementia, progressive nonfluent aphasia, and semantic dementia.[1] Although FTD is usually sporadic, autosomal dominant forms occur and often are associated with parkinsonism and linkage to chromosome 17 (FTDP-17). Tau mutations appear to be causative in some FTDP-17 kindreds but in others tau linkage has been excluded.[5]

Efforts to better characterize the FTD subtypes may result in improved understanding of their etiopathogenesis and also may allow clinical distinction from AD. In this issue, Galton et al.[6] use structural MRI to compare the pathoanatomic correlates of semantic dementia (SD), the temporal lobe variant of FTD, with AD. Individuals with SD have deficits in word retrieval and word meaning (semantics) such that speech, although fluent, is progressively devoid of content words.[7] Other cognitive functions such as episodic memory are relatively preserved in early stage SD. Because different aspects of memory (see the Appendix) are affected in SD compared with AD, Galton et al. proposed that the two disorders would differ in volumetric measures of specific temporal areas. For example, because episodic memory loss is greater in AD, they expected greater medial temporal deterioration in AD than in SD. The results, however, indicated medial temporal lobe atrophy in both groups, although hippocampal atrophy was bilateral in individuals with AD but asymmetric (left greater than right) in individuals with SD. The individuals with SD also had greater atrophy of the temporal poles. Similar results recently have been reported by other investigators.[8]

The findings from this study are intriguing. The medial temporal atrophy in the individuals with SD with relatively intact episodic memory performance suggests that memory functions may depend on nontemporal cortical substrates to a greater extent than commonly assumed. Moreover, Galton et al. measured 14 temporal areas and found decreased volumes in five areas in the AD group (compared with control individuals) versus 11 in the SD group. Although volumetric studies do not address the functional health of brain structures, the unexpected pattern of less temporal atrophy in the group with more impaired episodic memory supports the idea

See also page 216

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that frontal lobe pathology may underlie at least some of the memory deficits observed in AD.[9] It would be useful to extend the studies in temporal regions reported by Galton et al. to frontal and other cortical areas for correlation with neuropsychological deficits and to provide further insights into brain–behavior relationships.

The Galton et al. paper provides excellent neuropsychological and structural profiles of individuals with AD and SD. Neuroimaging cannot resolve etiologic dilemmas, however, as it simply reflects pathoanatomy regardless of the underlying histology. Without neuropathologic confirmation of SD in cases studied by Galton et al., it is possible that unsuspected cases of atypical AD contaminated their sample and contributed to the unanticipated findings of medial temporal atrophy in SD. In fact, there is evidence that AD pathologic burden in frontal, temporal, or parietal lobes can be related to performance on specific neuropsychologic functions attributed to those regions.[10] Such data suggest that "focal" cognitive deficits may result from "focal" cortical damage in AD. Although SD has a distinct cognitive syndrome, in the absence of definitive biomarkers or known genotypes the unequivocal discrimination of SD and the other FTD from AD still depends on clinicopathologic correlation.

Appendix

General memory categories and measures*

1. Skill learning: Performance changes owing to practice; Pursuit Rotor Learning, Reverse-mirror tracking

2. Perceptual representation system: Representation involved in identity of objects; Benton Copy task

3. Semantic memory: Meaning-based information; Category fluency task, Pyramids and Palm Trees test, Famous Faces Test

4. Short-term memory: Highly accessible information from recent inputs, maintained for brief periods; Digit span forward for verbal information, Corsi Blocks forward for visual patterns

5. Working memory: Memory used in the active manipulation of information; Serial subtraction (e.g., 100–7), Digit span backward, Corsi Blocks backward

6. Episodic (long-term) memory: Reinstates autobiographical event; Logical memory paragraph recall, California Verbal Learning Test, Benton Delayed Recall

7. Source memory: Memory for source of information—e.g., who said what? List discrimination aspect of California Verbal Learning Test

*This categorization is a guide for neuropsychological tasks that primarily, but not exclusively, tap into different types of memory. These memory types can be studied via implicit tests (which primarily reflect performance changes without direct recollection of original event) and explicit tests (which primarily reflect performance changes with direct recollection of encoding event). For further details of tests and discussion of memory types, see references 11 and 12.

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