
Notes: Primary progressive aphasia (PPA) is a neurodegenerative disorder with language impairment as the primary feature. Different subtypes have been described and the 3 best characterized are progressive nonfluent aphasia (PNFA), semantic dementia (SD) and logopenic/phonological aphasia (LPA). Of these subtypes, LPA is most commonly associated with Alzheimer's disease (AD) pathology. However, the features of PPA associated with AD have not been fully defined. Here we retrospectively identified 14 patients with PPA and either pathologically confirmed AD or cerebrospinal fluid (CSF) biomarkers consistent with AD. Analysis of neurological and neuropsychological features revealed that all patients had a syndrome of LPA with relatively nonfluent spontaneous speech, phonemic errors, and reduced digit span; most patients also had impaired verbal episodic memory. Analysis of the pattern of cortical thinning in these patients revealed left posterior superior temporal, inferior parietal, medial temporal, and posterior cingulate involvement and in patients with more severe disease, increasing involvement of left anterior temporal and frontal cortices and right hemisphere areas in the temporoparietal junction, posterior cingulate, and medial temporal lobe. We propose that LPA may be a "unihemispheric" presentation of AD, and discuss this concept in relation to accumulating evidence concerning language dysfunction in AD.


Notes: Posterior cortical atrophy (PCA) is a neurodegenerative syndrome that is characterised by progressive decline in visuospatial, visuoperceptual, literacy, and praxic skills. The progressive neurodegeneration affecting parietal, occipital, and occipitotemporal cortices that underlies PCA is attributable to Alzheimer's disease in most patients. However, alternative underlying causes, including dementia with Lewy bodies, corticobasal degeneration, and prion disease, have also been identified, and not all patients with PCA have atrophy on clinical imaging. This heterogeneity has led to inconsistencies in diagnosis and terminology and difficulties in comparing studies from different centres, and has restricted the generalisability of findings from clinical trials and investigations of factors that drive phenotypic variability. Important challenges remain, including the identification of factors associated not only with the selective vulnerability of posterior cortical regions but also with the young age of onset of PCA. Greater awareness of the syndrome and agreement over the correspondence between syndrome-level and disease-level classifications are needed to improve diagnostic accuracy, clinical management, and the design of research studies.Dementia Research Centre, Institute of Neurology, University College London, London, UK.


Notes: With the prospect of prevention trials for familial Alzheimer's disease on the horizon, understanding the natural history of the illness has never been so important. Earlier this year in The Lancet Neurology, Acosta-Baena and colleagues published the results of the largest and longest retrospective study of pre-dementia clinical stages in familial Alzheimer's disease to date. By reviewing serial neuropsychological assessments of individuals from a large Colombian kindred affected by the E280A mutation in the Presenilin 1 gene, they defined three stages of pre-dementia cognitive impairment. Using survival analyses, the authors estimated the median age at onset and rate of progression through each of these stages towards dementia and ultimately death. Their study provides valuable insights into the time course of cognitive decline associated with this mutation. Furthermore, the study highlights some of the challenges of defining pre-dementia clinical stages in familial Alzheimer's disease and the need for the field to develop a consistent terminology.

tomography imaging of amyloid deposition in presenilin 1 mutation carriers. *Brain, 134*, 293-300.

Notes: (11)Carbon-Pittsburgh compound B positron emission tomography studies have suggested early and prominent amyloid deposition in the striatum in presenilin 1 mutation carriers. This cross-sectional study examines the (11)Carbon-Pittsburgh compound B positron emission tomography imaging profiles of presymptomatic and mildly affected (mini-mental state examination >/= 20) carriers of seven presenilin 1 mutations, comparing them with groups of controls and symptomatic sporadic Alzheimer's disease cases. Parametric ratio images representing (11)Carbon-Pittsburgh compound B retention from 60 to 90 min were created using the pons as a reference region and nine regions of interest were studied. We confirmed that increased amyloid load may be detected in presymptomatic presenilin 1 mutation carriers with (11)Carbon-Pittsburgh compound B positron emission tomography and that the pattern of retention is heterogeneous. Comparison of presenilin 1 and sporadic Alzheimer's disease groups revealed significantly greater thalamic retention in the presenilin 1 group and significantly greater frontotemporal retention in the sporadic Alzheimer's disease group. A few individuals with presenilin 1 mutations showed increased cerebellar (11)Carbon-Pittsburgh compound B retention suggesting that this region may not be as suitable a reference region in familial Alzheimer's disease.


Notes: A diagnosis of dementia is devastating at any age but diagnosis in younger patients presents a particular challenge. The differential diagnosis is broad as late presentation of metabolic disease is common and the burden of inherited dementia is higher in these patients than in patients with late-onset dementia. The presentation of the common degenerative diseases of late life, such as Alzheimer's disease, can be different when presenting in the fifth or sixth decade. Moreover, many of the young-onset dementias are treatable. The identification of causative genes for many of the inherited degenerative dementias has led to an understanding of the molecular pathology, which is also applicable to later-onset sporadic disease. This understanding offers the potential for future treatments to be tailored to a specific diagnosis of both young-onset and late-onset dementia.

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Notes: The clinical and neuroanatomical correlates of specific apraxias in neurodegenerative disease are not well understood. Here we addressed this issue in progressive nonfluent aphasia (PNFA), a canonical subtype of frontotemporal lobar degeneration that has been consistently associated with apraxia of speech (AOS) and in some cases orofacial apraxia, limb apraxia and/or parkinsonism. Sixteen patients with PNFA according to current consensus criteria were studied. Three patients had a corticobasal syndrome (CBS) and two a progressive supranuclear palsy (PSP) syndrome. Speech, orofacial and limb praxis functions were assessed using the Apraxia Battery for Adults-2 and a voxel-based morphometry (VBM) analysis was conducted on brain MRI scans from the patient cohort in order to identify neuroanatomical correlates. All patients had AOS based on reduced diadochokinetic rate, 69% of cases had an abnormal orofacial apraxia score and 44% of cases (including the three CBS cases and one case with PSP) had an abnormal limb apraxia score. Severity of orofacial apraxia (but not AOS or limb apraxia) correlated with estimated clinical disease duration. The VBM analysis identified distinct neuroanatomical bases for each form of apraxia: the severity of AOS correlated with left posterior inferior frontal lobe atrophy; orofacial apraxia with left middle frontal, premotor and supplementary motor cortical atrophy; and limb apraxia with left inferior parietal lobe atrophy. Our findings show that apraxia of various kinds can be a clinical issue in PNFA and demonstrate that specific apraxias are clinically and anatomically dissociable within this population of patients.

The purpose of this study was to devise quantitative methods for the assessment of praxic skills of the upper limbs by developing a computerised task which permits each component of a sequence of actions to be timed precisely. Furthermore, two versions of such a quantitative measure were developed to investigate the relationship between meaningful and meaningless movements. The praxic skills of 35 patients with Alzheimer's disease (AD) and 75 healthy controls were assessed on two 3-item sequential movement tasks involving either meaningful or meaningless actions. A qualitative rating scale assessment of gesture imitation and pantomime was also administered. AD patients were significantly slower than controls on both the sequential movement tasks. Indeed, the correlation between AD patients' abilities on the novel and traditional tasks provided evidence that the sequential movement tasks constitute valid measures of praxis. Within the AD population, disease severity was also found to have a minimal and inconsistent influence upon praxis. The apraxia assessment results are considered in relation to the debate over whether apraxia constitutes an early or late feature of AD, and also to theoretical claims about the cognitive neuropsychological deficit underlying ideational apraxia.


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Patients with familial Alzheimer's disease and a subset known to have presenilin mutations were compared with sporadic cases on a comprehensive battery of cognitive tests. These included measures of memory, intelligence, language and perception. The three groups were very comparable, in terms of severity, on global measures of dementia. However, their profiles/patterns of cognitive impairment differed in two respects; the group with sporadic Alzheimer's disease were significantly more impaired on tests of object naming and object perception than either the group with familial Alzheimer's disease or group with familial Alzheimer's disease and presenilin mutations, yet they scored at a significantly higher level on the measure of verbal intelligence. This study provides further evidence of the heterogeneity of the disease process.


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What is to be understood by the term Pick's disease? Is this a clinical syndrome(s) of frontotemporal lobar atrophy, or a more specific clinicopathological concept of frontotemporal lobar atrophy with Pick bodies and/or Pick cells on neuropathology? The author discusses these concepts in an historical context as an introduction to this symposium.


Notes: Dementia Research Group, National Hospital for Neurology and Neurosurgery, London, United Kingdom. K.homan@sm.ic.ac.uk Subtle phenotypic differences between familial Alzheimer's disease (FAD) pedigrees can be identified which may reflect the genetic and allelic heterogeneity of the disease. Positron emission tomography (PET) of APP mutation and chromosome 14- linked FAD pedigree members reveals biparietal bitemporal hypometabolism. Scanning of asymptomatic at-risk individuals reveals a similar, but quantitatively less severe, pattern of hypometabolism.