ARCHIVAL REPORT

Small Vessel Disease, but Neither Amyloid Load nor Metabolic Deficit, Is Dependent on Age at Onset in Alzheimer's Disease

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Background: There is controversy concerning whether Alzheimer's disease (AD) with early onset is distinct from AD with late onset with regard to amyloid pathology and neuronal metabolic deficit. We hypothesized that compared with patients with early-onset AD, patients with late-onset AD have more comorbid small vessel disease (SVD) contributing to clinical severity, whereas there are no differences in amyloid pathology and neuronal metabolic deficit.

Methods: The study included two groups of patients with probable AD dementia with evidence of the AD pathophysiologic process: 24 patients with age at onset $<$60 years old and 36 patients with age at onset $>$70 years old. Amyloid deposition was assessed using carbon-11–labeled Pittsburgh compound B positron emission tomography, comorbid SVD was assessed using magnetic resonance imaging, and neuronal metabolic deficit was assessed using fluorodeoxyglucose positron emission tomography. Group differences of global and regional distribution of pathology were explored using region of interest and voxel-based analyses, respectively, carefully controlling for the influence of dementia severity, apolipoprotein E genotype, and in particular SVD. The pattern of cognitive impairment was determined using *z* scores of the subtests of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery.

Results: Patients with late-onset AD showed a significantly greater amount of SVD. No statistically significant differences in global or regional amyloid deposition or neuronal metabolic deficit between the two groups were revealed. However, when not controlling for SVD, subtle differences in fluorodeoxyglucose uptake between early-onset AD and late-onset AD groups were detectable. There were no significant differences regarding cognitive functioning.

Conclusions: Age at onset does not influence amyloid deposition or neuronal metabolic deficit in AD. The greater extent of SVD in late-onset AD influences the association between neuronal metabolic deficit and clinical symptoms.

Key Words: AD, age at onset, Alzheimer's disease, amyloid load, metabolic deficit, small vessel disease

Since Alois Alzheimer's seminal publications (1,2) there has been continuing controversy concerning whether Alzheimer's disease (AD) with early onset and AD with late onset represent variants of the same clinicopathologic entity or are separate brain diseases with distinct etiology, pathophysiology, and clinical symptoms (3,4). Although no qualitative pathologic or clinical differences have been identified, many studies reported quantitative heterogeneity of early-onset AD and late-onset AD with regard to core features of the disease (neurofibrillary tangles, senile plaques, amyloid deposition, neuronal metabolic deficit, and pattern of cognitive symptoms). This heterogeneity is considered by DSM-IV, which treats early-onset AD and late-onset AD as disease variants dependent on age of onset.

Previous studies demonstrated more severe loss of neurons (5) and synapses (6) and higher neuritic plaque count in the frontal parietal lobe (6) in patients with early-onset AD. A more severe neuronal metabolic deficit (7,8) and an increased amyloid deposition (9,10) have been demonstrated in vivo in early-onset AD using the positron emission tomography (PET) tracers fluorodeoxyglucose (FDG) (11) (for neuronal metabolic deficit) and carbon-11–labeled Pittsburgh compound B ([^{11}C]PiB) (12) (for amyloid deposition). With regard to pattern of cognitive symptoms, atypical presentations such as prominent language or visuospatial impairment (13,14) and more severe deficits in praxis and attention skills (13,14) were found to be more frequent in patients with early-onset AD. Patients with late-onset AD were reported to score significantly lower on memory and naming tests and orientation (13–15).

Amyloid deposition, neuronal metabolic deficit, and cognitive functioning, which we use as indicators and consequences of AD pathology in the present study, are influenced by numerous factors, which need to be considered when comparing potential subgroups or variants of AD. Specifically, amyloid deposition (16), neuronal metabolic deficit (17), and cognitive functioning (18) are

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dependent on severity of dementia, which is a correlate of disease stage. Amyloid deposition (19) and neuronal metabolic deficit (20) are enhanced by the presence of the apolipoprotein E (*APOE*) ε4 allele.

Another factor that significantly influences the manifestation and possibly the development of AD pathology is comorbid cerebrovascular lesions (CVL), in particular small vessel changes (21). The prevalence of comorbid CVL increases with age (22) and is a common histopathologic finding in patients with AD (23). In the presence of CVL, a lower density of amyloid plaques and neurofibrillary tangles is found at comparable dementia severity (24) suggesting that AD and CVL have additive effects on the development of clinical symptoms. The consequence of small vessel disease (SVD) can be assessed using magnetic resonance imaging (MRI); white matter hyperintensities (WMH) can be evaluated with fluid-attenuated inversion recovery (FLAIR) MRI, and lacunar infarcts can be evaluated with T1-weighted MRI (25). The extent of WMH is a risk factor for AD dementia (26). In patients with late-onset AD, WMH are more pronounced (27) and are associated with an increased rate of amyloid deposition (28).

The above-mentioned parameters that influence amyloid deposition, neuronal metabolic deficit, and cognitive functioning were not consistently taken into account in previous studies comparing early-onset AD and late-onset AD. We hypothesized that early-onset AD and late-onset AD differ neither with regard to core features of AD pathology that are demonstrable in vivo (i.e., amyloid deposition and neuronal metabolic deficit) nor in terms of clinical symptoms when clinical severity, APOE genotype, and SVD are factored in. We compared the quantity and regional distribution of amyloid deposition, the degree and regional pattern of neuronal metabolic deficit, and the pattern of cognitive impairment between patients with early-onset AD and patients with late-onset AD, controlling for overall severity of dementia, *APOE* genotype, sex, and amount of SVD. Additionally, we assessed the relevance of controlling for SVD when comparing amyloid deposition and neuronal metabolic deficits between patients with early-onset AD and patients with late-onset AD because this was consistently not done in previous studies.

Methods and Materials

Patient Recruitment and Inclusion and Exclusion Criteria

Patients were recruited from the research outpatient unit for cognitive disorders at the Department of Psychiatry, Klinikum rechts der Isar, Technische Universitaet Muenchen, Munich, Germany. The patients had been referred for diagnostic evaluation of cognitive impairment by general practitioners, neurologists, psychiatrists, or other institutions and had undergone a standardized diagnostic procedure. The study protocol was approved by the medical faculty's ethics committee and by radiation protection authorities. All patients provided written informed consent before any study-specific procedures were undertaken.

The standard diagnostic work-up included an interview with the patient and an informant; psychiatric, neurologic, and physical examinations; neuropsychological evaluation including the Mini-Mental State Examination (MMSE) (29) and the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery (30); routine laboratory screening; and *APOE* genotyping. The severity of cognitive impairment was rated on the Clinical Dementia Rating (CDR) scale (31); the subscale scores were used to calculate the CDR sum of boxes (CDR SOB). Cranial MRI was performed to assess structural brain abnormalities. In addition to this, study participants underwent cranial FDG-PET to determine neuronal metabolic deficit and [^{11}C]PiB-PET to assess brain amyloid deposition. All assessments were completed within a 3-months period in each patient.

Study participants met the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association diagnostic criteria for probable AD (32). Additionally, patients were required to have AD typical FDG uptake on PET (33) to enhance the likelihood of underlying AD pathology (34) (i.e., hypometabolism in the temporoparietal and posterior cingulate cortex with relative sparing of the primary sensorimotor cortex on visual inspection). Participants also met the new National Institute on Aging and Alzheimer's Association criteria of probable AD dementia with evidence of the AD pathophysiologic process (35). Patients with very mild to moderate dementia as defined by global CDR scale ratings of .5, 1, or 2 were included. The onset of symptoms was estimated from caregivers' observations. Because these estimations are often imprecise, we sought to reduce misclassification by defining early-onset AD as an age of onset ≤60 years and late-onset AD as an age of onset ≥70 years ("onset groups").

Patients were not included in the study if they met diagnostic criteria for other neurologic or psychiatric disorders, including Parkinson's disease, normal-pressure hydrocephalus, progressive nuclear palsy, or major depression. Patients were also excluded if they exhibited dilated perivascular spaces or any major abnormalities on MRI. The National Institute of Neurological Disorders and Stroke and the Association International pour la Recherché et l'Enseignement en Neurosciences criteria were used to exclude vascular dementia (36). Patients with other possible causes of cognitive impairment, such as psychotropic medication (e.g., antidepressants, antipsychotics), substance abuse, or major abnormalities in routine blood testing, were not enrolled. Findings on [^{11}C]PiB-PET were not used as inclusion criteria.

Laboratory Screen and *APOE* Genotyping

Routine blood screening included a standard serologic chemistry group, complete blood cell count, blood glucose, vitamin B_{12} and folic acid levels, thyroid hormone levels, and serologic tests for syphilis and Lyme borreliosis. The *APOE* genotype was determined following a standardized protocol using a polymerase chain reaction–based assay, which simultaneously uses two distinct restriction enzymes (37).

Brain Imaging

Structural MRI, FDG-PET, and [^{11}C]PiB-PET of the brain were performed using standard procedures as described previously (16). Patients underwent cranial MRI examination on a 1.5-tesla Siemens MAGNETOM Symphony (Siemens Healthcare, Erlangen, Germany) MRI scanner using a standardized imaging protocol that consisted of a three-dimensional T1 dataset (repetition time [TR] = 1520 msec; echo time [TE] = 3.93 msec; matrix = 256 × 256; flip angle = 15°; 1-mm slices); axial T2-weighted turbo spin echo images (TR = 4510 msec; TE = 104 msec; 19 slices; voxel dimensions = .6 mm × .5 mm × 6.0 mm); coronal T1-weighted spin echo images (TR = 527 msec; TE = 17 msec; 19 slices; voxel dimensions = .9 mm × .9 mm × 6.0 mm); T2-weighted gradient echo images (TR = 725; TE = 29; 19 slices; voxel dimensions = .7 mm × .7 mm × 6.0 mm); and axial FLAIR images (TR = 9000 msec; TE = 105 msec; inversion time = 2500 msec; 3-mm slices).

A Siemens ECAT HR+ PET scanner (Siemens/CTI, Knoxville, Tennessee) was used to obtain FDG-PET images. The patients