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# Age at Onset and SPECT Imaging in Alzheimer's Disease

*P. Caffarra*[a]
*A. Scaglioni*[b]
*L. Malvezzi*[b]
*P. Previdi*[c]
*L. Spreafico*[d]
*D. Salmaso*[e]

[a] Institute of Neurology, University of Parma, and
[b] Division of Neurology, Fidenza, Parma;
[c] Division of Neurology, Mantua;
[d] Nuclear Medicine Section, Legnano, Milan;
[e] Institute of Psychology, CNR, Rome, Italy

**Key Words**
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**Abstract**
It is generally accepted that presenile Alzheimer's disease (AD) has faster progression and severer clinical manifestation than senile onset AD. Recently a relative left frontal hypoperfusion was only found in patients with presenile AD by using SPECT imaging. The aim of the present report was to ascertain whether the same conclusion could be drawn matching the population with respect to the severity of the cognitive profile and disease duration. Twenty subjects for each group were studied with SPECT and no differences emerged between groups. It is postulated that presenile and senile onset AD represent aspects of the same biological process.

Accumulating evidence suggests that Alzheimer's disease (AD) is the major cause of dementia today, affecting 5–6% of the population over 65 and approximately 25% over 80. Several studies have reported that AD may be divided into clinical and cognitive subgroups [1, 2]. Usually it is believed that early onset AD takes a more fulminant course, involving greater language impairment and a more cognitive decline than late-onset AD [2–4]. Conversely there are studies which did not find any difference in language severity between the early and late-onset AD [5] or in rate of progression and institutionalization [6]. The neurobiological basis remains controversial, although a number of investigators have observed severer neuropathological and neurochemical changes in young AD subjects than in senile patients with AD [7, 8]. An attempt to answer this question has been recently proposed by Jagust et al. [9], using single photon emission tomography (SPECT) which has recently become available. For many years one of the more promising agents for demonstrating regional cerebral blood flow were the $^{123}$I-labeld amine derivatives and in the past two years the $^{99m}$TcHM-PAO [10–14]. Furthermore SPECT has proved to be potentially useful in detecting AD by demonstrating patterns of reduced cerebral blood flow in temporoparietal association cortex [13, 15–17] comparable to those obtained with a more sophisticated procedure, such as positron emission tomography (PET) [18, 19].

Returning to the main question of this report, the relationship of age at onset of AD and its clinical severity, Jagust et al. [9] reported a relative left frontal hypoperfusion in presenile but not in senile-onset patients using SPECT imaging. They concluded that available data provide evidence for an involvement of left-frontal hemisphere in patients with early onset Alzheimer's disease. Nevertheless the groups of patients described in their article, although not differing in educational level or disease duration, diverged in terms of cognitive profile (MMS presenile group = 10.8 vs MMS senile group = 18.6; $p < 0.02$).

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Paolo Caffarra, MD
Institute of Neurology
University of Parma
Via del Quartiere n. 4
I-43100 Parma (Italy)


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These findings have prompted us to replicate the study, with the further constraint of matching presenile and senile groups also for cognitive level. In this case any neurophysiological difference, in terms of cerebral perfusion, could be considered as further evidence of a biological heterogeneity.

## Subjects and Methods

Forty subjects with SPECT and cognitive data available, selected among approximately 130 demented patients referred to the Dementia Research Unit of the University Neurological Department in Parma and Division of Neurology in Mantua, Italy, between 1988 and 1990, were retrospectively studied. Patients were chosen on the basis of age at onset of the disease and the same cluster of neuropsychological tests. Selection criteria included the NINCDS-ARDRA [20] and DSM-III-R criteria [21] for probable AD, level of severity according to the Clinical Dementia Rating Scale [22], as well as thorough medical and laboratory investigation, including CT scan or NMR, serum B12 and folate level, thyroid functions in order to exclude any possible cause of secondary dementia. The Modified Ischemic Score [23] was less than 2 and depression or anxiety were excluded using the Hospital Anxiety Depression Scale [24] and clinical interview. In AD patients age at onset of behavioral disorders was based on interviews with a general practitioner, relatives or friends. Obviously this variable is approximate, depending primarily on the neurobehavioral mode of the onset and on the cultural background of the patient's family.

Psychological assessment included Mini Mental State (MMS) examination [25] and the Brief Battery for Mental Deterioration (BBDM) [26]. The MMS assess memory, language, orientation and praxis and is scored by counting the correct responses. The maximum score is 30 and a score of less than 24 or 23 is usually regarded as evidence of organic brain impairment, although it has no diagnostic value. The BBDM adopted the discriminant analysis to obtain the probability level of normality and nonnormality and encompasses several cognitive functions as orientation, verbal and visual short and long-term memory, verbal reasoning and attention.

SPECT imaging was conducted within 1 month of neuropsychological testing. All subjects were injected with eyes and ears unoccluded in a quiet room. The injected dose of $^{99m}$Tc HM-PAO was 550–750 MBq (15–20 mCi) and imaging was performed 15–30 min after injection. Data acquisition and reconstruction were performed with a conventional rotating gamma camera computer system (APEX 415) equipped with a high-efficiency, low-energy collimator.

SPECT data acquisition required 120 projections 3° apart in a 64 × 64 bytes matrix (zoom 1.5). Data acquisition time was 20 min. The entire study contained $3 \times 10^6$ to $4 \times 10^6$ counts.

The raw data, after uniformity correction and nine point smoothing, were reconstructed by filtered backprojection using a Hamming filter. Following attenuation correction, coronal, sagittal and orbitomeatal (OM) tomograms were reconstructed. Each slice was 2 pixels thick (about 0.8 cm).

For each subject two slices were considered, corresponding to the basal ganglia level (BG) and to the mid-ventricular level (V), respectively at 4 and 5.6 cm above the OM line, considered as reference plane.

**Table 1.** Demographic characteristics of presenile and senile-onset AD patients

| | Presenile | | Senile | |
|---|---|---|---|---|
| | mean | SD | mean | SD |
| Patients | 20 | | 20 | |
| Age, years | 61 | 6.7 | 72.2 | 3.9* |
| Gender, M/F | 5/15 | | 7/13 | |
| Education | 5.6 | 2.5 | 4.3 | 1.3 |
| Disease duration | 3.3 | 1.5 | 2.3 | 2.2 |
| MMSE | 18.6 | 6.4 | 17.2 | 4.2 |

* $t = 6.5$; d.f. = 38; $p < 0.001$.

At each level four regions of interest (ROI; 6.2 × 6.2 pixels large) were symmetrically located on each hemisphere, four on the left and four on the right of the cortical ribbon: inferior frontal (IF: level BG), dorsolateral frontal (DF; level V), anterior temporoparietal (aTP: level BG and level V), posterior temporoparietal (pTP: level BG and level V) and occipital (O).

ROIs were manually drawn with reference to a standard anatomic atlas correlated with CT scan [27, 28]. The semiquantitative assessment of rCBF was obtained as a ratio of activity distribution in the cortical ROIs to the activity in the cerebellar ROIs. Cerebellar activity was chosen as reference because neuropathological studies have shown this area relatively intact in AD [29].

Although recently criticized [17] for the long interval necessary to complete the scintigraphic examination, we did not find a high refusal rate by the patients. A further ratio was obtained in accordance to that previously described [9]. This ratio provides information on the asymmetry of the cerebral perfusion and is calculated as the activity density in the left hemisphere minus the activity density in the controlateral hemisphere, divided by the mean of left and right. A negative value is representative of the relative left-hemisphere hypoperfusion.

## Analysis and Results

*Demographic Variables.* There was no difference between level of education, disease duration, gender and cognitive profile between early and late onset AD patients (table 1). There was also no difference between groups for handedness, extrapyramidal signs or family history of dementia.

*Regional Analysis.* The mean values for each ROI and levels are illustrated in tables 2 and 3, respectively. Multivariate analysis of variance for repeated measures was employed, where group was a between-group factor, while level, ROI and hemisphere were within-group factors. ANOVA revealed a significant effect of (a) level (F =

**Table 2.** Mean values of cortical/cerebellar ratios at basal ganglia level for each ROI for both groups

| | LH | RH |
|---|---|---|
| *Presenile* | | |
| IF | 0.793 (0.096) | 0.797 (0.1) |
| aTP | 0.801 (0.079) | 0.831 (0.09) |
| pTP | 0.823 (0.084) | 0.833 (0.08) |
| O | 0.900 (0.091) | 0.910 (0.09) |
| *Senile* | | |
| IF | 0.791 (0.064) | 0.806 (0.073) |
| aTP | 0.797 (0.066) | 0.812 (0.076) |
| pTP | 0.815 (0.061) | 0.837 (0.095) |
| O | 0.897 (0.071) | 0.894 (0.063) |

LH: Left hemisphere; RH: right hemisphere. Standard deviations are in parentheses.

**Table 3.** Mean values of cortical/cerebellar ratios at ventricular level for each ROI for both groups

| | LH | RH |
|---|---|---|
| *Presenile* | | |
| DF | 0.777 (0.110) | 0.791 (0.093) |
| aTP | 0.771 (0.090) | 0.796 (0.095) |
| pTP | 0.768 (0.095) | 0.808 (0.093) |
| O | 0.817 (0.113) | 0.844 (0.096) |
| *Senile* | | |
| DF | 0.763 (0.074) | 0.791 (0.079) |
| aTP | 0.764 (0.055) | 0.793 (0.052) |
| pTP | 0.800 (0.076) | 0.834 (0.078) |
| O | 0.800 (0.076) | 0.834 (0.078) |

LH: Left hemisphere; RH: right hemisphere. Standard deviations are in parentheses.

43.414; d.f. = 1,38; $p < 0.0001$); (b) ROI ($F = 31.441$; d.f. = 3,114; $p < 0.0001$) and (c) hemisphere ($F = 15.632$; d.f. = 1,38; $p < 0.0001$).

Group was not significant ($F = 0.018$; d.f. = 1; $p = 0.894$). Level × ROI interaction was also significant ($F = 12.419$; d.f. = 3,14; $p < 0.0001$). The mean for level × ROI interaction was for basal ganglia level IF = 0.80; aTP = 0.81; pTP = 0.83; O = 0.90 and for ventricular level SF = 0.78; aTP = 0.78; pTP = 0.79; O = 0.83. Post-hoc analysis performed on each ROI showed a significant difference between the first three ROIs and the occipital ones ($F = 423.5$; d.f. = 2.38; $p < 0.001$). In order to ascertain whether the severity of the cognitive impairment was an important intragroup factor, the MMS total score was considered. Each group was empirically divided according to the MMS total score: below or equal 19 or above 19. This produced four subgroups as indicated in table 4. Within each MMS group there were no statistical differences between presenile and senile patients also for disease duration. ANOVA analysis made considering MMS as a between-group factor indicated no effects for MMS and their interactions. Even the study of the correlation between MMS and ROI did not show any significant effect.

**Table 4.** Mean and SD of MMS total score for presenile and senile AD subjects divided according to the empirical severity score of 19 (as indicated in the text there is no difference between groups)

| Group | n | MMS | | Disease duration | |
|---|---|---|---|---|---|
| | | mean | SD | mean | SD |
| MMS ⩽ 19 | | | | | |
| Presenile | 9 | 13.0 | 3.775 | 3.888 | 1.76 |
| Senile | 12 | 14.5 | 2.468 | 2.307 | 2.05 |
| MMS > 19 | | | | | |
| Presenile | 10 | 23.7 | 2.869 | 2.727 | 1.27 |
| Senile | 7 | 21.9 | 1.464 | 2.428 | 2.99 |

*Hemispheric Asymmetries.* The relationship between hemispheric asymmetry and dementia was examined in two ways: (a) through a global hemispheric index (L–R)/(L+R)/2, where negative values are indicative of left hypoperfusion, and (b) through the asymmetry ratio of each brain region. The mean of the hemispheric index was as follows: presenile (–0.024; SD 0.028), senile (–0.021; SD 0.043). No significant effect between groups and for points (a) and (b) was found.

## Discussion

The major conclusion of this study is that presenile AD subjects did not show greater severity on SPECT perfusion than senile subjects, thus reinforcing the statement that the two forms of dementia, when accurately matched for disease duration and cognitive impairment, seem to

represent a unitary process, at least for the neurophysiological measures employed. There is however evidence from earlier studies using neuropsychological tools that patients with early-onset AD are more impaired than patients with late-onset AD. Loring and Larger [30] have demonstrated that presenile patients performed significantly more poorly on test of intelligence, sequential reasoning, visuo-coordination, attention and perception than older subjects, although patients were matched for disease severity and general mental status. Seltzer and Sherwin [4], studying a large series of subjects, concluded that the general view of considering presenile and senile AD as unitary degenerative process, may not be valid. Their hypothesis, based only on a mental status examination, revealed greater language impairment in early-onset AD. Emphasis has also been placed on marked neuropathological differences between early- and late-onset AD with severer morphological and biochemical alteration in the former group [8].

Nevertheless there is also evidence that early- and late-onset AD are a unitary neuropsychological entity [3, 5, 31]. Furthermore biochemical studies focussed on cerebrospinal concentration of AchE and choline levels failed to demonstrate differences between early- and late-onset dementia of Alzheimer type [31]. These data agree with those of other authors [1], who identified a bimodal distribution of dementia for age at onset, but no clinical differences between the two groups of AD. Despite a large amount of neuropsychological evidence, few reports have focussed on cerebral perfusion combined with cognitive evaluation in presenile and senile AD. Grady et al. [33] failed to replicate previous findings [34] about differences in metabolic asymmetry of early- versus late-onset AD. The more significant data they reported were a marked right parietal metabolic dysfunction in early-onset patients, without any neuropsychological impairment on test of right parietal lobe function, such as block design.

The second point of interest resulting from our study is the relative left-hemisphere hypoperfusion in both groups of patients. Incidentally we were unable to find significant correlations between severity of cognitive decline and perfusion asymmetry, thus confirming previous investigations [15]. However as it has been demonstrated [15], an agreement between clinical manifestation and pattern of abnormal hypoperfusion was found in selected patients, particularly those with aphasic type onset. Left/right asymmetry has been found in patients with AD using PET [35, 36, 38, 41], SPECT [9, 37] and $^{133}Xe$ inhalation technique [39], although the opposite pattern has also been reported [34]. Half the patients of Grady et al. [33] had left/right asymmetry and half had right/left asymmetry. The reason for this phenomenon remains unclear, if not completely unknown. Recently, a prevailing left-hemisphere impairment in AD irrespective of age at onset has been demonstrated [40]. These data have received support also from biochemical and anatomical findings [42, 43] and could suggest a greater vulnerability of the left hemisphere to a degenerative process such as Alzheimer's disease, regardless of age at onset.

This susceptibility was interpreted in many ways and several explanations were proposed: a greater amount of gray matter in the left than the right hemisphere [44], greater complexity of left-hemisphere function, or selective action of AD process against neurons with specific biochemical marker more represented in the left than in the right hemisphere [40].

Finally a less extensive explanation may be addressed to our study. It is possible that methodological factors such as instrument resolution or regional analysis might have played a role in producing such results. Nevertheless the large series of patients (20 for each group), the extremely wide range of disease severity across the groups should in part protect against this bias.

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