
Lack of Prognostic Significance of SPECT Abnormalities in Non-demented Elderly Subjects with Memory Loss

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ABSTRACT: Objective: To determine if hypoperfusion abnormalities on single photon emission computed tomography (SPECT) are associated with poorer cognitive function at baseline or increased risk of decline in cognitive function and progression to dementia in memory-impaired but non-demented elderly subjects meeting the criteria for aging associated cognitive decline (AACD). **Design:** Cross sectional study of 36 AACD subjects comparing hexamethyl propylene-amine oxime (HMPAO) SPECT results rated by visual inspection with base line cognitive functioning. Prospective study of these AACD subjects with clinical and neuropsychological follow-up over 35 months. **Setting:** The memory clinic and nuclear medicine unit of a university teaching hospital. **Subjects:** Thirty-six subjects meeting the criteria for AACD recruited from patients seen on a physician referral basis. **Main outcome measures:** 1) Baseline cognitive function as measured by the Mini Mental State Examination (MMSE), Boston naming, Logical Memory I subtest of the WAIS-R, and verbal fluency, correlated with SPECT status. 2) Decline in cognitive function as measured by clinical exam and the MMSE, with progression to dementia on follow-up being correlated with SPECT status at baseline. **Results:** 18 of the 36 subjects progressed to dementia (probable Alzheimer's Disease) over follow-up. No correlation was found between the presence or absence of SPECT abnormality and MMSE or other cognitive measures. There was no correlation between the presence or absence of SPECT abnormality at initial examination, and cognitive decline according to the MMSE, or with the occurrence of clinical dementia on follow-up. **Conclusions:** We conclude that SPECT abnormalities assessed by visual inspection do not correlate with severity of impairment in AACD individuals, and are not useful in predicting progression to dementia in AACD subjects.

RÉSUMÉ: Anomalies tomodensitométriques chez les vieillards non déments. But: Notre objectif était de déterminer si des anomalies d'hypoperfusion, à la tomographie à émetteur gamma (SPECT), sont associées à une fonction cognitive altérée à l'évaluation initiale ou à un risque accru de déclin des fonctions cognitives et à une progression vers la démence chez des sujets âgés non déments mais ayant des troubles de mémoire et qui satisfont aux critères de l'échelle du Déclin cognitif associé au vieillissement (DCAV). **Plan de l'étude:** Il s'agit d'une étude transversale chez 36 sujets comparant les résultats de HMPAO SPECT, évalués par inspection, avec la fonction cognitive initiale. Nous avons étudié de façon prospective ces sujets avec DCAV au moyen d'un suivi clinique et neuropsychologique de plus de 35 mois. **Cadre de l'étude:** Cette étude a été réalisée dans une clinique de la mémoire et une unité de médecine nucléaire d'un hôpital universitaire. **Sujets:** Trente-six sujets qui rencontraient les critères de DCAV ont été recrutés parmi les patients référés à la clinique par un médecin. **Mesure principale des résultats:** 1. La fonction cognitive initiale, telle que mesurée par le "Mini Mental state examination" (MMSE), l'Épreuve de dénomination sous confrontation de Boston, le Sous-test de mémoire logique de l'Échelle clinique de mémoire de Weschler I, l'Épreuve de fluidité verbale, a été corrélée avec les résultats du SPECT. 2. Le déclin de la fonction cognitive mesuré par un examen clinique et le MMSE, avec progression vers la démence au cours du suivi, a été corrélé aux résultats du SPECT initial. **Résultats:** 18 des 36 sujets ont progressé vers la démence (maladie d'Alzheimer probable) au cours du suivi. Nous n'avons trouvé aucune corrélation entre la présence ou l'absence d'anomalies au SPECT et le MMSE ou les autres mesures cognitives. Il n'y avait pas de corrélation entre la présence ou l'absence d'anomalies au SPECT à l'examen initial et le déclin cognitif selon le MMSE ou le développement d'une démence au cours du suivi clinique. **Conclusions:** Nous concluons qu'il n'y a pas de corrélation entre les anomalies au SPECT, qui sont notées par inspection visuelle, et la sévérité de l'atteinte chez les sujets avec DCAV et que ces anomalies ne sont pas utiles pour prédire la progression de la démence chez ces sujets.

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Numerous studies have demonstrated a high incidence of parietal and/or temporal hypoperfusion in subjects with probable Alzheimer's disease (AD) using single photon emission computed tomography (SPECT).¹⁻³ Estimates vary between 51 and 96 percent for parieto-temporal defects, and between 81 and 100 percent for any abnormality in probable AD subjects. Many authors have suggested that SPECT may be useful in the diagnosis of AD and in the differentiation of AD from other forms of dementia.⁴⁻¹⁰ Furthermore, the degree of temporal lobe decreased regional cerebral blood flow in AD subjects may even predict their rate of decline over follow-up.⁹ On the other hand some authors have questioned the utility of SPECT for routine diagnostic purposes in mildly impaired AD patients.¹¹⁻¹⁶

One recent SPECT study (Celsis, et al.)¹⁷ evaluated elderly subjects with cognitive decline who did not meet the criteria for probable AD. These subjects have been demonstrated to be at

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high risk for progression to dementia.^{18,19} This group, recently referred to as aging-associated cognitive decline (AACD) by a committee of World Health Organization²⁰ consists of individuals who have had a gradual decline in memory and/or other cognitive functions for at least six months, corroborated by neuropsychological testing. Individuals must score at least one standard deviation below age-adjusted norms on relevant neuropsychological tests, but the level of impairment must be insufficient to make a diagnosis of dementia by commonly used criteria such as the NINCDS-ADRDA criteria.²¹ The AACD criteria also specify that other neurologic or systemic disease likely to cause impairment in cognitive functioning be excluded by clinical examination and appropriate laboratory investigations, as with the NINCDS-ADRDA criteria for AD.

Rubin et al.¹⁸ studied a similar group which they refer to as "questionable dementia". These subjects all scored 0.5 on the Washington University clinical dementia rating scale.²² This level of function implies mild consistent forgetfulness, but no impairment of orientation, and slight or no functional impairment in judgment, community affairs, hobbies and personal care. They found that of 16 members in this group, 11 progressed to dementia in a follow-up of 84 months. Similarly, Tuokko et al.¹⁹ studied a group of subjects referred for a change in memory functioning who did not meet the NINCDS-ADRDA criteria for dementia. They found that 18 of 45 of their subjects in this group progressed to dementia on follow-up 12-18 months later. In contrast, studies of elderly subjects with only subjective memory loss without clear objective evidence of impairment, have shown them to be much less likely to progress to dementia over the short term.²³

Several investigators have attempted to derive neuropsychological instruments to predict progression to dementia in subjects with mild memory decline.²⁴⁻²⁷ While several tests have been reported to correlate with progression to dementia, none have been shown to reliably predict such progression in individual subjects. Imaging studies such as SPECT would therefore be diagnostically useful if abnormal patterns were found to predict progression in these subjects. Celsis et al.¹⁷ studied 18 such individuals who were followed over a two-year period, during which five progressed to dementia. Several of these five were distinguished by the presence of a temporoparietal asymmetry of cerebral blood flow on initial SPECT, providing intriguing evidence that SPECT patterns might be prognostically useful in this group of individuals.

In this paper we report a group of non-demented elderly subjects with mild memory impairment who met the criteria for AACD. These subjects have undergone SPECT as part of their initial workup, and have been followed long enough that a significant proportion have progressed to dementia. In this study we report the results of their SPECT examinations and correlate them with the subsequent clinical course, in particular, progression to dementia.

METHODS

Subjects

Thirty-six subjects meeting the above criteria for AACD were recruited from patients seen on a physician referral basis in the Jewish General Hospital/ McGill University Memory Clinic. All had a history of memory decline in the last 1-4 years report-

ed by the patient, caregiver (usually the spouse), or both. The mean duration of reported memory loss prior to presentation was 1.6 years. All subjects were documented to have mild memory impairment on neuropsychological testing, which included the Logical Memory I and II components of the Wechsler Memory Scale,²⁸ the Knopman and Ryberg test of verbal memory,²⁹ and the Mini-mental status exam (MMSE),³⁰ along with other standardized neuropsychological measures (Table 1). Deficits in other cognitive areas were minimal or, more commonly, non-existent. They did not meet the NINCDS-ADRDA criteria for the diagnosis of probable AD or dementia due to the lack of other associated cognitive deficits or to the lack of impairment of daily functioning. All were classified according to the Washington University clinical dementia rating scale (CDR),²² and met the criteria for "0.5" on that scale as described above. There was no evidence on clinical evaluation of systemic or other neurological disease sufficient to interfere with cognitive function. Structural brain disease was excluded by CT and/or MRI, and blood work was done including CBC, routine chemistry, thyroid function, serum B12, folate, and VDRL. All subjects scored less than 4 on the Hachinski ischemic scale.³¹

All subjects underwent neuropsychological evaluation which included, in addition to the tests noted above, a shortened version of the Boston naming test,³² letter and category fluency,³³ tests of block design³⁴ and clock drawing,³⁵ a word to picture matching task (with perceptual distractors) as a screening test for visual perceptual ability,⁴⁰ as well as the digit symbol and digit span sub-tests of the WAIS-R verbal intelligence scale.³⁴

Procedure

SPECT was carried out using 20 mCi of technetium 99mTc-hexamethyl propylene-amine oxide (HMPAO). To optimize soft tissue clearance, there was a 90-120 minute delay from the time of injection to the commencement of imaging. Imaging was performed with a single head rotating gamma camera (Elsint 409) equipped with a high resolution low energy collimator. Data were obtained from the 140 KEV photo peak (20% window) over a 360 degree rotation and a 64 X 64 matrix. A step and shoot format was utilized with an acquisition time of 30 sec/frame and a zoom factor of 1.33.

After non-uniformity correction, transaxial views were generated via a filtered back projection algorithm utilizing a METZ filter with a power of 3 and a system resolution of 14 mm full width, half maximum. The resulting images were re-oriented to the orbito-meatal line, and orthogonal, coronal, and sagittal projections were then generated. Each set of images was then normalized to the maximum pixel count before viewing. Images were read blindly by two nuclear medicine specialists, and were subsequently rated according to the classification scheme of Holman et al.³⁶ shown in Table 2.

The subjects were followed at 9-12 month intervals with both clinical assessment and repeat neuropsychological examination.

Cross sectional data on SPECT images of 58 subjects from the same clinic population who met the NINCDS-ADRDA criteria for probable AD, as well as 20 normal controls, have been reported separately.¹¹

Differences between subjects who declined and those who did not were assessed by t-test. Outcome data were analyzed by analysis of variance, using both outcomes of decline documented on MMSE, and clinical diagnosis of dementia, as outcome

Table 1: Age-associated cognitive decline (AACD) subjects: Neuropsychological test results at initial presentation, compared to published norms. The percentage of AACD subjects scoring at least 1 s.d. below normal for age on each test of cognitive function is also indicated.

Test	No. Subjects	Average +/-S.D.	Range	Normal +/-S.D.	% below 1 S.D.
Education	36	10.8 +/- 3.1	4 to 18		
MMSE	36	26.9 +/- 3.0	21 to 30	29.3 +/- 0.9	
Boston naming	27	79% +/- 15	43 to 100%	89.5 +/- 13%	30%
Digit Span	34	6.1 +/- 1.2	3.5 to 8	6.4 +/- 1.0	21%
Knopman	36	2.7 +/- 2.2	0 to 7	6.0 +/- 1.8	61%
Logical Memory 1	35	8.1 +/- 3.8	2 to 16	11 +/- 3.0	49%
Logical Memory 2	35	7.5 +/- 5.5	0 to 18	9.6 +/- 3.4	37%
Fluency (F & S)	36	22.5 +/- 8.6	7 to 45	27.8 +/- 7.6	25%
Fluency Animals	36	12.9 +/- 4.1	5 to 23	15.0 +/- 3.2	28%
Digit Symbol	14	31.3 +/- 7.8	15 to 46	43.7 +/- 8.3	7%
Block Design (/51)	16	16.2 +/- 8.4	2 to 29	23.5 +/- 9.9	13%
Visual Perceptual Screen	28	29.7 +/- 0.5	28 to 30	29.8 +/- 0.3	0%

variables. Correlation of the presence of clinical and SPECT features with outcome were assessed using Chi-square analyses.

RESULTS

At the time of initial evaluation, the 36 AACD subjects had an average age of 71 +/- 7 years (range 58 to 84) and an average MMSE of 26.9 (range 21-30, s.d. = 3.0). There were 19 males and 18 females and they had 10.8 +/- 3 years of education. A summary of their neuropsychological results is given in Table 1. Thirty-four of the subjects scored at least 1 s.d. below the age-adjusted mean on one or more memory test administered (Logical Memory 1 and 2 of the Wechsler memory scale,³⁴ and the delayed verbal memory test of Knopman and Ryberg²⁹), while two subjects were impaired only on non-memory cognitive tasks. In addition, there were mild cognitive deficits (on picture naming, digit span, verbal fluency, and block design) seen in 23 of the 36 subjects, not sufficient in any case to warrant a diagnosis of dementia (see Table 1).

The SPECT scans were read blindly by two nuclear medicine specialists. The classification of Holman was applied as in Table 2. It should be noted that there was no disagreement between the 2 raters as to the appropriate SPECT pattern assignment of any patient. We thus had excellent inter-rater reliability.

The number of AACD subjects with each SPECT pattern is

Table 2: Brain SPECT pattern classification of Holman, Johnson et al.³⁶

SPECT Pattern	Description
A	Normal
B	Bilateral posterior temporal and/or parietal defects
C	Bilateral posterior temporal and/or parietal defects with additional defects
D	Unilateral posterior temporal and/or parietal defects with or without additional defects
E	Frontal defects only
F	Other large defects
G	Multiple small defects

given in Table 3, along with the average MMSE, Boston naming, logical memory I, and verbal fluency scores at the time of SPECT acquisition for subjects in each category. Thirteen subjects had normal SPECT scans, and 23 had "abnormal" patterns. At initial evaluation, these latter subjects with SPECT abnormalities (patterns B-G) had an average MMSE score of 27.6, while those with normal SPECT studies actually had a slightly worse average score of 27.0. These differences were not significant on t-test. Similarly, the average scores on the Boston naming and verbal fluency tests were slightly worse in those subjects with normal SPECT scans, while the logical memory I average score was minimally better. None of these differences reached significance ($p < .05$) on t-test. Nor was there any group difference between subjects with normal and abnormal SPECT results when analyzed in terms of age, education, duration of symptoms, or any other neuropsychological variable. The only variable showing an asymmetric distribution was the presence of clinical depression; 8 of the subjects with normal scans were rated as clinically depressed, compared with only 4 subjects showing abnormal scan patterns (three being SPECT patterns typical for AD, and one being a non-typical pattern). This was significant by chi-square ($df = 2, \chi^2 = 7.1, p < .05$).

Annual clinical evaluation including neuropsychological testing was carried out on the cohort of subjects. Two subjects died prior to their first annual follow-up, and were reportedly not deteriorated compared to their baseline evaluation. Another two subjects died following one year follow-up (at which time they were considered cognitively intact). The other 32 subjects have had ongoing clinical assessment to the present time. Excluding the two who died prior to follow-up (who have not been entered into follow-up analysis), there have been thirty-four AACD subjects followed for an average of 35 +/- 13 months (range 13-56). Over that time, the MMSE of the entire group has declined by an average of 3.5 points (range -2 to 13 points decline). Longer follow-up led to a greater degree of deterioration documented; for the 7 subjects with two years or less follow-up, the decline averaged 1.0 on the MMSE, while for the other 27 subjects (mean follow-up of 37 months), the decline averaged 4.5 on the MMSE.

Eighteen of the subjects have shown progressive deterioration, and are now classified clinically as showing dementia

Table 3: SPECT and selected initial neuropsychological results in AACD subjects. Number of AACD subjects with each SPECT pattern (total n = 36), is shown along with the mean neuropsychological test result within that group of subjects. The overall results for any normal (SPECT pattern A) versus abnormal (SPECT patterns B-G) are also compared.

SPECT Pattern	No. Subjects (%)	MMSE (Av.)	Boston naming (%)	Logical memory I	Fluency (animal)
A	13 (36)	27	68	8.3	11.2
B	4 (11)	28	76	7	12.7
C	1 (3)	28	100	8	12
D	12 (33)	28.3	83	6.8	13.3
E	3 (8)	26.3	90	6.7	14
F	2 (6)	23.5	74	6.5	13
G	1 (3)	30	76	11	13
B-G	23 (64)	27.6	82.3	7	13.2

(probable Alzheimer's Disease in all cases). In one of these subjects, the MMSE was originally taken as 21 (out of 30), although she appeared functionally intact, and was therefore diagnosed as AACD. On follow-up, the MMSE was still 21/30, but there had been clear cognitive and functional deterioration extending beyond memory, warranting the label of dementia. In the other 17 cases showing deterioration to dementia, the MMSE had fallen by 2 or more points over follow-up. Of the remaining subjects, still considered as AACD on follow-up, one subject had a decline on MMSE of 3 points (from 28 to 25) after 30 months follow-up, but the other 17 had MMSE declines of less than 2 with no clinical or neuropsychological progression. Analysis by t-test was carried out between initial variables for subjects who eventually progressed to dementia, vs. those individuals who did not progress to dementia over follow-up. There was no significant difference between the two groups in terms of initial age, education, or duration of follow-up ($p = .16, .06,$ and $.08$ respectively). Neither was there any difference between those subjects in terms of any of the neuropsychological variables listed in Table 1. Progression to dementia was analyzed in terms of the initial clinical profile (no cognitive deficit, memory impairment only, memory plus other cognitive deficit, non-memory deficits only). Analysis by chi-square revealed no pattern or relationship between the clinical profile and progression ($df = 3, \chi^2 = 6.63$). Thus, progression to dementia at time of follow-up did not appear to be correlated with any clear aspects of the initial clinical profile, or the presence of any initial neuropsychological abnormality in our group of subjects.

The average initial and follow-up MMSE scores grouped according to SPECT pattern are presented in Table 4. Those with abnormal SPECT examinations declined by an average of 3.7 points on the MMSE while those with normal SPECT's declined by 3.5 points. The initial and follow-up MMSE scores were subjected to a repeated measures 2 X 2 ANOVA with SPECT status (normal, abnormal) as the between groups measure and the MMSE (time 1, time 2) as the within subjects measure. This demonstrated a main effect of time of testing [$F(1,32) = 17.9, p < .001$], indicating that collapsed across groups there was a significant decline in MMSE. There was no main effect of SPECT status [$F(1,32) = 0.26, p = .6$], implying that there was no overall relation between SPECT status and MMSE. In particular, there was no repeated measures by SPECT status interaction [$F(1,32), p = .99$]. This demonstrates that the presence of SPECT abnormality was not associated with any worse decline in the MMSE. Similar results were obtained when only

those subjects with SPECT patterns considered more "typical" for AD (patterns B, C, D) were considered, and those subjects with a more atypical SPECT pattern (patterns E-G) for AD were excluded from analysis.

There was no correlation between initial SPECT pattern, and subsequent progression to dementia in the 34 subjects over a follow-up period. This was the case whether SPECT patterns were analyzed as normal vs. abnormal ($\chi^2 = .52, df = 1, NS$) or normal vs. "typical for AD" (patterns B, C, D) vs. "patterns more atypical for AD" (patterns E-G) ($\chi^2 = 1.16, df = 2, NS$). The same finding held when each SPECT pattern was evaluated separately compared with progression to dementia ($\chi^2 = 5.6, df = 6, NS$). Twelve of 23 subjects with an abnormal SPECT progressed to dementia, while six of eleven subjects with a normal SPECT progressed to dementia. All those subjects who did not progress remained in the AACD category.

Similarly, using as a cut-off score a decline by two or more points on the MMSE (which was characteristic of most subjects eventually receiving a diagnosis of dementia), eleven of 23 subjects with an abnormal SPECT declined significantly, while seven of eleven with a normal SPECT had a similar decline (Chi square = $.15, df = 1, NS$). We were therefore unable to find any correlation between the presence or absence of SPECT abnormality and progression as measured by either clinical diagnosis or change in the MMSE.

DISCUSSION

Previous studies have shown an incidence of SPECT abnormality in AD subjects of 68 to 100 percent based on either visual inspection or significant differences from controls using semi-quantitative methods.^{1-10,36} In the AD subjects reported by

Table 4: Follow-up of AACD subjects: initial and follow-up MMSE scores divided according to initial SPECT pattern (n = 34).

SPECT Pattern	No. Subjects (%)	Initial MMSE	F/U MMSE
A	11 (32)	27.1	23.6
B	4 (11)	28	24
C	1 (3)	28	15
D	12 (35)	28.3	25.2
E	3 (9)	26.3	24.3
F	2 (6)	23.5	21
G	1 (3)	30	29
B-G	23 (68)	27.6	23.9

our group,¹¹ 76 percent had some SPECT abnormality. The AD subjects in these studies have all been defined by the NINCDS-ADRDA criteria, thereby implying an 85-90% chance of having pathology consistent with AD prior to having the test.³⁷⁻³⁹ The possible additional diagnostic precision achieved with the use of SPECT in this group of patients is therefore very limited. Where SPECT is potentially of more value in increasing diagnostic precision is in those subjects with memory impairment not meeting the criteria for dementia, who have been demonstrated to have a high risk of progression to dementia.^{18,19} It is these subjects who are still very functional who have the most potential for therapeutic benefit from future therapies designed to arrest the progression of the disease, but who are currently excluded from most drug trials. However, the point in the course of the disease process at which perfusion abnormalities can be demonstrated with SPECT has not been clearly elucidated.

We have found a high rate of SPECT abnormality in this AACD group, 64% of cases, which is close to the rate of abnormal SPECT findings found in the probable AD subjects by our group and others.¹⁻¹¹ We therefore doubt that semi-quantitative analysis would have yielded different results compared to our visual inspection of images, and this has been the general result in other centres that have applied both approaches (Claus, personal communication). In spite of this high rate of abnormality, we found no correlation between the presence or absence of SPECT abnormality and progression as measured by change in MMSE or by frank progression to dementia. On examination of Table 4, it is also clear that decline is similar for subjects with each specific type of SPECT abnormality as well. The 35 month follow-up, while shorter than that of Morris et al.,²⁶ was sufficient to allow progression to dementia in 50% of our cohort. Given the high rate of SPECT abnormalities encountered in the AACD group, it is doubtful that the lower sensitivity of visual inspection of SPECT images (as opposed to quantitative analysis) is the cause of its lack of prognostic usefulness in our group of subjects. Rather, there appears to be a high rate of SPECT abnormality in subjects with AACD, irrespective of whether they went on to progress to AD over the subsequent year or not.

It is possible that with further follow-up more subjects with SPECT abnormalities will progress to dementia. It may also be, however, that many AACD subjects have SPECT abnormalities for reasons other than underlying preclinical Alzheimer's disease, and that such abnormalities therefore do not imply an increased risk of progression to dementia.

In our study, we sought to utilize conventional visual SPECT analysis as it is carried out in most clinical centres; we did not

apply more specialized data analysis tools such as semi-quantitative analysis, and cannot address their usefulness in predicting progression in these subjects. However semi-quantitative analysis remains of limited availability for routine clinical use at present. We are therefore led to conclude that SPECT, when analysed by conventional means, is not useful in predicting decline to dementia in AACD subjects.

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Table 5: AACD subjects: progression to probable AD according to SPECT pattern (n = 34).

SPECT	No. Subjects	No. Progressing to AD
A	11	6
B	4	2
C	1	1
D	12	5
E	3	2
F	2	2
G	1	0
B-G	23	12

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