SPECT as An Aid for Clinicians in the Diagnosis of Alzheimer's Disease: A case report and review of current diagnostic approaches and the need for early accurate diagnosis to optimize treatment

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Abstract : **A case of 66 year-old male with Alzheimer's dementia with classical ^{99m}Tc-ECD SPECT imaging findings is reported. The history, physical examination, and investigation, are described. Biological markers which are now used for the diagnosis of Alzheimer's dementia and current treatment are discussed.**

เรื่องย่อ : SPECT ช่วยในการวินิจฉัยโรคสมองเสื่อมชนิดอัลไซเมอร์ : รายงานผู้ป่วยและทบทวนหลักการวินิจฉัยโรคและความจำเป็นที่ต้องวินิจฉัยโรคให้เร็วเพื่อการรักษาที่เหมาะสม

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รายงานผู้ป่วยชายอายุ 66 ปี ป่วยด้วยโรคสมองเสื่อมชนิดอัลไซเมอร์ ที่ได้รับการตรวจวินิจฉัยด้วย ^{99m}Tc-ECD SPECT imaging ที่มีลักษณะความผิดปกติที่เป็นแบบฉบับ และผลการสืบค้นด้วยวิธีต่าง ๆ ที่ช่วยในการวินิจฉัยโรค และหลักการรักษาโรคอัลไซเมอร์ในปัจจุบัน

INTRODUCTION

Dementia is a condition that results in a decline in memory and other cognitive functions that affect daily life. The most common form of dementia is Alzheimer's disease (AD) which accounts for approximately two thirds of all causes of dementia.

The clinical criteria for the diagnosis of Alzheimer's disease were first reported in 1984[1]. The information needed to apply these criteria is obtained by standard methods of examination: the medical history; neurologic, psychiatric, and clinical examinations; neuropsychological test; and laboratory

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studies. New practice recommendations reported in 2001 added structural neuroimaging with either a noncontrast CT or MR scan to the routine initial evaluation of patients with dementia[2]. Although SPECT (Single Proton Emission Computed Tomography) and PET (Positron Emission Tomography) were not recommended for routine use in the diagnostic evaluation of dementia at the time of report, there have been several reports that documented the usefulness of SPECT and PET[3,4]. Thus, we present a patient with dementia who underwent ^{99m}Tc-ECD Brain SPECT which helped to make the diagnosis of Alzheimer's disease.

CASE REPORT

A 66 year-old gentleman presented with history of forgetfulness over the past 6 years. The symptoms started one year prior to his first visit to a nearby clinic and he was diagnosed as having forgetfulness associated with age. The symptoms gradually deteriorated further in the following year and he had difficulty in performing daily activities. He could not take care of himself. There was no history of weakness or paralysis. He was brought to Siriraj Hospital after two years of memory loss and was seen in the memory clinic where he was fully investigated.

On physical examination, he was fully conscious with normal heart, lungs and abdomen. Examination of the central nervous system revealed normal orientation, normal cranial nerve examination and no motor or sensory deficit with normal deep tendon reflexes. There was no cerebellar sign, but the palmomental sign was positive on the right side. Thai mental state examination score (TMSE) were 17/30. Laboratory test results were unremarkable.

His CT scan (Figure 1) showed asymmetrical atrophy of the right anterior temporal lobe, widening of the right sylvian fissure, and unilateral right temporal horn dilatation. There were multiple spots of hypodensity at the basal ganglia and periventricular white matter bilaterally. The differential diagnoses made were Alzheimer's disease, and multi-infarct dementia (MID) or vascular dementia.

^{99m}Tc- ECD Brain SPECT images of the patient showed moderate to severe bilateral temporoparietal hypoperfusion suggestive of Alzheimer's disease (Figure 5A).

Follow-up

The patient was diagnosed as having Alzheimer's disease. AChE-I (donepezil) was started. The patient's memory improved and he was able to perform activities of daily living more easily.

Five months after the treatment, the patient developed delusions and the medication was changed from donepezil to rivastigmine. Six months later he developed agitation and sodium valproate was added until the symptoms improved 4 months later. One and a half years later, the patient developed hallucinations and aggressiveness and attacked his family members. He was admitted to the hospital and was treated with an increased dose of rivastigmine (12 mg/day), clozapine 75 mg/day in divided doses sertaline 25 mg/day and trazodone 50 mg/day. His aggression was brought under control.

DISCUSSION

Alzheimer's disease (AD) is the commonest cause of dementia and the second most common is vascular dementia or mixed vascular and AD dementia. Patients with AD present with cognitive, behavioral, and functional decline. Table 1 illustrates the criteria for a diagnosis of definite, probable, and possible AD[1]. A definite diagnosis of AD requires that the patient meets the clinical criteria of probable AD and has pathological evidence of AD at autopsy or on cerebral biopsy. Probable AD requires that the patient meets the criteria on history, physical and psychological examination and a mental state questionnaire. The onset of symptoms can occur between 40 and 90 years of age. The decline worsens over time and should be present for at least 6 months. The patient must not be deleterious and must not have any other disorder capable of producing dementia. Possible AD can be diagnosed when another brain disorder or systemic disease capable of producing dementia in the patient is present. This criteria have an inter-rater reliability of 65-75%[5] and their accuracy varies from 85-95%[6,7].

Table 1. Criteria for definite, probable, and possible Alzheimer's disease (AD)

Definite AD
- Clinical criteria for probable AD
- Histopathological evidence of AD (autopsy or biopsy)

Probable AD
- Dementia established by clinical examination and documented by mental state questionnaire
- Deficits confirmed by neuropsychologic testing
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40 and 90 years
- Absence of systemic disorders or other brain diseases capable of producing a dementia syndrome

Possible AD
- Presence of a systemic disorder or other brain disease capable of producing dementia but not thought to be the cause of the dementia
- Gradual progressive decline in a single intellectual function in the absence of any other identifiable cause (e.g. memory loss or aphasia)

Unlikely AD
- Sudden onset
- Focal neurologic signs
- Seizures or gait disturbance early in the course of the illness

In the past decade, several biological markers for AD have been discovered. The biomarkers serve as diagnostic aids and provide insights into the etiological mechanism underlying the disease process. They can be used to monitor the effect of treatment. Neuroimaging and biochemical markers measured in body fluids are popular tools to increase early and accurate diagnosis of AD.

Neurofibrilliary tangles and amyloid plaques are the hallmark of AD pathology. β-amyloid 40 and 42 are biomarkers of plaques in vascular amyloid deposits and are found in early onset familial AD. Tau is a neuronal protein bound to axonal microtubules and has a role in cytoskeletal structure and axonal transport. Insoluble tau, such as phosphorylated tau, is a major component of neurofibrilliary tangles. The inflammatory process in the brain produces tumor necrosis factor α (TNF α), transforming growth factor β (TGF β) or granulocyte - macrophage colony stimulating factor (GM-CSF) which is an important cytokine for microglial activation and inflammation. The platelet amyloid precursor protein (APP) ratio is found to be decreased in AD patients.

Table 2. Biomarkers in Alzheimer's disease (AD)

Body fluids	Findings in Alzheimer's disease	Sensitivity
CSF[8,9] : Total tau	Increased	60 - 85%
Phospho – tau	Increased	> 80%
Aβ 42	Decreased	85 - 94%
Plasma[10,11] : Aβ 42	Increased in familial AD and 10% of sporadic AD	
Aβ 40	Increased in familial AD and 10% of sporadic AD	
Platelets[12,13] : APP ratio	Decreased	80%

AD = Alzheimer's disease, Aβ = amyloid beta, APP = amyloid precursor protein

In Alzheimer's disease, CT and MRI may show diffuse cerebral atrophy which is more severe at the temporal lobe and hippocampus which is a pathological hallmark of AD, widened sulci, enlarged lateral ventricle and sylvian fissure, and white matter hypodensity[14,15]. (Figure 1)

Other causes of dementia may show different findings on CT and MRI as follows:

In Pick disease, CT and MRI may show circumscribed lobar atrophy, and frontal-temporal lobe atrophy, which are not specific[14,15].

Subdural hematoma (SDH), CT findings vary depending on the stage of bleeding or clot. Acute SDH shows a hyperdense crescentric collection, but subacute SDH shows isodensity, and chronic SDH shows hypodensity[14,15]. (Figure 2)

In vascular dementia, CT and MRI may show multiple areas of cortical and/or subcortical infarction appears as a hypodense area on CT scan and as areas with reduced signal intensity on MRI T1WSE and increased signal intensity on T2WSE scans. There may be widening of the ventricular system and cortical sulci[14,15]. (Figure 3)

In normal pressure hydrocephalus (NPH), CT and MRI may show ventricular system dilatation and periventricular low density around the frontal or occipital horns which is resulted from interstitial edema[14,15]. (Figure 4)

In HIV encephalopathy, CT and MRI may show diffuse cortical atrophy and white matter low density especially in the frontal and parieto-occipital lobes[14,15].

Due to the abnormal findings from other causes of dementia as described above, CT and MRI of the brain may help in the differential diagnosis of dementia and are useful for excluding other neurological diseases.

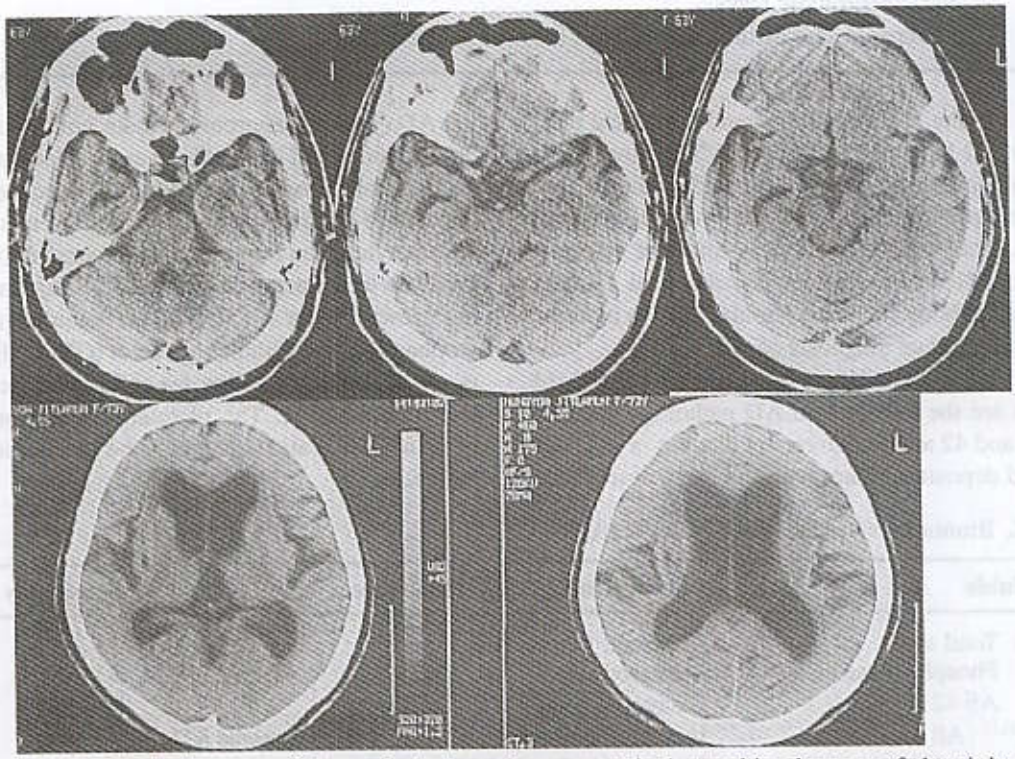

Figure 1. Axial CT brain scan of the patient showed asymmetrical atrophic changes of the right anterior temporal lobe with evidences of cortical reduction, widening of the right sylvian fissure and unilateral right temporal horm dilatation.

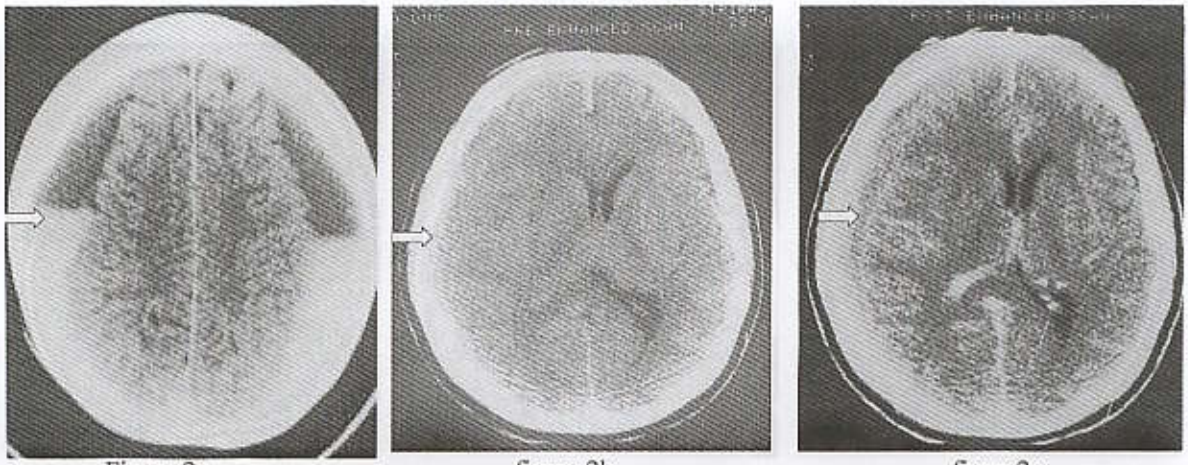

Figure 2a figure 2b figure2c

Figure2d

Figure 2. Axial CT brain scan of a patient with acute subdural hematoma (Figure 2a) appears as crescentric shape of hyperdensity of acute blood clot. Figure 2b shows isodensity of the hematoma on the right side which is hardly seen in pre-contrast study but is well demonstrated on the post-contract study as in figure 2c. Figure 2d demonstrates lysis of blood clot in chronic subdural hematoma. A contrast study is helpful in subacute subdural hematoma.

Brain SPECT using ^{99m}Tc HMPAO or ^{99m}Tc ECD is used as functional brain imaging to show regional cerebral blood flow. In Alzheimer's disease, PET shows a classical pattern of bilateral temporo-parietal hypometabolism where as ^{99m}Tc-HMPAO SPECT shows hypoperfusion of the corresponding areas. Thus in centers in which PET is not available, SPECT should be a reasonable substitute[3,4,16], although not as good. In the past decade, there has been a significant improvement in treatment of Alzheimer's disease which delays disease progression and improves symptoms. Today, an early diagnosis should be made before significant irreversible neurodegeneration occurs so that proper treatment can be instituted before severe irreversible neurological deficit ensues.

PET and SPECT can be helpful in this regard. Several groups have reported that PET and SPECT show a classical pattern of bilateral temporo-parietal hypometabolism and hypoperfusion, respec-

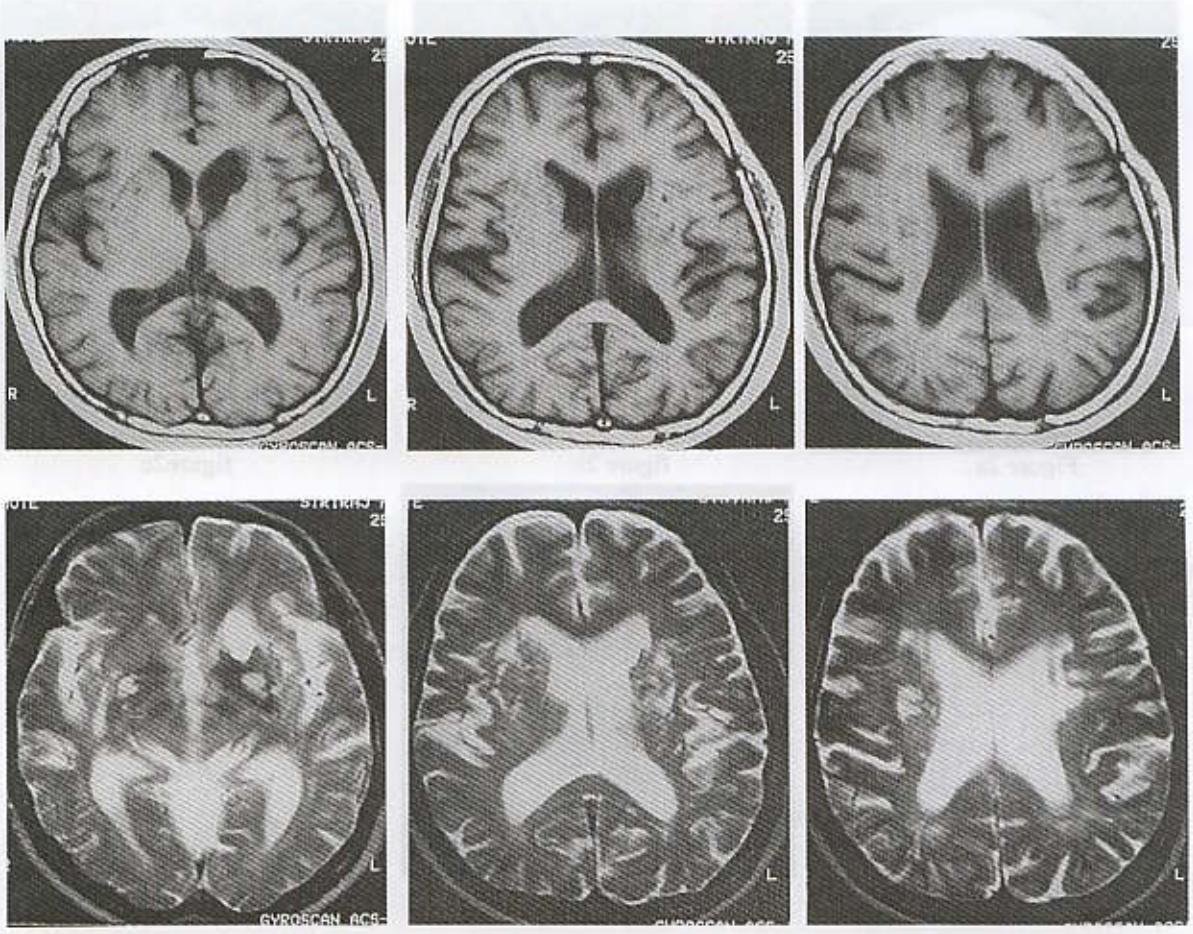

Figure 3. An axial T1WSE (upper row) and Axial T2WSE (lower row) of a patient with multiple lacunar infarction, the lacunar infarction appears as low signal intensity on T1WSE and high signal intensity on T2WSE. In this patient, there are areas of lacunar infarction in the basal ganglia and periventricular white matter bilaterally.

tively, which occur before clinical or neuropsychological test abnormalities are severe enough to justify a clinical diagnosis of possible or probable Alzheimer's disease using the NINCDS-ADRDA criteria[3,4]. The largest series of the use of PET in diagnosing cases of dementia and where autopsy confirmation was available included 22 patients with various types of dementia (69% AD). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the PET pattern of bilateral temporo-parietal hypometabolism were 87.5 to 93%, 62.5 to 67%, 81.3 to 87.5%, 67 to 83.3% and 81.8%, respectively[17]. Based on two Class I studies with autopsy-confirmed diagnoses in a large number of subjects, the sensitivity and specificity of SPECT for the differentiation of AD from non-AD dementia by SPECT pattern of hypoperfusion in the temporo-parietal lobe(s) were 86 to 95% and 42 to 73%, respectively[18,19]. In a clinical-pathologic study of 70 patients with dementia, followed to autopsy; 14 con-

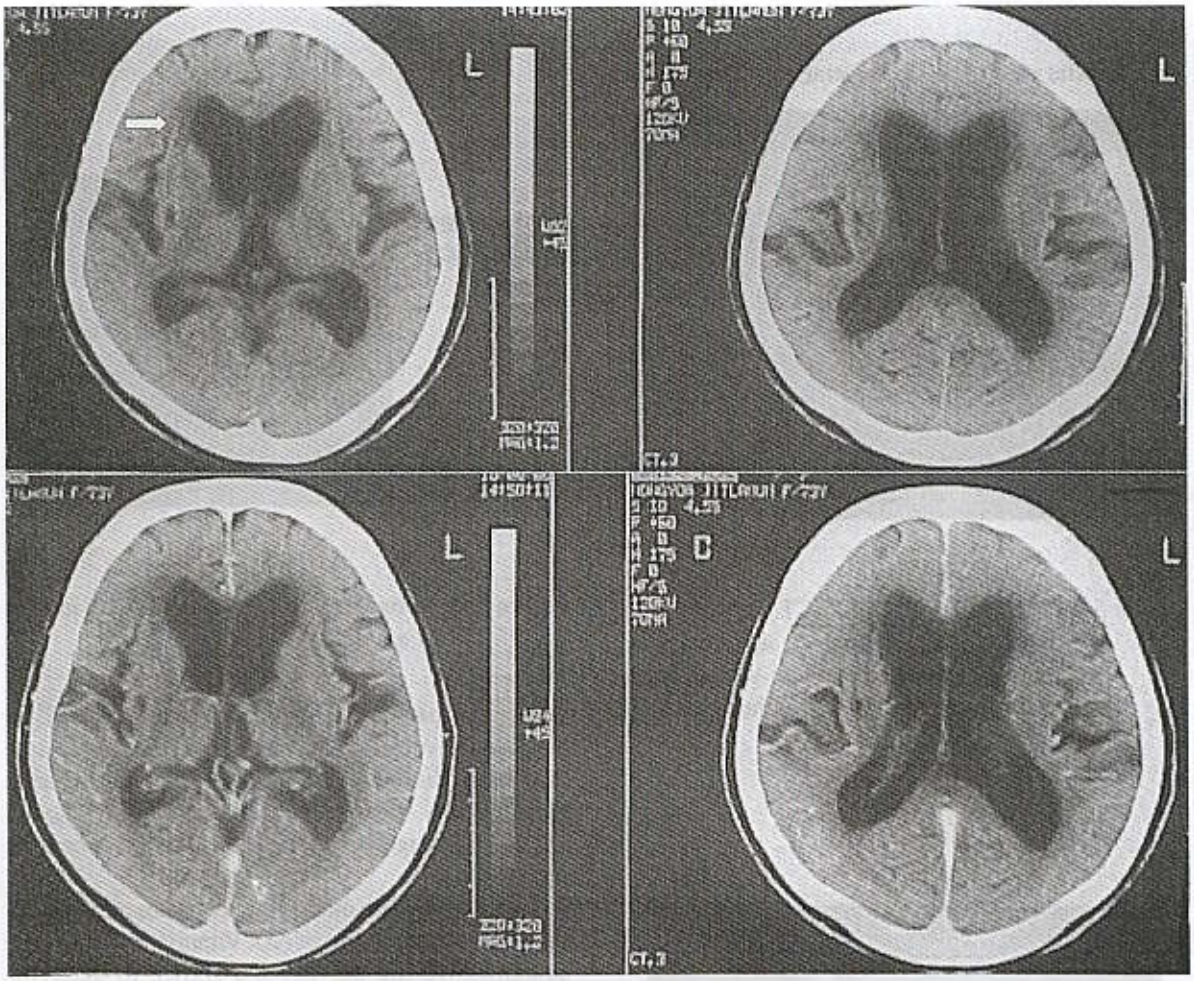

Figure 4. Axial CT pre- (uppper row) and post- contast (lower row) in a patient who had clinical dementia with urinary incontinence and an ataxic gait. There is a combination of disproportionate dilatation of the lateral ventricle (tense-round appearance of the frontal horn) to the depth of the cerebral sulci and periventricular white matter (arrow).

trols followed to autopsy; and 71 controls (no autopsy performed), SPECT perfusion imaging was analyzed. When all participants (patients and controls) were included in the analysis, the clinical diagnosis of "probable" AD was 84% likely to correlate with pathologic diagnosis of Alzheimer's disease. A positive SPECT scan raised the likelihood of AD to 92%, whereas a negative SPECT scan lowered the likelihood to 70%. SPECT was more useful when the clinical diagnosis was "possible" AD, with a likelihood of 67% without a SPECT scan, 84% with a positive SPECT scan, and 52% with a negative SPECT scan. Thus, in the evaluation of dementia, SPECT imaging can provide clinically useful information indicating the presence of AD in addition to the information from clinical evaluation alone[20]. A report of a study on economic impact of using PET in the clinical work-up of dementia showed that appropriate use of PET for evaluating early dementia in geriatric patients added valuable information to the clinical work-up without adding to the overall costs of evaluation and management. This resulted in a greater

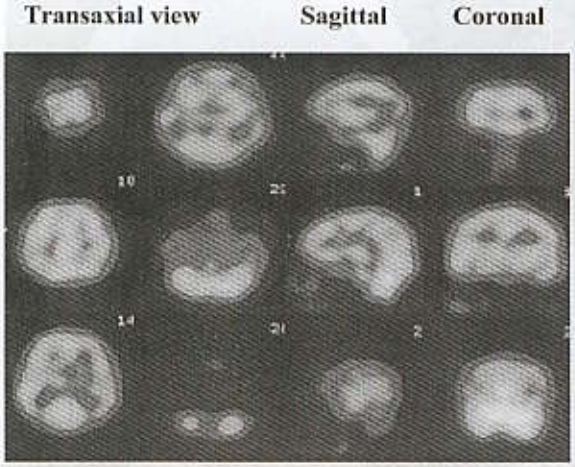

Figure 5A. ^{99m}Tc-ECD Brain SPECT images of the patient show decreased uptake in the bilateral posterior parieto-temporal regions suggestive of Alzheimer's disease.

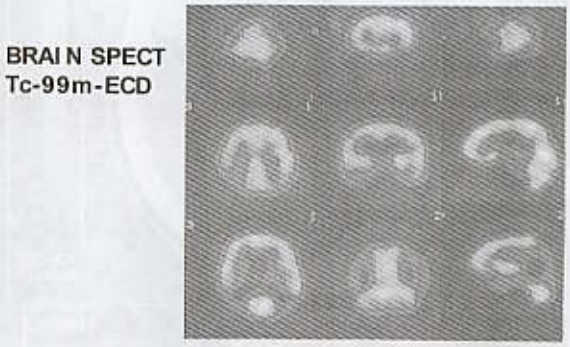

Figure 5B. Normal ^{99m}Tc-ECD Brain SPECT images of a parkinson's disease patient.

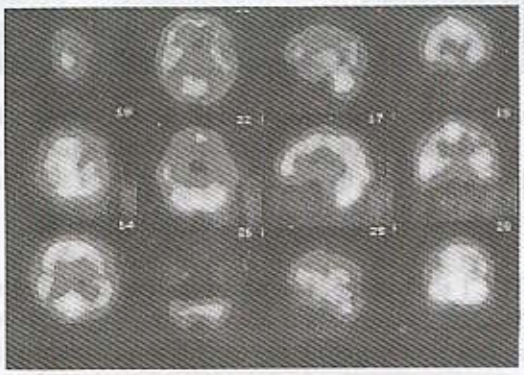

Figure 5C. ^{99m}Tc-ECD Brain SPECT images of a patient with multiinfarct dementia showing multiple areas of decreased uptake in the left frontoparietal and bilateral parietal lobes.

number of patients being accurately diagnosed for the same level of financial expenditure. It is now possible to diminish patients' morbidity of dementia economically with earlier treatment[21].

Management of AD consists of five components.

1. Disease modifying therapies aimed at reducing the progression of AD. Vitamin E 2000 iu and selegiline 10 mg per day are shown to defer the occurrence of milestones in AD progression namely nursing home placement, loss of activities of daily living (ADL) or progression to severe dementia[22].

2. Cholinesterase inhibitor (ChEI) therapy to improve, stabilize, and reduce the rate of cognitive decline. Four ChEIs are available including tacrine, donepezil, rivastigmine and galantamine. Tacrine is hepatotoxic and is used very little nowadays. The ChEIs have similar efficacy in clinical trials. They have different pharmacologic mechanisms and have variable patients' responses to treatments. These agents improve behavior, reduce emergence of new abnormal behaviors, enhance cognition, defer or stabilize loss of ADL and improve global function[23].

3. Psychotropic agents are used to treat behavioral disturbances or neuropsychiatric symptoms.

4. Behavior modification and management to cope with neuropsychiatric symptoms and loss of daily function.

5. Working with caregivers to support how to cope with AD patients and their emotional needs.

Psychiatric management (bio-psycho-social approach)

In the late stage of Alzheimer's disease, psychiatric symptoms such as agitation, aggression, hallucination, and paranoid delusion are seen frequently and disturb families or caregivers. Antipsychotic drugs are the most commonly used drugs to treat disruptive behavior in elderly patients. The selection of a particular antipsychotic drug is guided by the side-effect profile of each drug or drug class in relation to the patient's history of response to a drug (or lack of response) and the nature of concomitant chronic illness and medication. Three side effects occur regularly and may be particularly troublesome for elderly patients. These side effects are sedation, orthostatic hypotension and extrapyramidal tract syndrome (EPS). Recently developed atypical antipsychotic drugs : clozapine, risperidone, olanzapine and quetiapine, are less likely to cause EPS than typical antipsychotic drugs.

This patient had been using many atypical antipsychotic drugs but these drugs could not control behavioral symptoms and caused EPS and other side-effects. Clozapine was used and could control aggression, agitation, and paranoid delusion without EPS side-effect. Clozapine is more efficacious in controling aggressive behavior than other antipsychotic drugs[24]. However the use of clozapine can lead to orthostatic hypotension [24-26], lower seizure thresholds[25], and blood dyscrasias[24-26], so it should be used with regular monitoring. Benzodiazepines , i.e. clonazepam and lorazepam, were used in addition to control behavioral disturbance but they could increase confusion or exacerbate disinhibition[27].

Cholinesterase inhibitor therapy has been shown to reduce agitation, delusion, anxiety, disinhibition, depression and aberrant motor behavior in some studies[26,27].

Non-pharmacological intervention utilizes an A-B-C approach[27] . "A" stands for the antecedents of behavior and indicates the need to analyse the circumstances that may have contributed to precipitating a behavioral event. "B" stands for the behavior itself and requires consideration of the meaning of the behavior from the patient and caregiver's perspective. "C" stands for the consequences of the behavior and indicates the need to consider what follows as a behavioral event to ensure that behavioral disturbances are not being reinforced by attention from the caregiver or some other positive rewards.

In addition, attention to the needs of the caregiver regarding referral to social welfare services, education about the disease, course, and prognosis, and psychosocial intervention such as release of guilt and depression, and environmental reconstruction, may help to decrease the burden of the caregivers, helping them to respond to behavioral disturbances in more positive ways.

CONCLUSION

Alzheimer's disease, once an untreatable disease, today is recognized as a disease which can be treated in many aspects. It is diagnosed primarily by clinical criteria, along with several biological markers and neuroimaging. PET and SPECT have been reported to be useful and of economic benefit to the diagnosis, especially in clinically difficult cases and early in the course of the disease. Now that there are several medications for treatment of Alzheimer's disease, it is essential that we diagnose Alzheimer's disease early and give appropriate treatment as soon as possible.

COMMENT

Alzheimer's disease is to be considered one of the most serious diseases of mankind. The sufferers are not only the patients but also their relatives and caregivers. The older the population, the greater the percentage of individuals afflicted with the disease, and as mean life expectancy is rising, the magnitude of this problem is growing. The disease also has severe financial consequences on families and the community. Now that several medications

are available for the treatment of Alzheimer's disease, early and accurate diagnosis is mandatory. With more research evidence of the efficacy of SPECT and PET, these should be one of the important tools needed to establish the diagnosis of dementia. I would like to express my appreciation to the presenters who have brought up this very important issue which needs our consideration.

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