VOLUMETRIC MAGNETIC RESONANCE IMAGING CHANGES IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DEMENTIA

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ABSTRCT

Nowadays, there is a particular interest in MCI because this syndrome is thought to be a transitional stage to Alzheimer's disease (AD) that may define a window for effective therapeutic interventions. However, not all patients with MCI will go on to develop AD .**Objectives.** To explore volume changes of the brain in mild cognitive impairment (MCI) and Alzheimer's disease (AD) compared with normal cognition (NC). ***Methods.*** This study included 40 subjects with NC, 36 patients with MCI, and 29 patients with AD. The severity of cognitive decline was graded according to the Clinical Dementia Rating (CDR), Volumes of the ERC, hippocampus, total grey matter, white matter volume and total intracranial volumes were manually measured based on coronal T1 weighted MR images. ***Results.*** Level and duration of education and MMSE were higher in control group than in MCI and Alzheimer's disease groups. ERC, hippocampus, total grey matter, white matter volume and total intracranial volumes were reduced in all regions compared with MCI and NC with highly significant difference ***Conclusions.*** Imaging are encouraging for improving diagnosis of the disease at an early stage and provide the rationale for early treatment and objective measures for therapeutic effects in clinical trials.

Keywords: MRI **,** mild cognitive impairment , dementia

INTRODUCTION

Nowadays, there is a particular interest in Mild cognitive impairment (MCI) because this syndrome is thought to be a transitional stage to Alzheimer's disease (AD) that may define a window for effective therapeutic interventions with the prospect of slowing progression or even preventing disease, however, not all patients with MCI will go on to develop AD. MCI is a well-defined clinical syndrome, which includes deficits in memory or other cognitive abilities [(1)] . An annual conversion rate of 6–25% from MCI to AD has been estimated [(2)] , The formation of long-term cognitive memory is dependent on
the medial temporal lobe (MTL) structures, which consist of the hippocampus, the entorhinal, perirhinal, and parahippocampal cortices. These structures are known to be critical for successful encoding of new events and facts into long-term memory [(3)] . In AD these structures show the first pathologic findings, which can be found already in the MCI state [(4)] . The last two decades of research using structural Magnetic Resonance Imaging (MRI) and metabolic Positron Emission Tomography (PET) with 2[18F]fluoro-2-deoxyd- glucose (FDG) as the tracer, have shown that probable Alzheimer's disease (AD) and mild cognitive impairment(MCI) are characterized by a specific pattern of cerebral morphometric reductions and hypometabolism. [(5)] The aim of our study to explore volume changes of the brain in mild cognitive impairment (MCI) and Alzheimer's disease (AD) compared with normal cognition (NC);

SUBJECTS AND METHODS

This study was carried out on 65 patients with age ranges from 55 to 80 years (36 patients with mild cognitive impairment and 29 patients with Alzheimer's disease) selected from our neurology outpatient clinic of Zagazig University Hospitals in the period from (April 2008 to 2011) beside 40 healthy elderly people with normal cognition(NC) with age ranges from 55 to 80 years, 20 men, 20 women, 36 patients with

mild cognitive impairment (MCI, 17 men, 19 women, and 29 patients with Alzheimer's disease (AD) 13 men, 16 women. All subjects with NC had neurological and neuropsychological tests and had scores within the normal range. Furthermore, subjects with NC were included only if they had no clinical histories psychiatric illnesses, epilepsy, hypertension, diabetes, major heart disease, or head trauma, and no sign on the MRI data of other major neurodegenerative diseases.

DIAGNOSIS OF DEMENTIA

The severity of cognitive decline was graded according to the Clinical Dementia Rating (CDR) Scale. The diagnosis of dementia was based on the criteria of the Diagnostic and statistical manual of mental disorders, 4th ed. (DSM-IV) [6] and the diagnosis of AD on the National Institute of Neurologic and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria . [7]

Diagnosis of MCI

MCI was diagnosed using the criteria proposed by Mayo Clinic Alzheimer's Disease Research Center. The criteria required: (1) memory complaint by patient, family, or physician; (2) normal activities of daily living; (3) normal global cognitive function; (4) objective impairment in memory or in one other area of cognitive function as evident by scores >1.5 S.D. below the age-appropriate mean; (5) CDR score of 0.5; and (6) absence of dementia[8,9] . All the MCI subjects included in the present study had memory impairment and most of them had multiple domain amnestic MCI.

All patients and controls were subjected to the following:

Full medical history taking

Thorough general, neurological examination and a detailed neuropsychological evaluation

laboratory investigations; complete blood picture, liver function testes, kidney function testes, blood glucose level, serum electrolytes and erythrocyte sedimentation rate.

4- **Magnetic resonance imaging (MRI) of the brain:**

MRI was done at MR unit of Radiology Department of Faculty of Medicine, Zagazig University Hospitals for all patients included in the study, using 1.5 tesla whole body MRI scanner, (Philips Medical System) equipped with standard head coil according to the following protocol.

MRI sequences at slice thickness 5mm first (using MR head coil) was done for qualitative assessment as follow:

A): T-1w sequence, axial and coronal, TR (time of repetition 500-600 msec) , TE (time of echo 12-20msec.).

B**)** T-2w sequence , axial, and coronal, TR (2800-4800), TE (80-110).

C) Flair sequence , axial and coronal TR (3500), TE (80).

Volumetric analysis was done using T1-weighted images, axial and coronal with slice thickness 1.5 mm.

All regions of interest on right and left cerebral hemisphere were manually traced using mouth driven cursor, then the volume of the region of interest was automatically calculate by summation the trace area of each slice multiplied by the slice thickness.

The following structures were measured;

hippocampus : right and left hippocampus were manually traced in the oblique coronal T1 weighted images

b. **Entorhinal cortex :** to the level of the limen insulae, and until the section behind the posterior limit of the gyrus intralimbicus. The lateral margin of the ERC was in the medial bank of the collateral sulcus, where it borders the perirhinal cortex. The borders of the ERC and perirhinal cortex depended on the depth of the collateral sulcus.

c. **Total grey matter.** volume image using thin-section dual-echo proton density– and T2-weighted images for GM, WM, and CSF from all sections that covered the whole brain.

d. White matter volume. The WML were evaluated by a MRI images with either proton density (PD) and T2 weighted images or with T2 weighted and FLAIR images. The sum of frontal, temporal, parieto-occipital, basal ganglia ,and infratentorial regions were used in the analysis.

e. Total intracranial volume. The amount and rate of atrophy were then calculated. The rate of atrophy was assumed to be constant within each individual) and was computed as the gradient of the line between TBV measurements at 2 time points, per individual, expressed as percentage change per year.

STATISTICAL ANALYSIS

The data were tabulated and statistically analyzed using **Epi-INFO** and SPSS Version 15 software package [10] **Descriptive statistics:**

The sample mean , standard deviation (SD), and standard error of the mean as well as the range were obtained for numerical variables, the frequency, distribution and percentage were calculated for categorized variables.

II. Analytic statistics:

Student 't' test , chi square "X" and correlation coefficient "r" were used for analysis of the results.

III. Level of significance: For all above mentioned statistical tests done, the result is considered significant if (P value):

P value of > 0.05 indicates non-significant results.

P value of < 0.05 indicates a significant results.

P value of <0.001 indicates highly significant results.

The smaller the P value obtained the more significant are the results.

RESULTS

This study was carried out on 65 patients with age ranges from 55 to 80 years with mean age 67.5±9.3 (36 patients with mild cognitive impairment and 29 patients with Alzheimer's disease) beside 40 healthy elderly people with normal cognition(NC) with age ranges from 55 to 80 years, 20 men, 20 women, with mean age 68.1 ±5.3 years, MMSE 29.0± 1.0), 36 patients with mild cognitive impairment (MCI, 17 men, 19 women, with mean age 67.3 ±8.2) years, MMSE 25.0± 1.7), and 29 patients with Alzheimer's disease (AD) 13 men, 16 women, with mean age 67.7 ± 7.1) years, MMSE 21.7 ± 2.1), age of onset of MCI earlier than Alzheimer's disease with no significant difference but duration of Alzheimer's disease was longer than MCI with significant difference as shown in table 1 and 2.

Level and duration of education were higher in control group than in MCI group and MCI more than in Alzheimer's disease group as will as in MMSE; CDR more in Alzheimer's disease group than in MCI with highly significant difference as shown in table 3.

Comparison between MCI, dementia patients and controls regarding volumetric measurements shows that there was highly significant difference regarding Hippocampus, ERC total gray matter and White matter volumes and significant difference regarding total intracranial volume in both groups of patients with smallest in dementia patients than control group as shown in table 4.

Table (1): Demographic data of patients and controls.

	Patients = 65		*Controls = 40*		*P*
Age/ y X ±SD	Range : 55-80 67.5±9.3		Range : 55-80 68.1 ±5.3		0.5
Gender	***No***	***%***	***No***	***%***	***P***
Male	30	46.2	20	50	
Female	35	58.8	20	50	0.7

Table (2): Demographic& Clinical data of *MCI patients* and *Dementia patients*.

	MCI patients 36		*Dementia patients 29*		*P*
Age/y X ±SD	67.3 ±8.2		67.7 ± 7.1		0.83
Gender	***No***	***%***	***No***	***%***	***P***
Male	17	47.2	13	44.8	0.84
Female	19	52.8	16	55.2	
Age of onset X ±SD	59.5±4.6		61.3±6.6		0.19
Duration X ±SD	Range : 1y-4 y 2.4 ± 1.2		Range : 3y-8y 4.9 ± 1.7		0.001

Table (3): ***performance characteristics of the MCI patients , dementia patients and control***

	MCI patients 36	*Dementia patients 29*	*Control n=40*	*P*
Education	**9.7± 3.2**	**8.5± 2.9**	**11.3±4.6**	**0.009**
MMSE	**25.0± 1.7**	**21.7 ± 2.1**	**29.0± 1.0**	**0.001**
CDR	**0.8 ± 0.4**	**1.6 ±0.2**	**0.0 ± 0.0**	**0.001**

Table (4): Comparison between *MCI patients*, *Dementia patients* and controls regarding volumetric measurements.

	MCI patients 36	*Dementia patients 29*	*Control n=40*	*P*
	M±SD	***M±SD***	***M±SD***	
Hippocampus				
right	15.78 ±2.24	13.65±2.18	16.69±3.25	**0.001**
left	14.22±2.37	12.95±2.87	15.47±2.66	**0.001**
Entorhinal Cortex				
Right	**7.68 ±1.68**	**6.71±1.65**	**8.621.39**	**0.001**
Left	**7.09 ±1.57**	**6.57 ±1.61**	**8.52±1.42**	**0.001**
Total	**14.77 ±3.25**	**13.28**±3.26	**17.1**4±2.81	**0.001**
Total grey matter	**655.** ±88.4	**571.8**± 78.6	**715.8**± 98.7	**0.001**
White matter volume (ml)	**432.6±59.8**	**398.5**±63.9	**475.3±57.9**	**0.001**
Total intracranial volume (ml)	**1295.7 ±134.7**	**1165.8±114.8**	**1366±146.4**	**0.05**

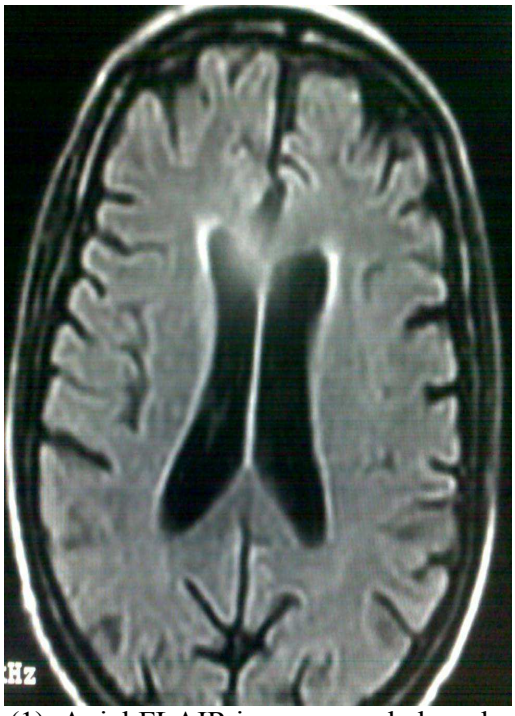

Fig (1) Axial FLAIR image revealed grade (0) with high signal cap and band.

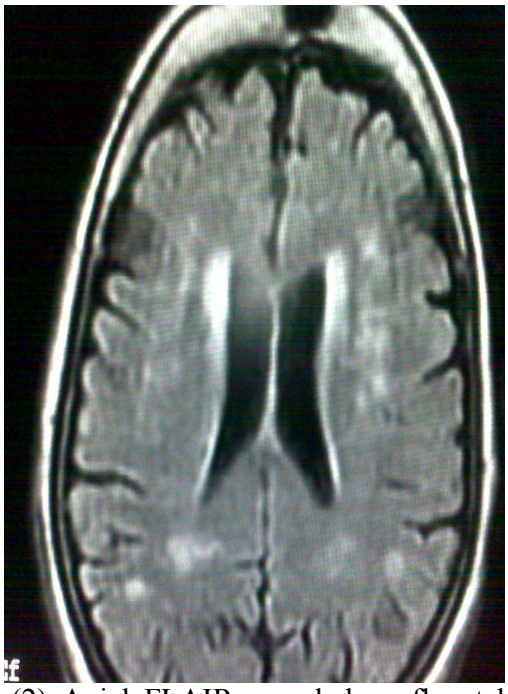

Fig (2) Axial FLAIR revealed confluent high signal intensities of grade (3) white matter lesion.

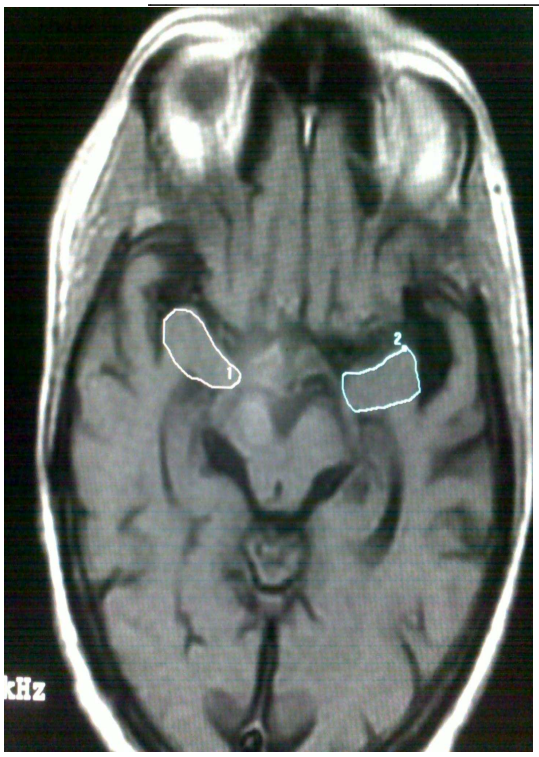

Fig (3) Axial T1w of AD with right hippocampus atrophy

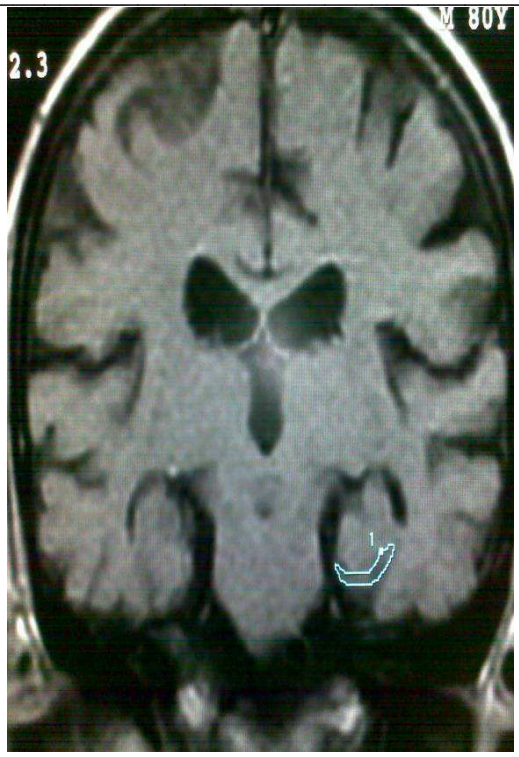

Fig (4) Coronal T1w of AD with left ERC atrophy.

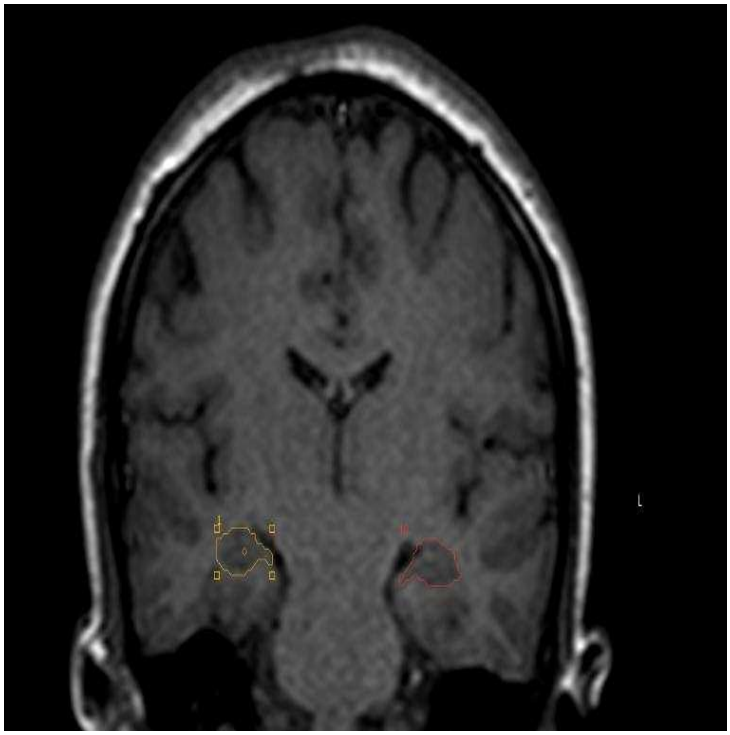

Fig (5) Coronal Tw1 of MCI revealed left hippocampus atrophy

DISCUSSION

In the absence of definitive Diagnostic instruments for Alzheimer disease (AD), structural magnetic resonance imaging (MRI) has emerged as an important tool for the characterization of morphological changes associated with the disease [11] Increased atrophy, for example, is a consistent structural neuroimaging finding that is a hallmark of AD. [12]

In our result the age of onset of MCI was earlier than Alzheimer's disease and female more common in dementia and MCI patients with no significant difference but duration of Alzheimer's disease was longer than MCI with significant difference Some authors[13,14] have demonstrated that dementia and specifically, AD are more common in women. However, others[15,16] have not found differences between genders.

Age increases the risk of dementia. Between 65 and 85 years of age, the prevalence doubles every 5.2 years. [13,15]

In our result, level and duration of education were higher in control group than in MCI group and MCI more than in Alzheimer's disease group as will as in MMSE and CDR more in Alzheimer's disease group than in MCI with highly significant difference this in agree with some studies[14,17] a lower educational level was a risk factor for the onset of dementia, though this has not been confirmed in other studies[18] . In a recent meta-analysis[19] , the relative risk (RR) for patients with a lower educational level was 1.8 for AD and was not significant for the other dementias. There are a number of hypotheses to explain the relationship between the years of education and dementia: 1) education may affect the results of some screening tests such as the MMSE, leading to an overestimation of the diagnosis of dementia in illiterate populations[19] ; 2) a higher educational level would delay the clinical expression of dementia. The "cognitive reserve" hypothesis postulates that a higher educational level would increase neuronal plasticity and connectivity. In our study, we have used MMSE, CRD.

As regarding the hippocampus atrophy in our study there was a significant reduction in total hippocampus volume right and left in Alzheimer patients and in mild cognitive impairment patients than normal cognition control group this was in agree with Previous studies, in the elderly, rates of hippocampal atrophy on MRI were found to be higher in cases with Alzheimer's disease and mild cognitive impairment compared with controls[18,19,20] . Also this is in line with clinical studies which showing that 80–90% of established patients with Alzheimer's disease have a small hippocampal volume. [21,22] Pathological validation studies have shown that hippocampal atrophy on MRI correlates with the specific Alzheimer's disease neuropathology[23,24]. In the elderly, follow-up studies in patients with Alzheimer's disease and mild cognitive impairment have shown an approximately two to four times faster rate of decline in hippocampal volume than in healthy controls. [25,26]

We have previously shown that even in elderly without cognitive symptoms or complaints, a small hippocampal volume on MRI predicts Alzheimer's disease.[27] Longitudinal MRI scanning of the hippocampus has been performed in a few studies. In a set of young patients with familial Alzheimer's disease, hippocampal volume change was found to be an earlier and better predictor compared with a single volume measurement. [28] However, in another follow-up study of 3 years among 27 elderly patients with Alzheimer's disease, longitudinal MRI hippocampal data did not improve diagnostic accuracy over a single volume measurement.[29]

It is well known that the entorhinal cortex occupies the key position for the communications between the hippocampus and the rest of the brain. Accordingly, the degeneration of the neuronal architecture of the entorhinal cortex destroys a large functional hippocampal pathway, respectively,

causing memory impairment and cognitive deficits associated with AD.[30]

Also in our study there was atrophy in entorhinal cortex in AD and MCI patients than control group this was in line with one cross-sectional study, volumetric MRI analysis of the entorhinal cortex and hippocampus provided in vivo evidence that entorhinal atrophy precedes hippocampal atrophy in AD.[31] In early studies, manually delineating the anatomical boundaries of the two structures on MRI, found that MCI patients have a smaller ERC and hippocampus than normal elders whereas patients with mild AD have more prominent reductions in the ERC and the hippocampus.[32] Other studies obtained similar results, although reductions in MCI have been variously reported as being either intermediate between normal and AD[33,34] or as being similar to AD.[35] Furthermore, the rates of volume loss in the ERC and hippocampus are significantly higher in MCI patients than in control subjects.[36]

Regarding white matter and total intracranial volume there was reduction in volume in dementia patients with significant difference. An assessment of white matter fibers using the imaging technique of DTI has revealed that the fibers connecting the hippocampus and posterior cingulated gyrus are impaired in AD subjects to a significantly greater degree compared with control subjects.[37] This suggests that white matter damage might relate to grey matter atrophy within the temporo-parietal brain network in AD. Although AD has long been considered a grey matter disease, imaging of white matter changes in MCI and early AD has been gaining interest as evidence has grown for a more prominent role of white matter in AD. Conventional MRI yields insufficient contrast to discriminate fiber tracts in white matter, but DTI—a new MRI variant is sensitivity to fiber integrity as well as orientation. Several studies reported significant alterations of DTI measures in the hippocampus[38,39], thalamus [40], posterior cingulum bundle[39,41] and several regions in posterior white matter[41] in MCI patients relative to control subjects. Moreover, regional specific DTI changes were found to correlate with specific cognitive functions[42]

As regarding the gray matter atrophy in our study there was a highly significant reduction in gray matter volume in Alzheimer patients and in mild cognitive impairment patients than normal cognition control group this was in agree with previous study using voxel-by-voxel analysis with a large number of subjects revealed that GM decreases did not differ significantly between patients with DLB and those with AD.[43]

CONCLUSIONS

Several imaging modalities are sensitive to changes of early AD and MCI, and can offer meaningful diagnostic predictions as well as imaging are encouraging for improving diagnosis of the disease at an early stage and provide the rationale for early treatment and objective measures for therapeutic effects in clinical trials However, more data are needed to evaluate the value of imaging for determining individual risk for future AD, which is fundamental for the counseling of patients and making therapeutic decisions.

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التغييرات الكمية في صور الرنين المغناطيسى للمخ في الضعف الادراكي الطفيف ومرض الزهايمر

تم إدخال مفهوم الإعاقة الإدراكية الطفيفة لوصف الأفراد الأكبر سنا الذين ينضوون إدراكيا بين تقادم السن الطبيعي والعته. في الوقت الحاضر، هناك اهتمام خاص في الإعاقة الإدراكية الطفيفة لأنه يعتقد أن هذه المتلازمة تكون مرحلة انتقالية لمرض الزهايمر، التي قد تحدد نافذة لتدخلات علاجية فعالة. ومع ذلك، ليس كل المرضى الذين يعانون من الإعاقة الإدراكية الطفيفة على المضي قدما الى مرض الزهايمر. وتم عمل هذه الدراسة لاستكشاف التغييرات الكمية في صور الرنين المغناطيسى للمخ في الضعف الادراكي الطفيف ومرض الزهايمر مقارنة مع الادراك العادي وشملت هذه الدراسة ٤٠ شخصا مع الادراك العادي كمجموعه ضابطه ، ٣٦ مريضا يعانون من الإعاقة الإدراكية الطفيفة، و ٢٩مريضا يعانون بمرض الزهايمر.وتم عمل الاتى لهم

١. أخذ التاريخ المرضى الكامل

٢. فحص اكلينيكى شامل عام وخاص بالجهاز العصبى

٣. الفحوص المختبرية؛ صورة الدم، وظائف الكبد وظائف الكلى، مستوى السكر في الدم، الشوارد في الدم و معدل الترسيب.

٤- التصوير بالرنين المغناطيسي (MRI) للدماغ

وأظهرت النتائج أن هناك نقص فى حجم بعض الاماكن بالمخ مثل منطقة الحصين، القشرة الشمية الداخلية، المادة الرماديه. المادة البيضاء وبالتالى حجم المخ ككل فى المرضى الذين يعانون من الإعاقة الإدراكية الطفيفة و المرضى الذين يعانون من مرض الزهايمر عن الشخاص الطبعيين و كان النقص فى المرضى الذين يعانون من مرض الزهايمر أكثر من المرضى الذين يعانون من الإعاقة الإدراكية الطفيفة