A STUDY ON "COGNITIVE PROFILE IN IDIOPATHIC PARKINSON'S DISEASE"

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CERTIFICATE

This is to certify that the dissertation entitled **A STUDY OF COGNITIVE PROFILE IN IDIOPATHIC PARKINSON'S DISEASE** is a bonafide record of work done by **Dr.S.RAJENDRAN** at the Institute of Neurology, Rajiv Gandhi Government General Hospital&Madras Medical College, Chennai, submitted as partial fulfilment of The TamilNadu Dr.M.G.R. Medical University rules and regulations for the award of **D.M.(Neurology)** degree under my direct guidance and supervision during the academic year 2011- 2014.

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DECLARATION

I solemnly declare that this dissertation titled **"A STUDY OF COGNITIVE PROFILE IN IDIOPATHIC PARKINSON'S DISEASE"** is done by me at the Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of **Prof. Dr. K. Bhanu, Dip.NB, DM**, Professor of Neurology, Institute of Neurology Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfilment of the university requirements for the award of the degree of D.M. Neurology

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CONTENTS

INTRODUCTION

Parkinson's disease (PD) is a degenerative disease named after James Parkinson (1755-1824) who described this condition in his publication in 1817 called 'Essay on Shaking Palsy.[1] Among the neurodegenerative diseases it ranks second after Alzheimer's disease (AD). It is more common in the elderly, although early onset disease is well known. It has characteristic clinical features of bradykinesia and at least one the following: muscular rigidity, 4-6Hz. rest tremor and postural instability. Diagnosis is usually made by the well validated criteria [2] called 'UKPDS' (UK Parkinson's Disease Society Brain Bank criteria). Apart from motor manifestations there are number of non-motor manifestations which is a common source of disability in PD. These include

1) neuropsychiatric features such as Cognitive deficits, depression, anxiety behavioral changes 2) autonomic symptoms including constipation 3) sleep disturbance 4) sensory disturbance such as pain and paresthesia 5) fatigue and 6) loss of sense of smell.

Clinicians have ignored cognitive deficits associated with Parkinson's disease for years. Due to short span of life in the past, it was believed that intellect and sensibilities were not affected. The life span has increased now with the use of effective treatment that is available making it possible for

patients with PD to live almost as much as non-affected individuals. Last few decades has witnessed increasing recognition of mild cognitive impairment (M CI) and dementia associated with PD (PD-D). Most patients with Idiopathic Parkinson's disease have cognitive deficits. But only a portion of PD patients develop dementia. [3]

Patients with PD usually present with motor features such as bradykinesia, rigidity and tremor. However on detailed neuropsychological testing, subtle cognitive deficits are almost always present even in early PD. [3] Cognitive profile in PD includes psychomotor slowing, bradyphrenia, apathy, impairment in retrieval of memory, set shifting, problem solving, poor viusospatial function, fluctuations in attention and concentration, and prominent mood and personality changes. [4] Language and praxis, however, remain largely intact. The cognitive impairment is subtle and does not exhibit recognizable functional restriction in daily activities, and may be missed in conventional screening and routine higher mental function assessment, but they can progress to frank dementia.[1]

REVIEW OF LITERATURE

Demography of Cognitive impairment in PD

Compared to age-matched controls, both the prevalence and the incidence of cognitive impairment are higher in PD patients. According to one study by Janvin et al, [4]annual rate of conversion of MCI-PD (mild cognitive impairment in PD) in to PDD (Parkinson disease dementia) was 15%. About 60 to 65% of people with mild cognitive impairment due to any cause develop clinical dementia during their lifetime.[3]In another study by Caveness et al [5]26% of 86 PD patients had MCI, with frontal- executive dysfunction being the most common, followed by amnestic deficit.[5] Among patients with PD, incidence rate of dementia was found to be 6 times more than in controls. [6] In cross sectional studies [7, 8, 9] 40% of patients with PD were associated with dementia. In longitudinal studies [10] 78% have been associated with dementia. Dementia was diagnosed in 62% of patients with PD, who did not have this condition at the baseline, compared to 17% of controls, during the 5 year follow up. [6]

Risk factors for cognitive impairment in PD

Number of risk factors associated with cognitive deficits in PD have been identified, in both prospective and cross-sectional studies. [11]

They are

1. Age at onset of PD. Overall risk of development of global cognitive impairment increases with age.
2. Rapid eye movement (REM) sleep behavior disorder [12]
3. Subtle involvement of executive functions, poor verbal fluency, and poor performance on verbal memory at baseline were independently associated with development of dementia.
4. Poor cognitive scores at baseline
5. Motor disability severity
6. Symmetrical disease presentation
7. Axial involvement, speech impairment and postural imbalance
8. Patients who were old and had motor symptoms which was quite severe at baseline had risk of developing dementia10 times comparing to younger patients whose motor symptoms were less severe. [13]
9. Confusion or psychosis while taking levodopa treatment
10. Autonomic failure when occurring early
11. Drug-related hallucinations when occurring early
12. Poor response to dopaminergic treatment
13. Olfactory tract and the frontal lobe in the close vicinity are known to be related to memory with memory and loss or decreased smell sensation can predate development of Parkinson's disease dementia [14]

Clinical features of cognitive impairment in idiopathic PD

The main clinical features are [8, 9, 10, 11]

Memory: There can be moderate impairment, retrieval deficits with relatively spared storage

Attention: There can be prominent impairment with fluctuations

Executive functions can be severely impaired

Visuospatial functions: There can be early and substantial impairment

Language: Impaired word finding and verbal fluency is recognized

Features associated with cognitive impairment in idiopathic PD are

Motor features:

- Symmetrical involvement
- Prominent postural instability and gait disorder
- Tremor dominance which is less frequent

Behavior features

- Apathy
- Hallucinations
- Delusions

Depressive symptoms

Idiopathic PD can be classified based on cognitive assessment as below

- Cognitively intact PD
- Minimal cognitive impairment [MCI-PD]
- Dementia [PDD]

Minimal Cognitive Impairment associated with PD (MCI-PD)

Mild cognitive impairment in PD (PD-MCI) is defined as cognitive impairment that is not normal for that age but with normal functional activities. Based on modified Peterson criteria, MCI-PD has been classified into [11]

- Single domain, non-memory related MCI(executive, visuospatial, or language)
- Multiple domain MCI
- Amnestic type MCI

It was found that single domain impairment is more common than multiple domain involvement. I was also conclusively found that non amnestic more often involved than nonamnestic impairment. There was significant heterogeneity in the cognitive domain involvement [8]

Progression of PD-MCI to PDD

PD-MCI is known to be a risk factor for PD [11]. The majority of PD-MCI cases convert to PDD over several years 9. The point prevalence of is about 30% [and] the cumulative prevalence is about 75% for PD patients who survive more than 10 years. [11]

Parkinson disease dementia (PDD)

Attention

Attention impairment is an early feature of PDD. [6] Just like Dementia of Lewy body disease [DLB] even in PD with dementia there is early and prominent impairment of attention and vigilance. Central processing time is prolonged in PDD resulting in longer response durations in measures of simple and choice reaction time.

Executive function:

Executive function is the capacity to plan, organize and perform behavior that is goal directed [11]. A deficit of executive function is a core feature of PDD. This deficit occurs early and is prominent throughout the course. These deficits involve tasks requiring concept formation, set elaboration, set maintenance and problem solving. When compared to

external cued behavior, the internal cued behavior is more affected in patients with PDD. [16]

Memory

In PDD all types of memory is impaired .[11]This includes explicit and implicit memory as well asworking memory. The severity and profile of impairment varies from that seen in amnestic syndrome .[10] In PDD recognition is significantly better with cues but free recall is affected, which means that the new information was stored but could not be readily retrieved. The memory stores in PDD patients were found to be correlated with executive function test scores. It therefore suggests that memory deficit may be due to difficulties in getting hold of memory traces which reflects a deficiency in internally cued search strategies, due to dysexecutive syndrome. Limbic type memory disorder prevalent in Alzheimer's disease (AD) where both storage and recall cues are impaired, is contrast to PDD associated memory disorder. [15]

Language

In PD core language functions are relatively preserved. Main feature of language dysfunction in PD are impaired verbal fluency and mild anomia. When the disease progresses it develops into transcortical type aphasia. Dysexecutive syndrome rather than true involvement of language functions is

believed to be the cause of language deficits in PDD, due to impairment of self-generated search strategies. Contrastingly aphasia type language abnormalities are prominent early in AD. [10]

Visuospatial function

PDD has another characteristic feature which is early and prominent viusospatial function deficit. Impairment of visual perception may be the core of the problem as tasks that require viusospatial analysis and orientation are found to be the most affected. Visuospatial abstraction and reasoning are more affected in PD when comparing to AD.

Behavior

Prominent behavioral symptoms and personality change in associated with PDD.

The most common neuropsychiatric symptoms are hallucinations, delusions, Depression, anxiety and apathy. Delusions and hallucinations may occur with treatment of dopaminergic agents, and occur more frequently with patients with dementia. When compared to AD, depressive features and visual hallucinations are more common in PD. [15]

Motor System

In PDD the motor involvement is more symmetric. The major difference between PD patients with dementia and those without it was a later age of onset of motor manifestation in PDD. [16] Tremor dominance is associated with relative preservation of mental ability; whereas bradykinesia, rigidity and postural instability have been correlated with more rapid decline and dementiastatus. [17] In a study of motor features, postural instability gait disorder (PIGD) subtype was found to be overrepresented in PDD in contrast to non-demented PD patients. [18] It is proposed that L-dopa responsiveness diminishes with emergence of cognitive impairment. [18] Proposed mechanism for this phenomenon is intrinsic striatal alpha synnuclein pathology, loss of dopamine D2 and D3 receptors.

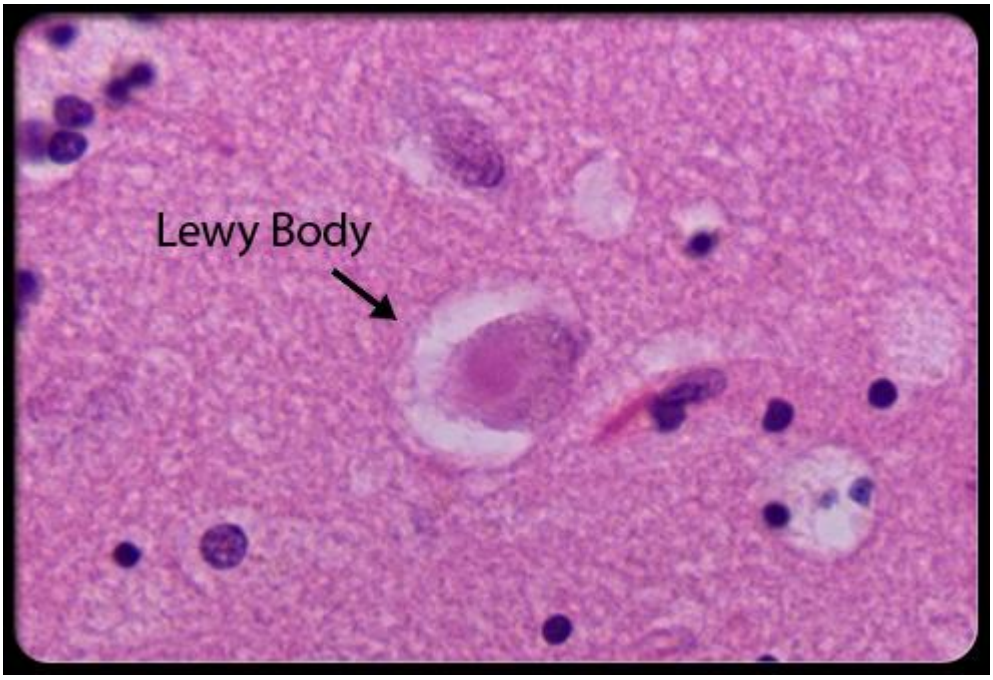
Pathophysiology in PD cognition

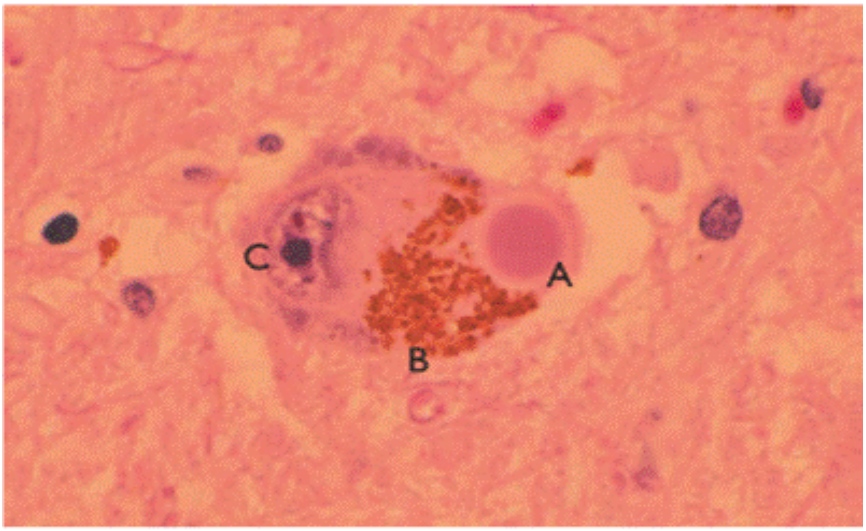
Deficiency of dopamine in the nigrostriatal pathway has initially been proposed to be the cause of cognitive impairment in PD .[19] Many young patients however may not show any cognitive impairment even when there is severe motor dysfunction. Cognition does not improve with levodopa. This is another reason against this theory; in fact it can get worsened especially in the later stages. There are reports that cholinergic deficits that occur due to degeneration of ascending cholinergic pathways cause cognitive impairment and dementia in PD patients. [16]

Deficits	Effect
Cholinergic deficit	Impairment in frontal dysfunction memory and attention
Dopaminergic deficiency	Dysexecutive syndrome
Noradrenergic deficits	Impaired attention
Serotonergic deficits	Depressive mood

Above is the proposed neurotransmitter deficits and resulting specific cognitive dysfunction [16]

Pathology





(A)The large pink circle is a Lewy body within a brain cell. (B)The brown section to the left of the Lewy body is normal brain pigmentation. (C)The nucleus, the cell's control center, is to the far left of the cell.

There have been some controversies in pathologyand type and the site seen in PD dementia. Three types of pathology been invoked, namely in subcortical structures, notably dopaminergic neuronal loss in substantia nigra (SN) and limbic and cortical areas.

In PD, pathological changes follow an ascending order, starting from brain stem also anterior olfactory nuclei, and then affecting cortical areas [19]. The spread of this kind pathologically from brainstem followed by the limbic and later neocortical areas may explain why dementia usually develops relatively late in classic PD. [19]

Genetics

Rare form of familial PD with dementia occurs. Major component of lewy body being alpha synnuclein, when expressed in excess, is important for

development of dementia. ApoE2 allele when present increases the likelihood of dementia in patients with PD as against those with AD where its presence is protective. [20]

Imaging

Several non-specific features have been described in structural and functional brain imaging. [21, 22] When compared to normal controls, in PDD patients widespread areas of cortical atrophy were found in both frontal temporal and lobe and left parietal lobe. [23,24,25,26] Grey matter reductions were found in frontal, temporal and parietal limbic lobes in these patients. In AD there is more severe atrophy of temporal lobe including hippocampal and para hippocampal areas, whereas in PDD there was severe atrophy of thalamus and occipital lobe .[27] Enlargement of ventricles and caudate atrophy are other structural changes in cognitive impairment of PD

How to diagnose cognitive deficits in PD?

Diagnosing cognitive deficits in PD is made difficult by confounding factors such as

- Apparent language dysfunction as a consequence of motor dysfunction
- Difficulty in deciding if impairment of daily activities is due to motor or cognitive dysfunction.
- Drug effects complicating diagnostic process.

Steps in diagnosing suspected dementia in PD:

The first step is Diagnosing dementia: differentiating dementia from pseudodementia of depression, delirium, and side effect of drugs. As a next step one has to differentiate Dementia in atypical Parkinsonism; PD with AD other dementias due to Vascular disease, tumor, Normal pressure hydrocephalus (NPH) and metabolic disease such as thyroid disease. As a third step, other conditions like essential tremor which can be associated with cognitive impairment.

NEUROPSYCHOLOGICAL TESTS

1. Mini-Mental State Examination

Several bedside tests are used in assessing the mental status. However, still the most commonly used test is Mini-mental state Examination (MMSE) by Folstein et al. [28] Maximum points given for MMSE are 30. For orientation in time: i.e. date, day, month, year and season 5 points are given; 5 points for orientation to place viz. floor, hospital, town, state and country.; 5 points for attention by serial 7 test or spelling the word "WORLD" backwards.; 3 points given for registration and 3 points for recall of the 3 items after a gap of 5 minutes. For naming watch and pencil, 2 points are given; one point for repetition of sentence; a total of 3 points is given for 3 stage command; one point for command for writing asking patient to close eyes, 1 point is given

to write a sentence and one point is given for copying two intersecting pentagons. The low normal cut off is estimated to be 29 for college graduates, 23 for elementary or junior high school completers and 19 for uneducated people. [29]

Advantages of MMSE: a) it requires limited time b) it is useful for documenting disability assessments and following drug trials and c) it is a useful screening test.

Disadvantages: a) the score depends on the educational status of population studied b) the test is biased to orientation and language which is less affected in frontal lobe involvement and right hemispheric lesion. c) It cannot differentiate diffuse from focal lesion.[28,31]

2. **Addenbrookes's Cognitive Examination- Revised (ACE-R).**

Devised from the Addenbrookes's hospital, Cambridge, UK, it is designed to diagnose and classify different types of dementia like Alzheimer's dementia (AD) and fronto-temporal dementia (FTD) and, without using any specialized equipment[30.] It includes MMSE and in addition language, memory and visuo spatial components. It consists of orientation (10 points) memory (35), attention (8), language (28), visuospatial ability(5) and verbal fluency (14) with the total maximum score of 100. The score is not influenced by age, sex or education.

3. Montreal Cognitive examination (MoCA)

The Montreal cognitive Assessment (MoCA) was developed as a quick screening instrument for mild cognitive deficit [31,32]. It assesses different cognitive domains namelyexecutive functions, attention and concentration,language, memory, visuoconstrucitonal skills, conceptual thinking, calculations and orientation. It would take 10 minutes to administer the test. Total maximum score is 30 points; a score of 26 or above is considered normal.

4. **Frontal Assessment Battery**.

This evaluates various executive cognitive functions by a battery of six subtests. [33,34] By this score the patient is evaluated which demonstrates the severity of dysexecutive function if any. The FAB subtests are very well correlated with frontal lobe damage caused by various etiology and are well demonstrated by Pet study of frontal lobe metabolism.[30] The test is also studied in frontal lobe dysfunction due to PD, PSP (progressive supranuclear palsy, FTD (Frontotempoorral dementia), MSA (multiple system atrophy) and also assessed the severity of dysfunctions. [34]FAB also has good psychometric properties because of the optimal inter rater reliability, concurrent validity and internal consistency. Guedji et al found in their recent study [34] that in Neuroimaging, FAB performance significantly correlates with perfusion in prefrontal cortex.

FAB test is done approximately within 10 minutes.[33] It has six subtests and each subtest has score from 0 (minimum) to 3 (maximum score). The total maximum score is 18.

Subtests of FAB:

a. Conceptualization:

It is based on traditional similarities. This evaluates the patient's ability to generate similarities between: 1) orange-banana 2) chair- table, 3) daisy-rose-tulip. The examiner asks: in what way they are alike. The patient cannot be helped in the other items. Full correct responses are fruits, furniture, and flowers respectively. Each right response is associated to one credit (none correct: 0, one correct= 1, two correct=2; three correct= 3).

b. Mental flexibility

The patient has to recall as many words as he can, beginning with the letter S in aone minute trial e.g. "say as many words as you can, beginning with the letter S; any words except surnames or proper nouns". Each correct word is scored as 1 point. The score in mental flexibility may be 0 (< 3 words), 1 (3 to 5 words), 2 (6 to 9 words), or 3 (> 9 words).

c. Motor programming

The patient is explained by the examiner about Luria's 'fist- palm- edge' motor series and repeated for three times. The patient is asked to copy the examiner as he does the sequence, and is asked to do independently. The patient who cannot perform 3 correct consecutive series even with the examiner's help receives no point. Patient who is unable to do on own but is able to do with the examiner's help receives 1point. 2 points are given to patient who performs at least three correct consecutive series alone, and 3 points given for six correct consecutive series.

d.Go- no- go test. This is based on inhibitory control. The subject should inhibit what he has just learned and is required to tap once when hearing a single tap. A series of there trials as 1-1-1 is given. After this, the examiner should ask the patient not to tap when hearing two taps. The examiner does there trials as 2-2-2. After this the examiner taps this sequence 1-1-2-1-2-2-2-1-1-2. The points are given as 0,1,2,3 respectively.

AIM OF THE STUDY

1. To identify the range of cognitive impairment if any inpatients with Idiopathic Parkinson's disease.

2. To identify subclinical cognitive impairment in newly diagnosed idiopathic Parkinson's disease.

MATERIALS AND METHODS

100 patients with Idiopathic Parkinson's disease who attended Neurological services at Rajiv Gandhi Govt. General hospital, Chennai were included for the study.

Study design: Single centre, non- randomized prospective study

Study period: Study was conducted between September 2012 and January 2014. Ethical committee approval was obtained.

Inclusion criteria

Newly diagnosed patients with Idiopathic Parkinson's disease aged between 55and 75 years and not started on anti parkinsonian drugs were included for the study.

Exclusion criteria

1. Very ill patients (moribund state)
2. Presence of depression (pseudodementia), behavior disorders or delirium
3. Symptomatic parkinsonism dementia complex [vascular,tumor,NPH]
4. Coincident degenerative dementia like AD

5. Degenerative diseases presenting with Parkinsonism and dementia namely Progressive supranuclear palsy (PSP), Cortico basal degeneration (CBD) and Dementia in Lewy body disease (DLB).
6. Vascular risk factors like Diabetes mellitus, Hypertension and also history of stroke

Following steps were used

Step 1: Written consent was obtained for all patients (Annexure).

Step 2: Detailed history including demographic details, thorough neurological examination including cognitive examination of lobar functions and were done for all patients,

Step 3: Idiopathic Parkinson's disease was diagnosed by applying UKPDS Brain Bank Clinical Criteria. (Annexure II)

Step 4: Patients with other causes of Parkinsonism were excluded by clinical examination and investigations including brain imaging. Patients having comorbid illness such as severe hypertension, diabetes or other neurological illnesses were excluded.

Step 5: Severity of motor disability was rated on Hoehn and Yahr scale. (Annexure III)

Step 5. The cognitive assessment was done by Neuropsychological tests MMSE (Mini mental state examination), ACE-R (Addenbrookes's cognitive

examination-Revised), MOCA (Montreal Cognitive Assessment) and FAB (Frontal assessment battery test).

Step 6: Administering Movement Disorder Society Task Force Criteria (Annexure IV) to classify Idiopathic Parkinson's disease patients into cognitively intact, PD-MCI and PDD.

SPSS software was used for statistical analysis. The study was analyzed by Chi square test and P value was obtained.

RESULTS AND ANALYSIS

The total number of patients included in the study was 100. The parameters analysed were 1) Age 2) Duration of illness 3) Educational status 4) Hoehn and Yahr stage 5) UPDRS score. Each of these parameters was compared with the individual cognitive scalenamely MMSE, ACE-R scale, MoCA and FAB test. Other non- motor manifestations quoted in the review of literature like behavioural disturbances, psychosis, mood disorders, sleep disorders, autonomic disturbances, sensory disturbances and sensation of smell are beyond the scope of this study, and therefore were not analyzed.

Out of 100 patients, 61 (61%) were males and 39 (39%) females (Fig. 1)

Figure 1: Sex distribution

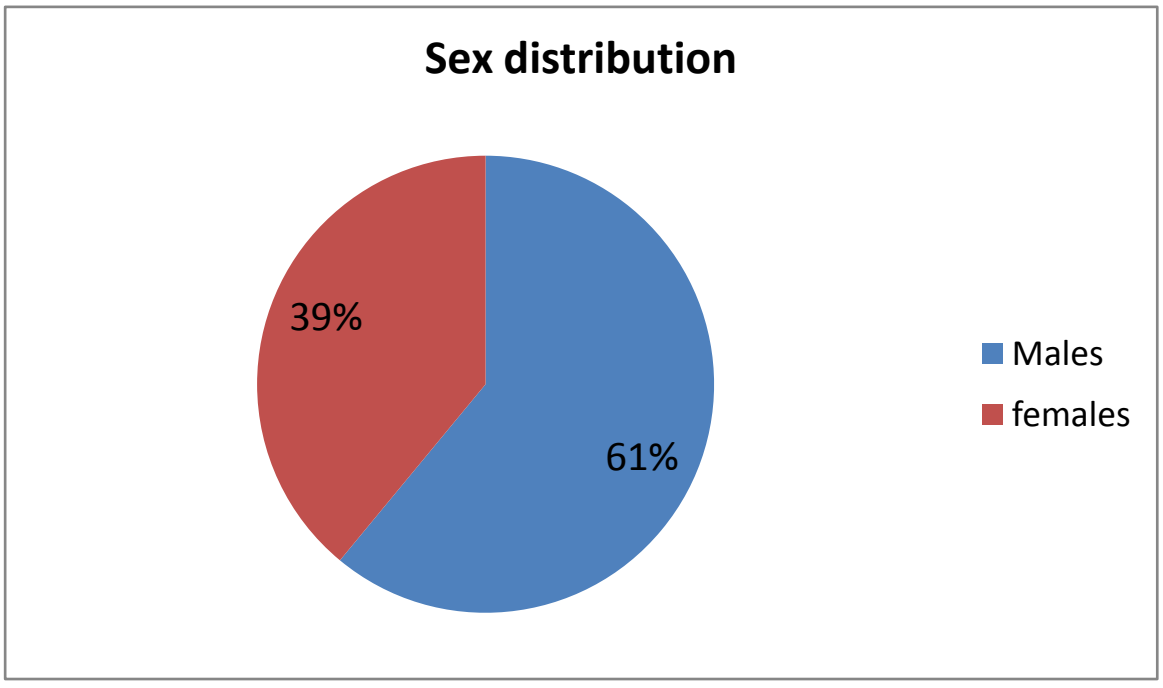


Figure 2: Age distribution of patients

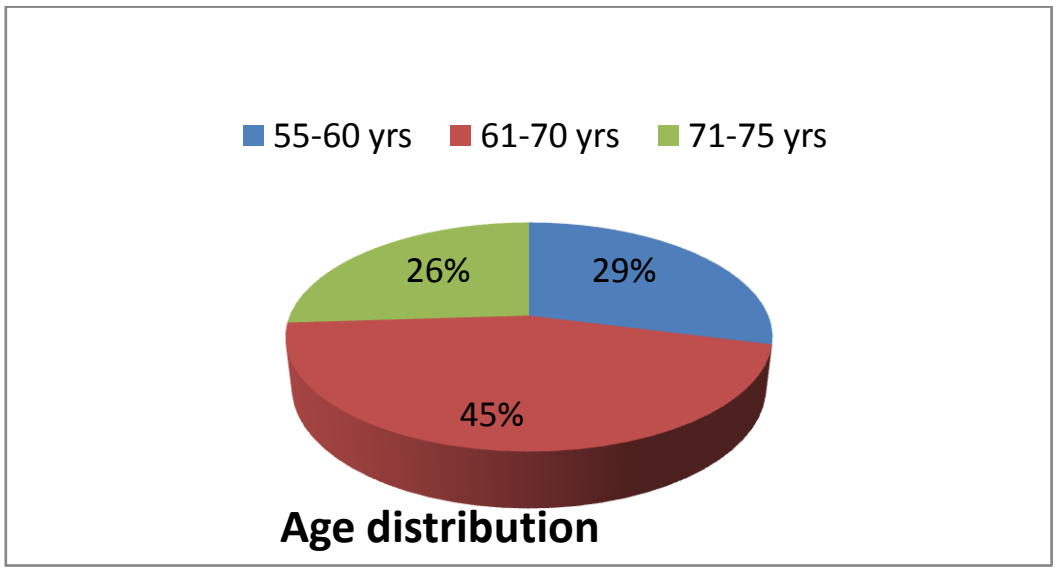


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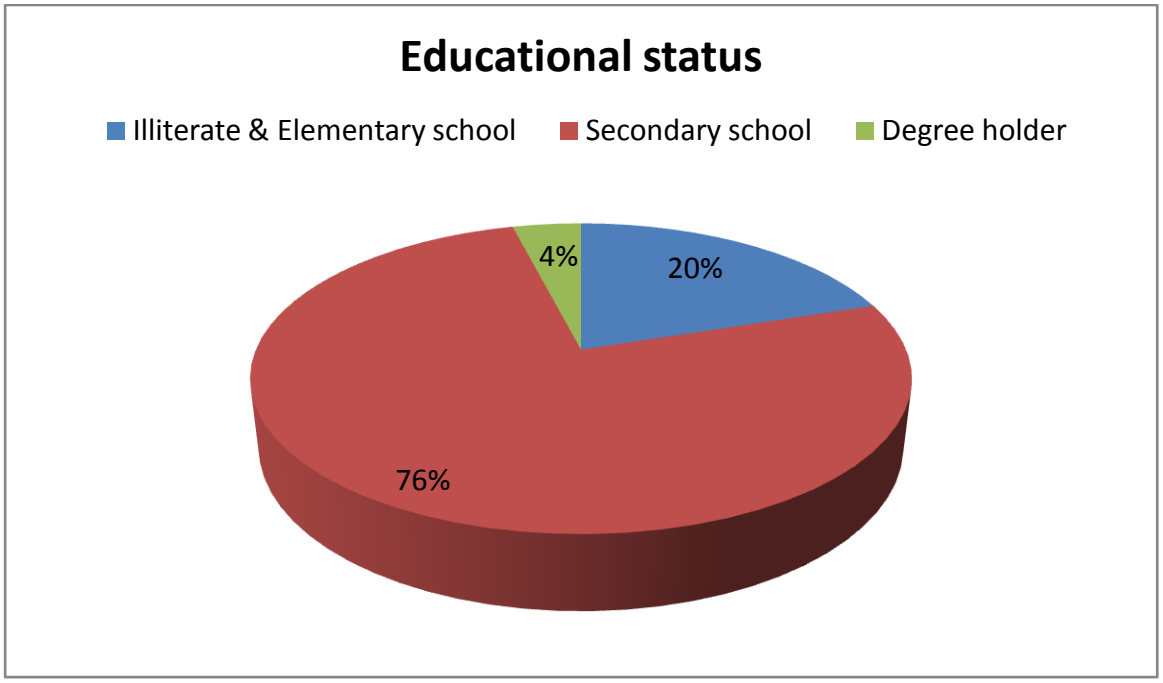
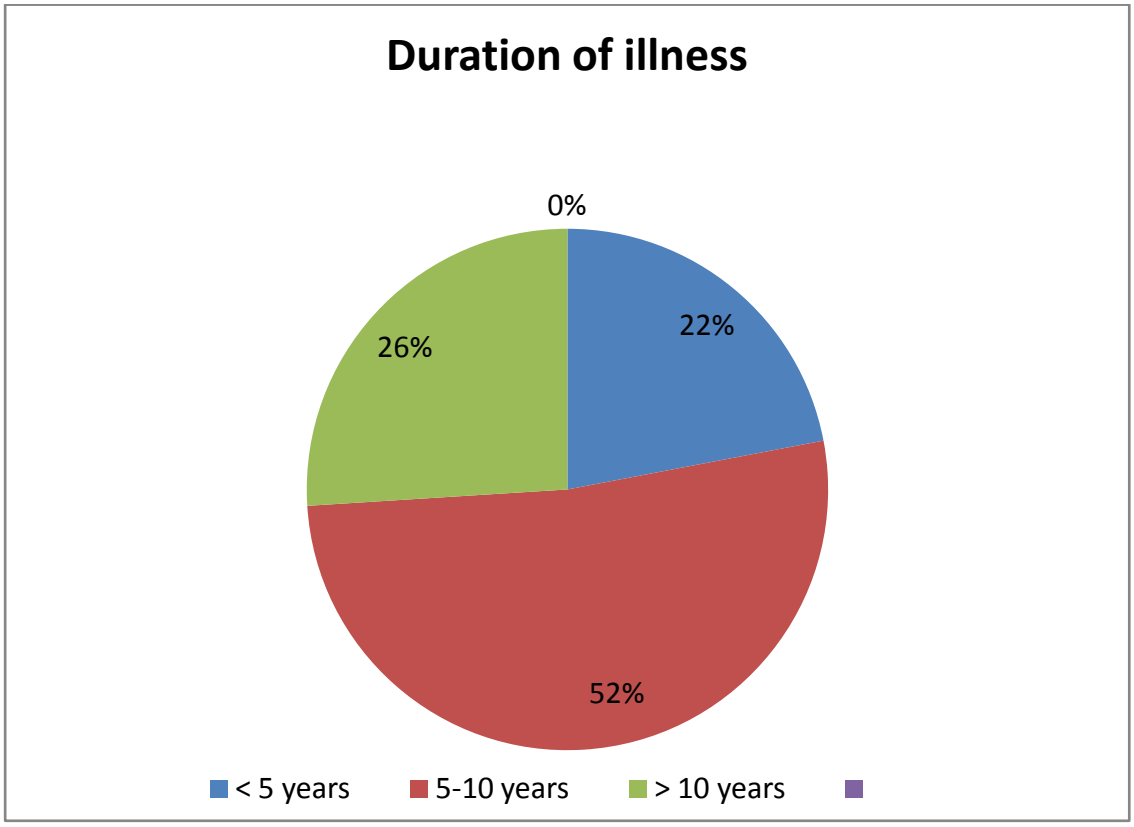
Figure 3. Educational status of patients



Out of the total number of 100 patients, 20(20%) were illiterate or studied up to 5th standard, 76(76%) studied up to secondary school and 4 (4%) were degree holders.

Figure 4 : Duratin of illness



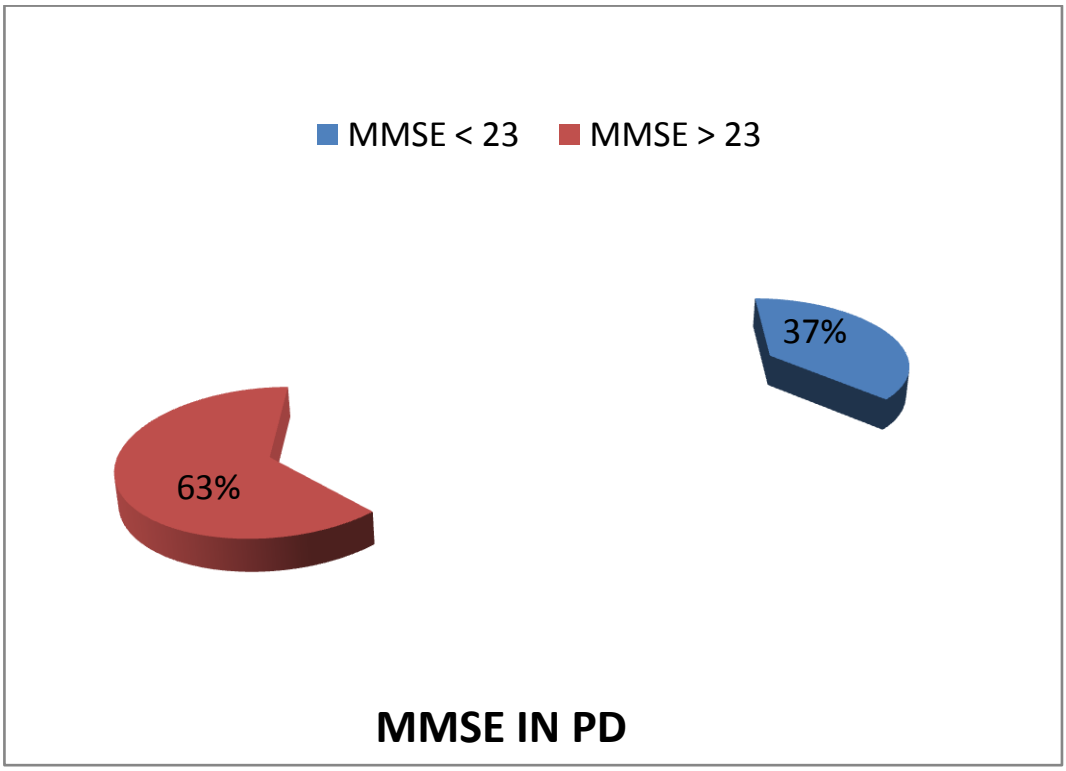
Out of 100 patients 26 patients (26%) had duration of less than 5 years, 22% had

duration of 5-10 years and 52% had duration more than 10 years (Figure 4)

RESULTS OF COGNITIVE EXAMINATION:

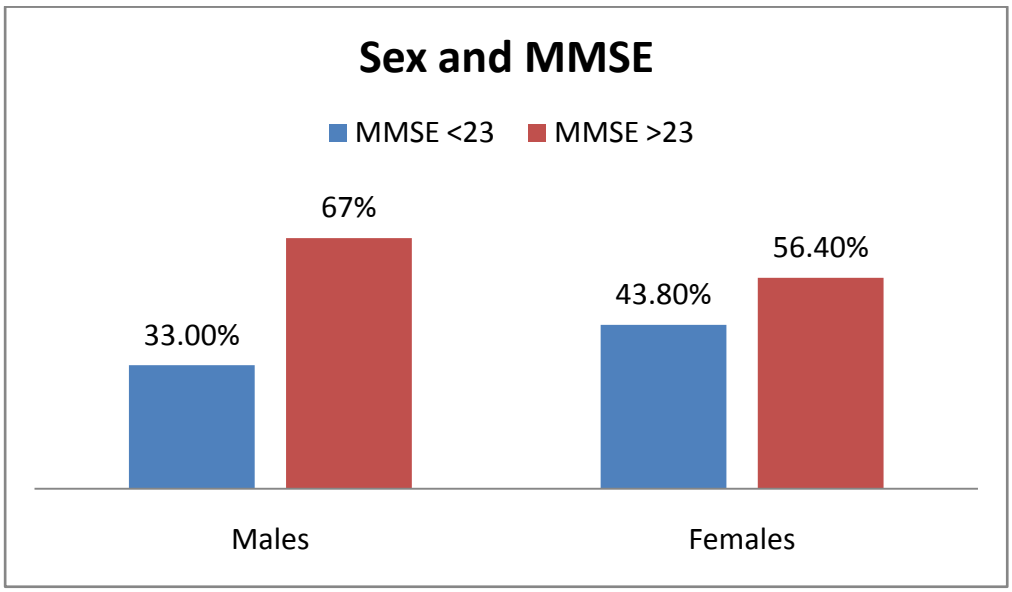
Analysis of MMSE in PD

Figure 5: Analysis of MMSE in PD



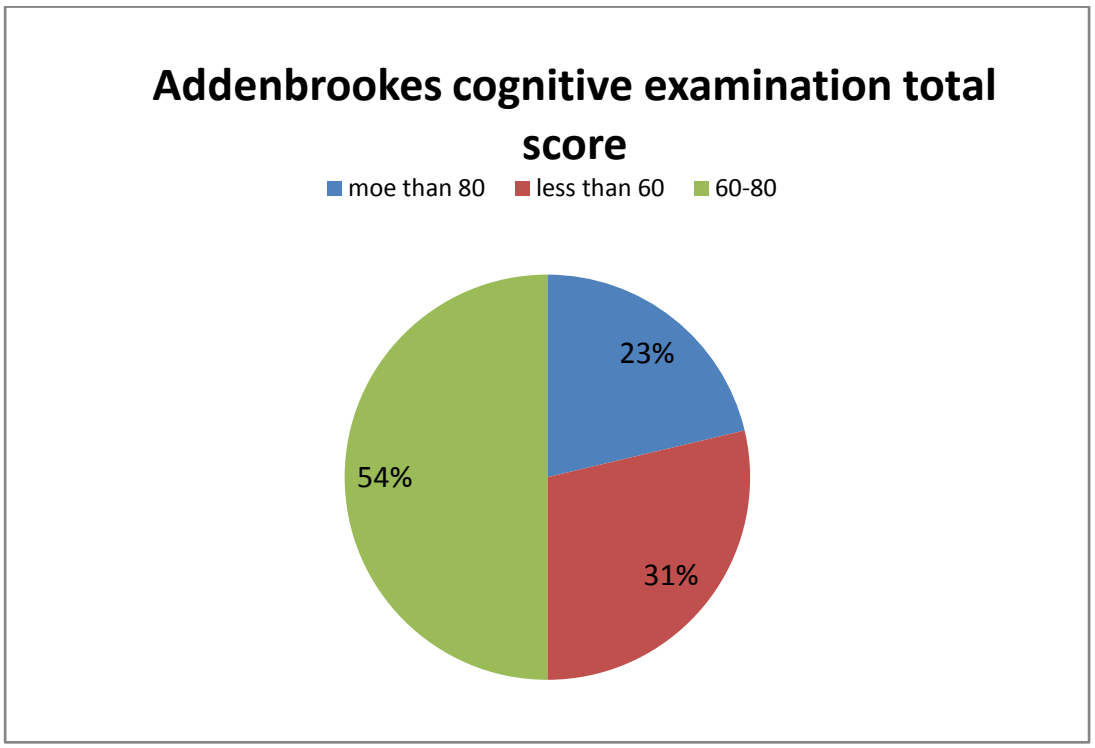
The MMSE was < 23 in 63% of patents with PD and > 23 in 37% of patients.

Figure 6: Sex distribution and MMSE



In males less than 23 score on MMSE was obtained by 32.8% of patients and score more than 23 was obtained by 67% of patients. In comparison, in females score less than 23 was obtained by 43.8% and score more than 23 was obtained by 56.4% of patients. (Fig. 6)

Figure-7: Addenbrookes cognitive examination total score



In Addenbrooke's cognitive examination out 100 patients studied 31 patients (31%) scored less than 60, 54% scored 60-80 range and 23% scored more than 80. The highest score is seen in the youngest age group of 50 to 55 years in PD patients and poorest score is seen in oldest age group of 71- 75 (fig. 8)

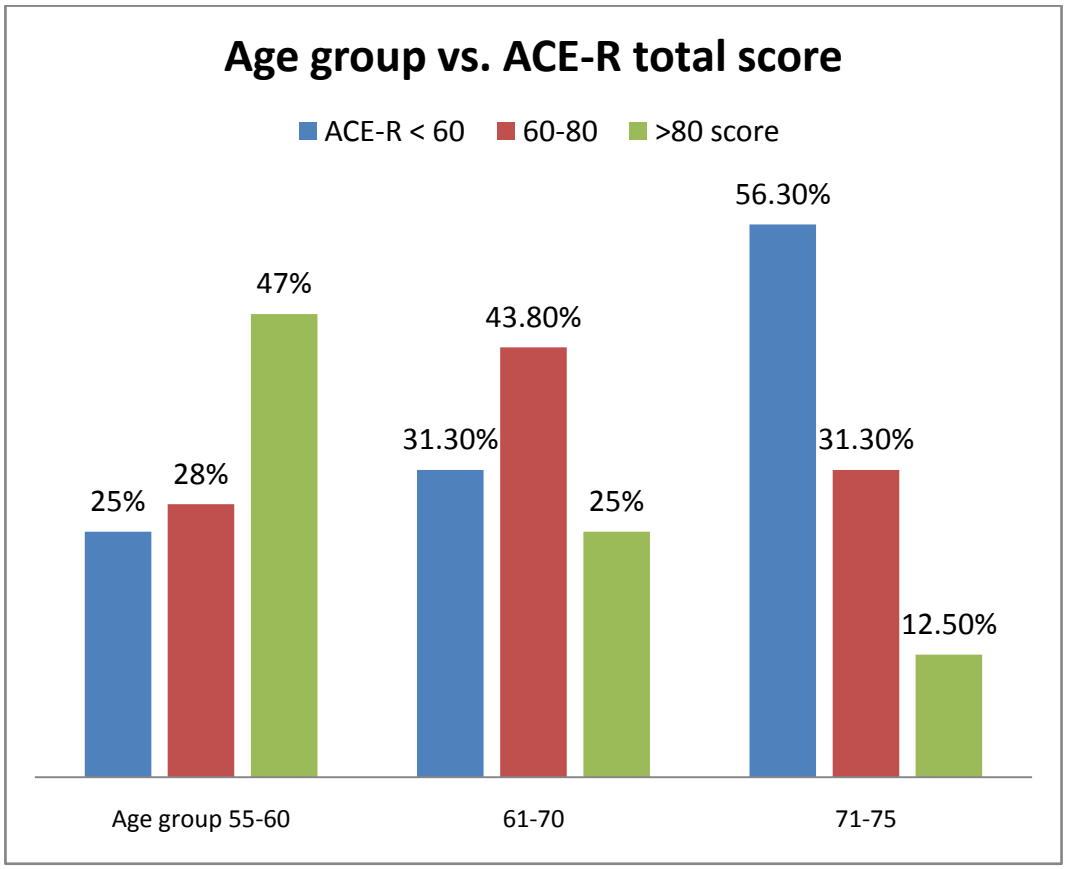
PARAMETER 1: Age

Table 1. Age distribution in PD patients and MMSE

Age group	MMSE	
	< 23	>23
55-60	9 (25%)	27(75%)
61-70	18(37.5%)	30(62.5%)
71-75	10(62.5%)	6 (37.5%)

Chi-square value: 6.692; P=0.035 (P<0.05) **Significant**

Figure 8: Age group versus ACE-R total score



The comparison of age group with ACE –R score is given in Table 2 below. It is clear that the ACE- R cognitive score is better in younger age group of PD patients and worsens with increasing age.

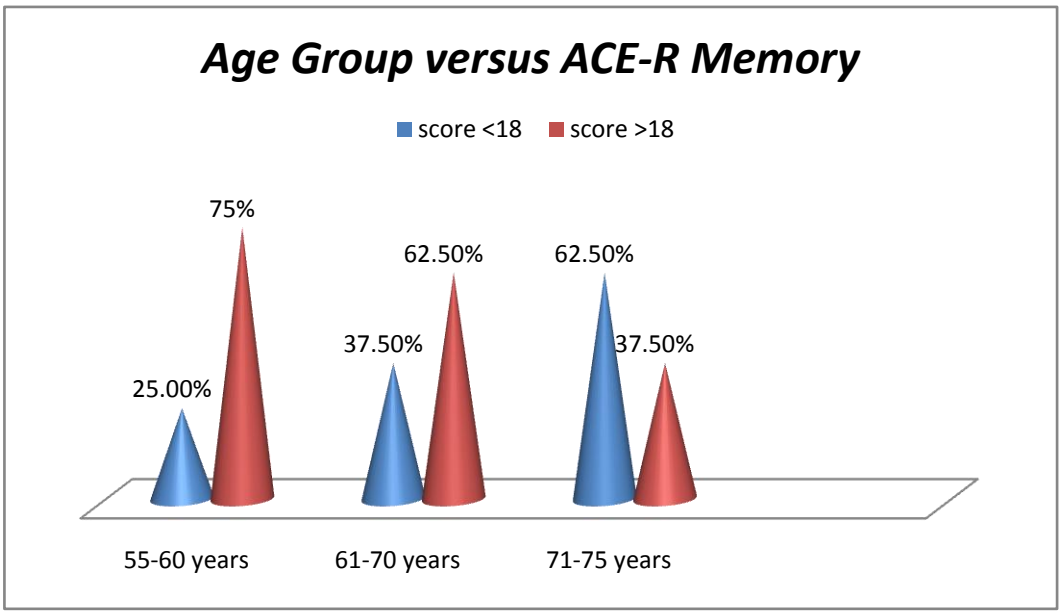
Table 2

Age Group	No of pts. with ACE-R score attention and orientation		Total
	<12	>12	
55-6	(10) 27.8%	(26)72.2%	36(100%)
61-70	(20) 41.7%	(28) 58.3%	48(100%)
71-75	(11)68.8%	(5) 31.3%	16(100%)

Chi-square value: 7.704; P=0.021 (P<0.05) **Significant**

In Addenbrooke‘s cognitive examination maximum score for attention and orientation was 18. It is seen that in the age group of 55- 60 years, 72% who scored more than 12 points when compared only 27.8% in age group 71-75 years.

Figure 9:



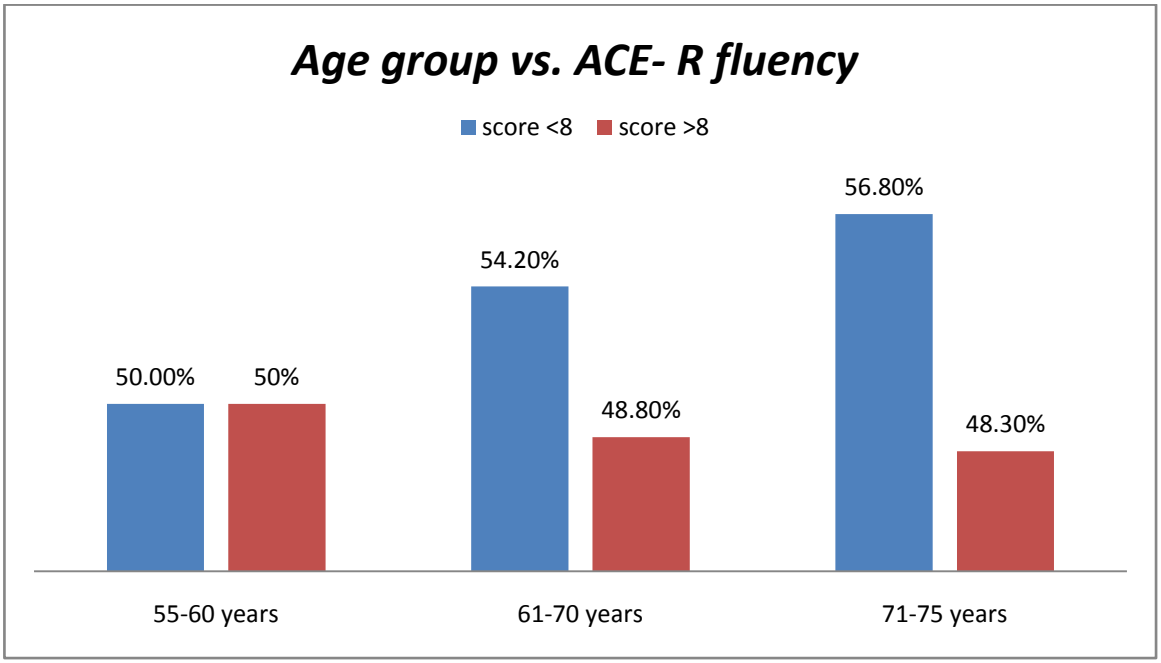
Chi-square value: 6.692; P=0.035 (P<0.05) **Significant**

In Addrenbrooke‘s cognitive examination total score for memory was categorized into those scoring less than and those scoring more than 18. As above (Fig.9) with increasing age more patients scored less than 18 on this test.

Age group vs. ACE-R Fluency

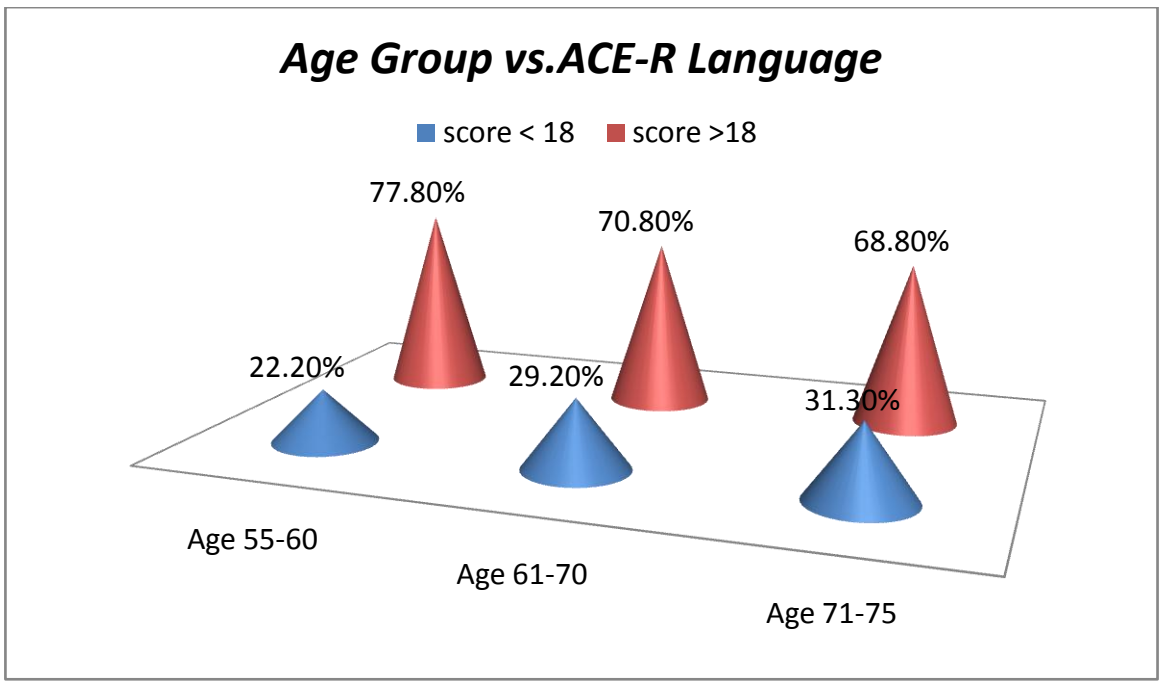
In Addenbrooke's cognition total scoring for verbal fluency was 14.While in the age group 55-60 years equal number of patients with score < 8 and > 8 points, in the older age group scores of <8 was more than scores of >8 (Fig.10)

Figure 10. Age group vs. ACE- R fluency



5) Maximum number of score for language testing in Addenbrooke‘s scale was 26. Age group 55-60 8 patients (22%) scored language score less than 18whereas the score was 29.6% for the age group 61-70 years and 56.8% for the age group 71-75 years (Fig- 11).

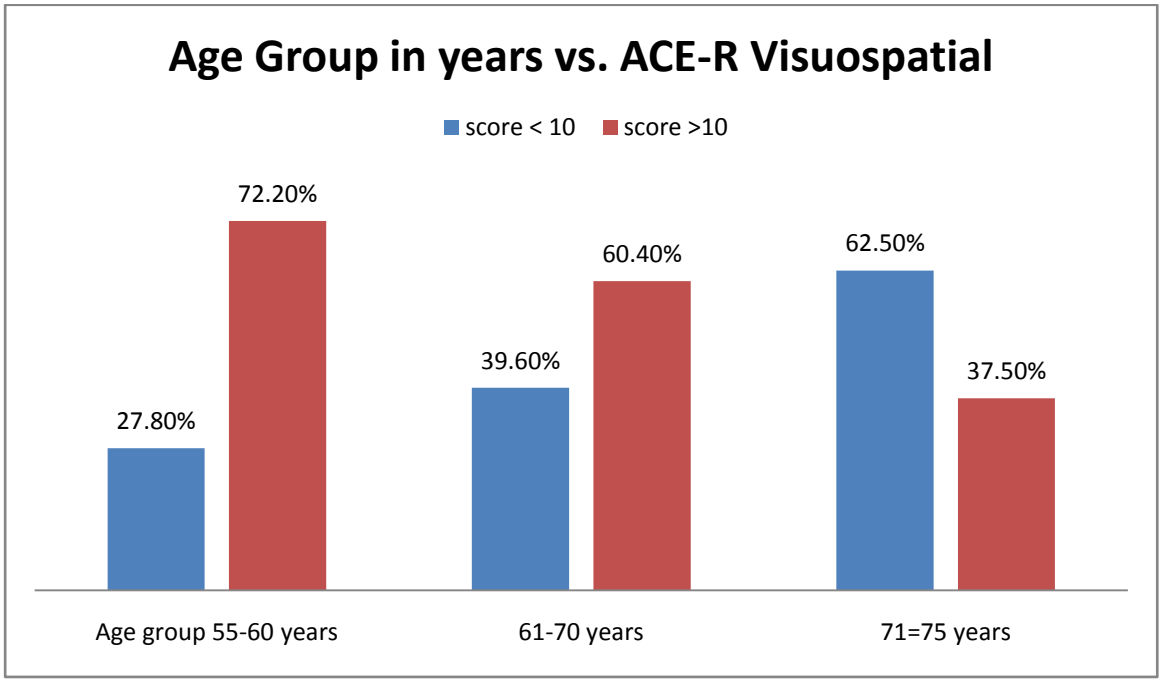
Figure 11. Age Group in years vs. ACE-R Language



As far as the ACE-R language testing is concerned although there is decline in ACE-R score with increasing age. However as seen in table above this is smooth and marginal and not as marked as in other cognitive domains.

Age and ACE-R visuospatial

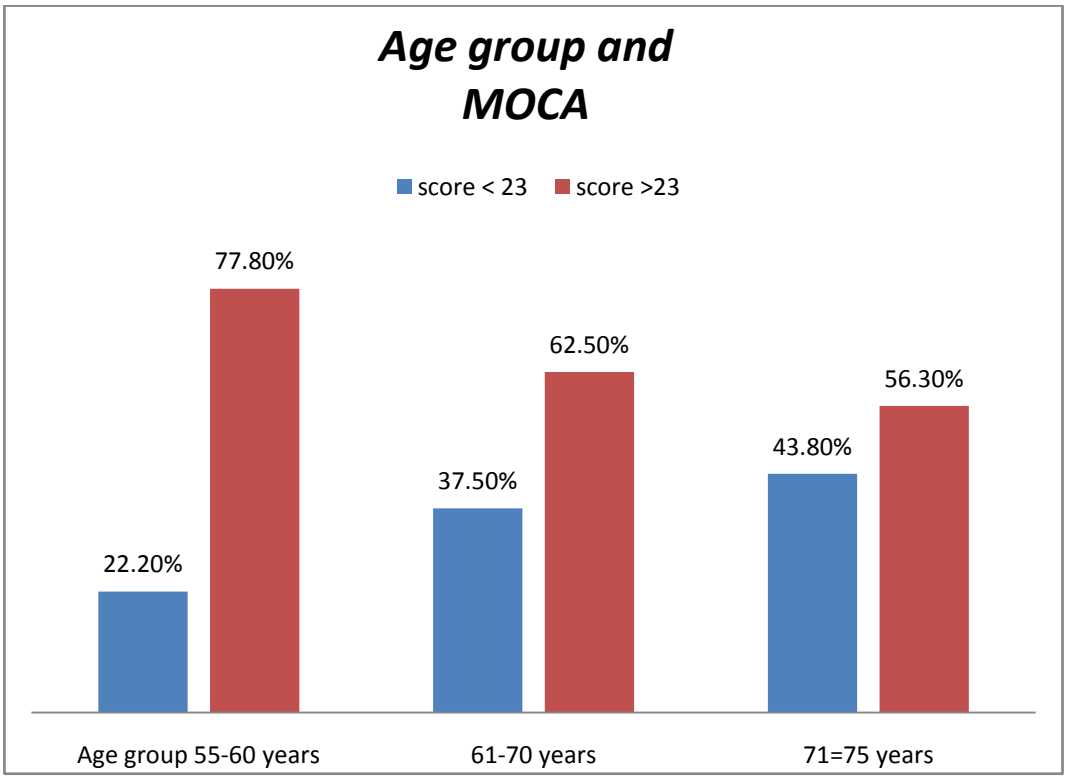
Figure 12.



Chi-square value: 5.6; 27 P=0.045 (P<0.05) **Significant**

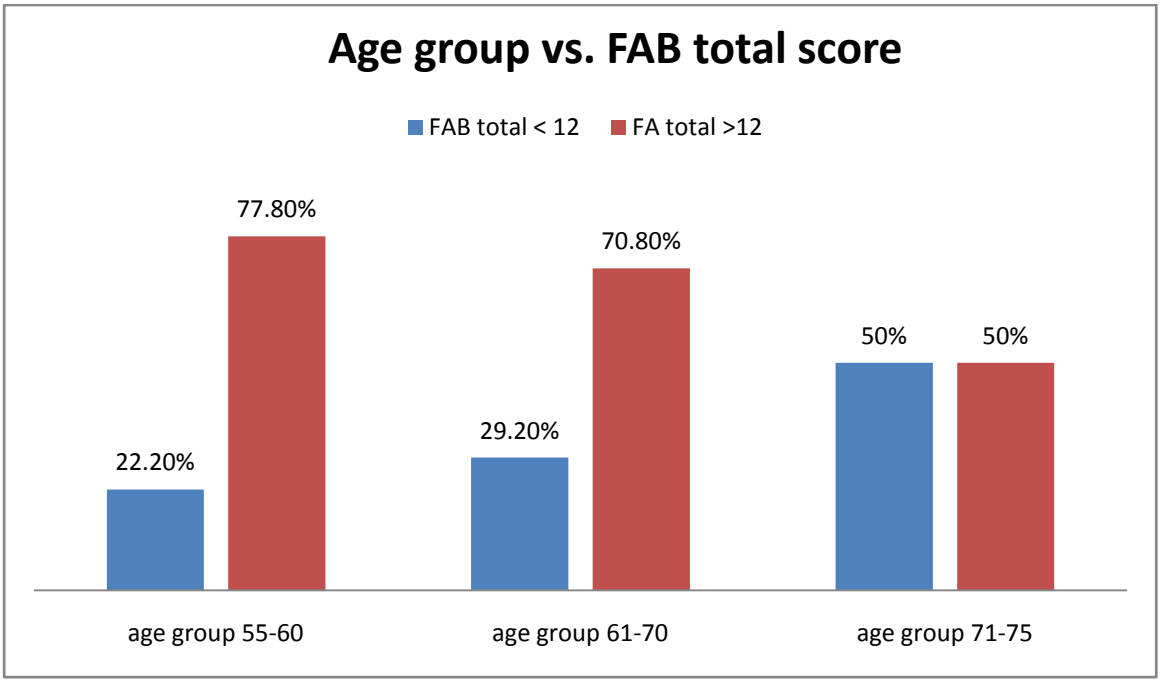
Older the age group in PD patients lesser ACE-R Visospatial score as in Fig.12

Figure 13: Age group and MoCA



When age group is compared with the cognitive test MoCA, it is found that in younger age group of 55-60 years more patients (77.8%) had scores more than 23 when compared to patients in the older age groups and only 22% scored less than 23

Figure 14.Age group vs. FAB total score



Chi-square value: 41.01 P=0.040(P<0.05) **Significant**

In the above figure increasing age shows reduction in total FAB score.

Figure 15: Education and MMSE

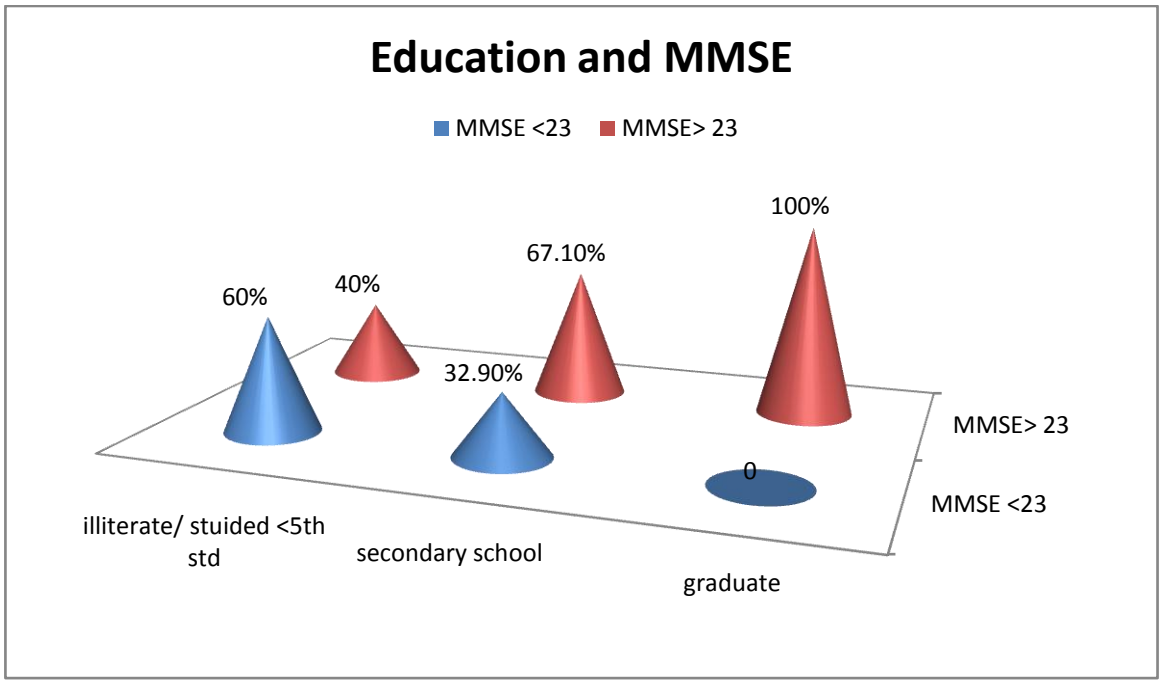
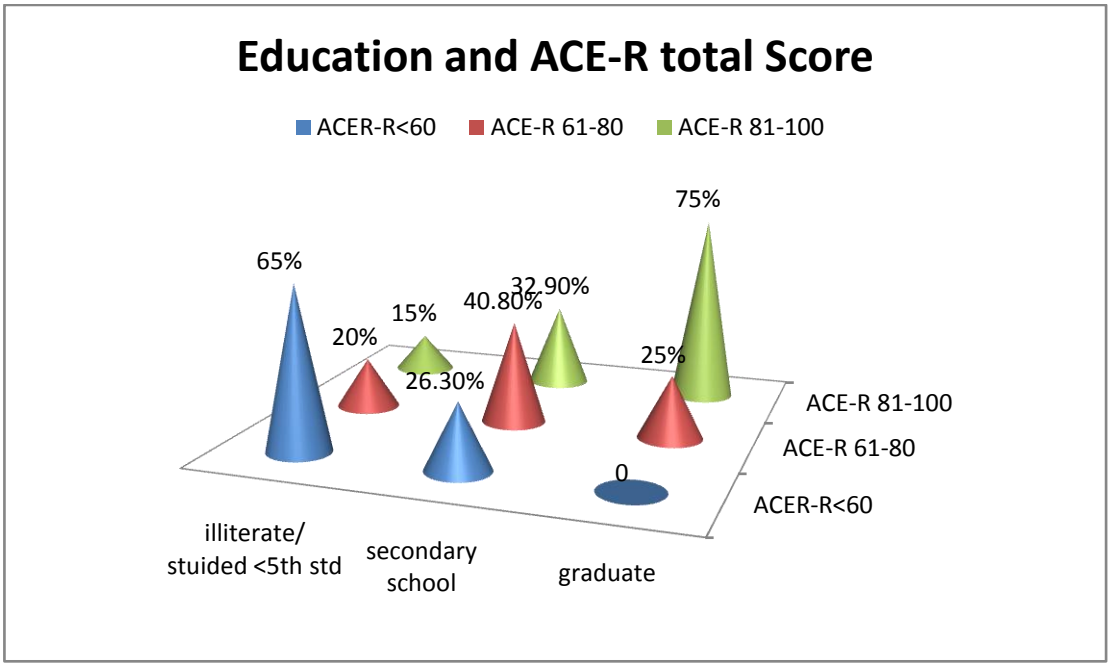
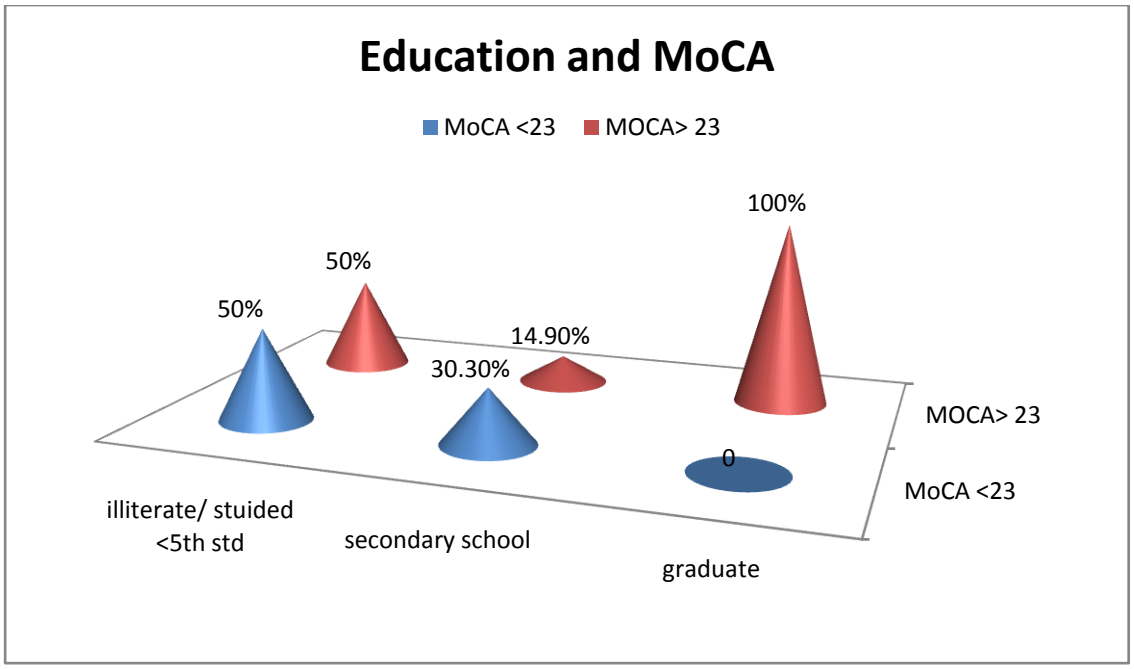


Figure 16: Education and ACE-R total Score



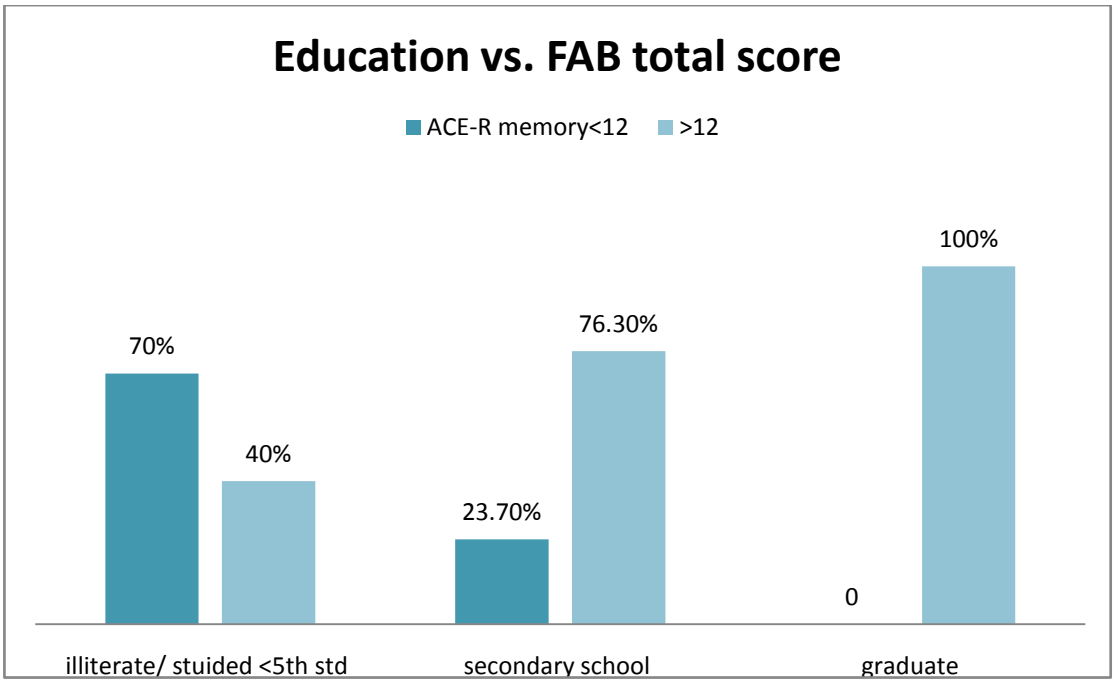
Chi-square value 14.834 P=0.005 (P<0.05) **Significant**

Figure 17: Education and MoCA



Chi-square value 4.842 P=0.045 (P<0.05) **Significant**

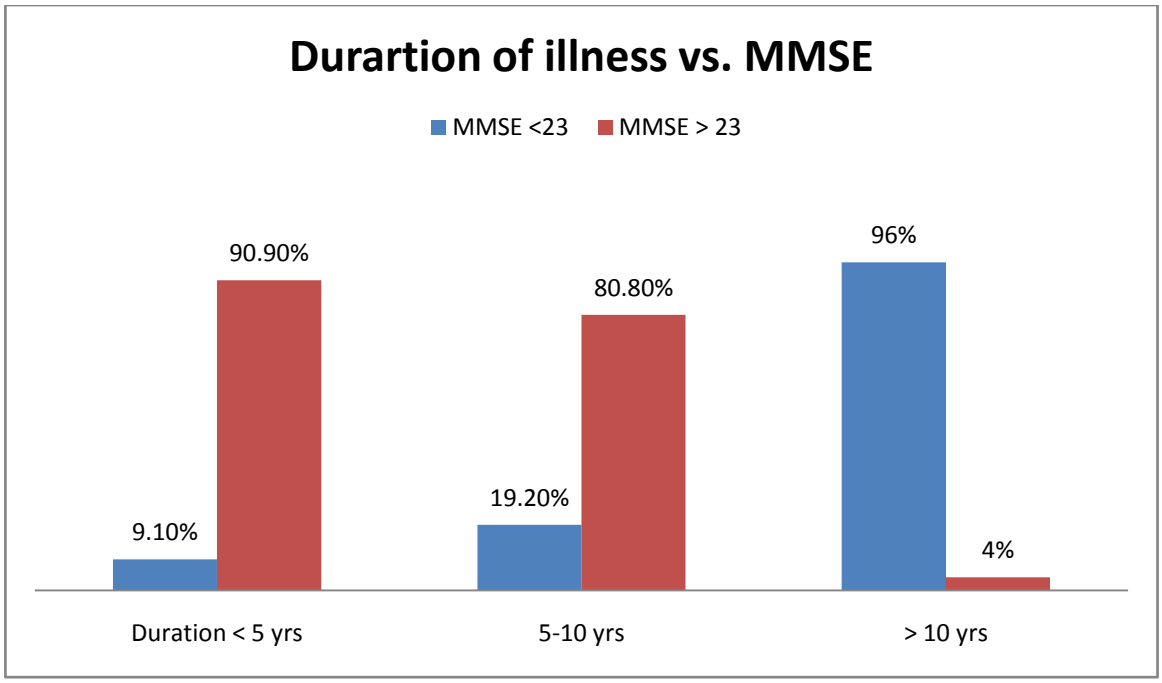
Figure 18*: *Education vs. FAB total score



Chi-square value: 11.729 P=0.003 (P<0.05) **Significant**

PARAMETER 2. Duration of illness

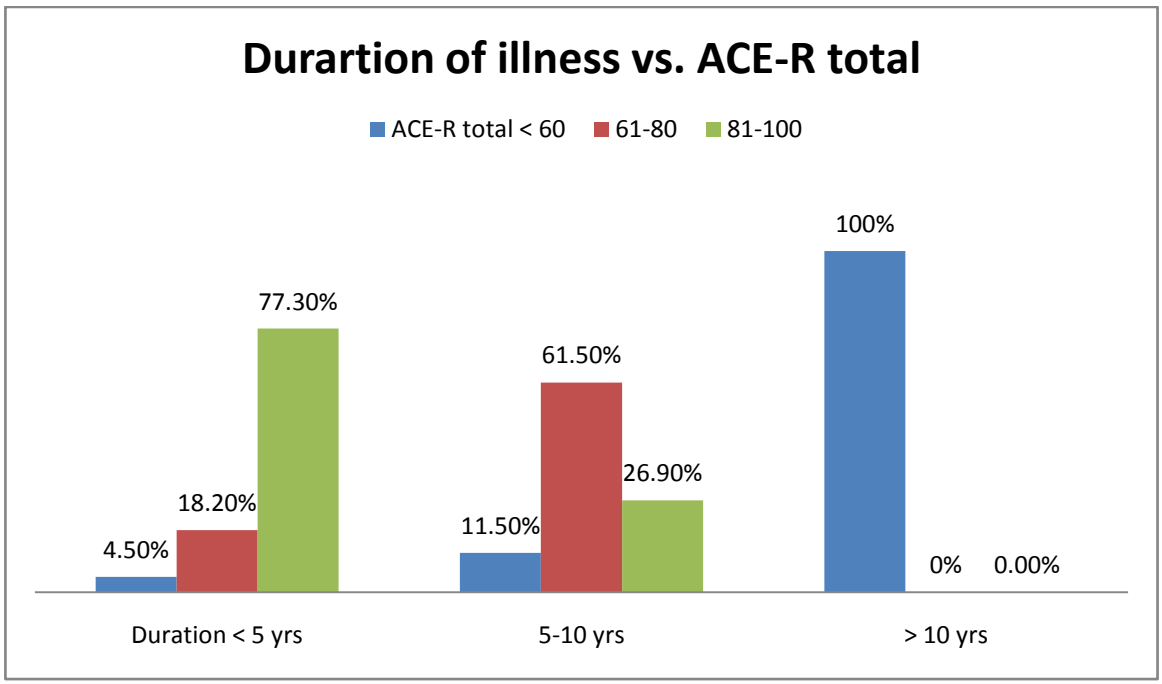
Figure 19:Duration of illness vs. MMSE



Chi-square value: 53.425, P=0.001 (P<0.05) **Significant**

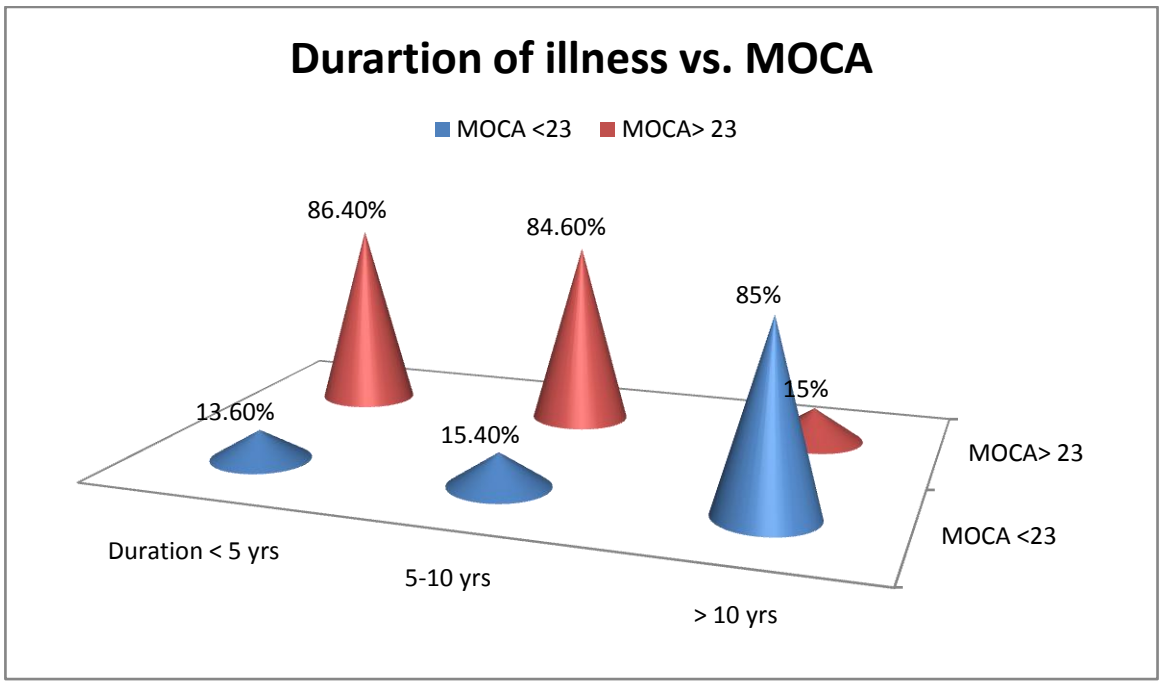
From the above figure it is seen that MMSE score progressively worsens with the longer duration of PD

*Figure 20: Duration of illness in years * ACE-R Total score*



Chi-square value: 92.27, P=0.001 (P<0.05) **Significant**

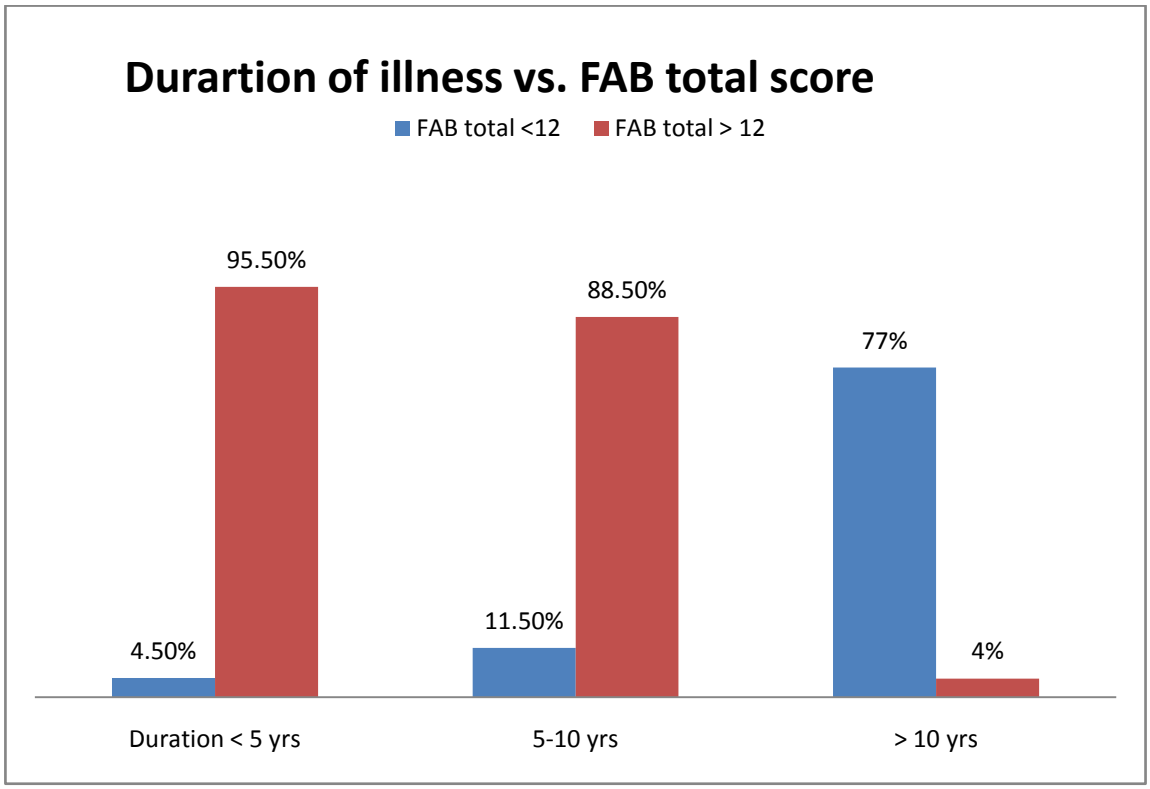
*Figure 21: Duration of illness in years * MOCA*



Chi-square value: 42.358, P=0.001 (P<0.05) **Significant**

In the above figure it is seen that longer the duration of illness, lesser is the cognitive score.

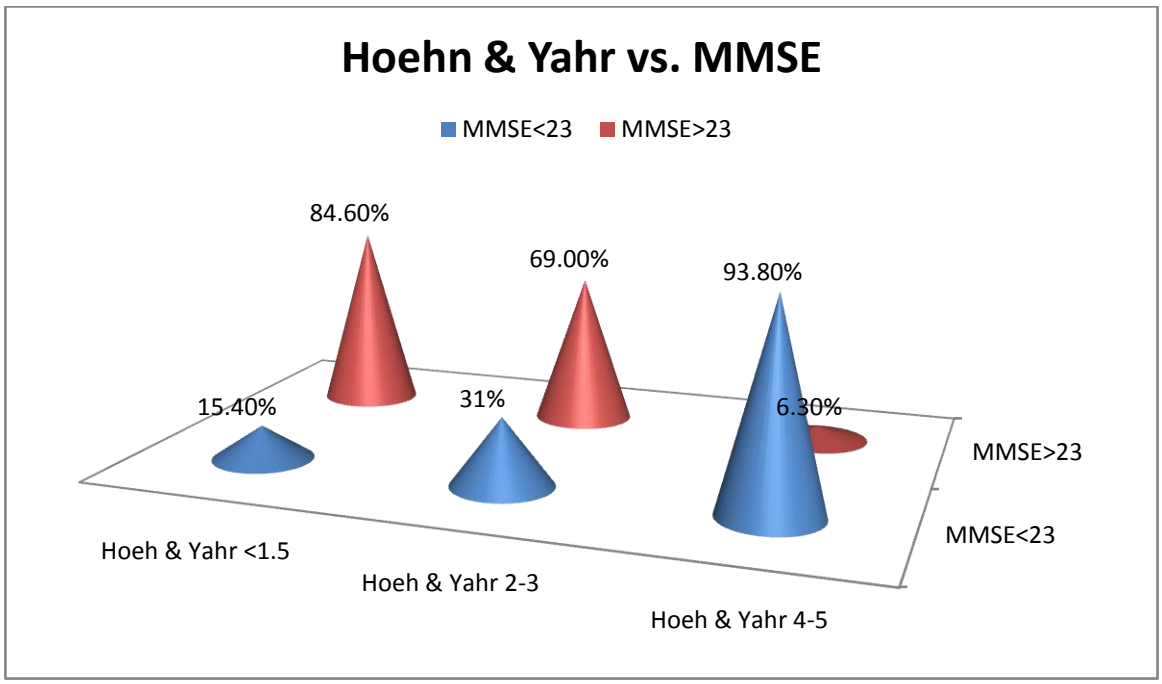
Figure 22: Duration of illness vs. FAB total score



Chi-square value: 57.542, P=0.001 (P<0.05) **Significant**

PARAMETER 3. Hoehn & Yahr scale

Figure 23: Hoehn & Yahr scale versus MMSE



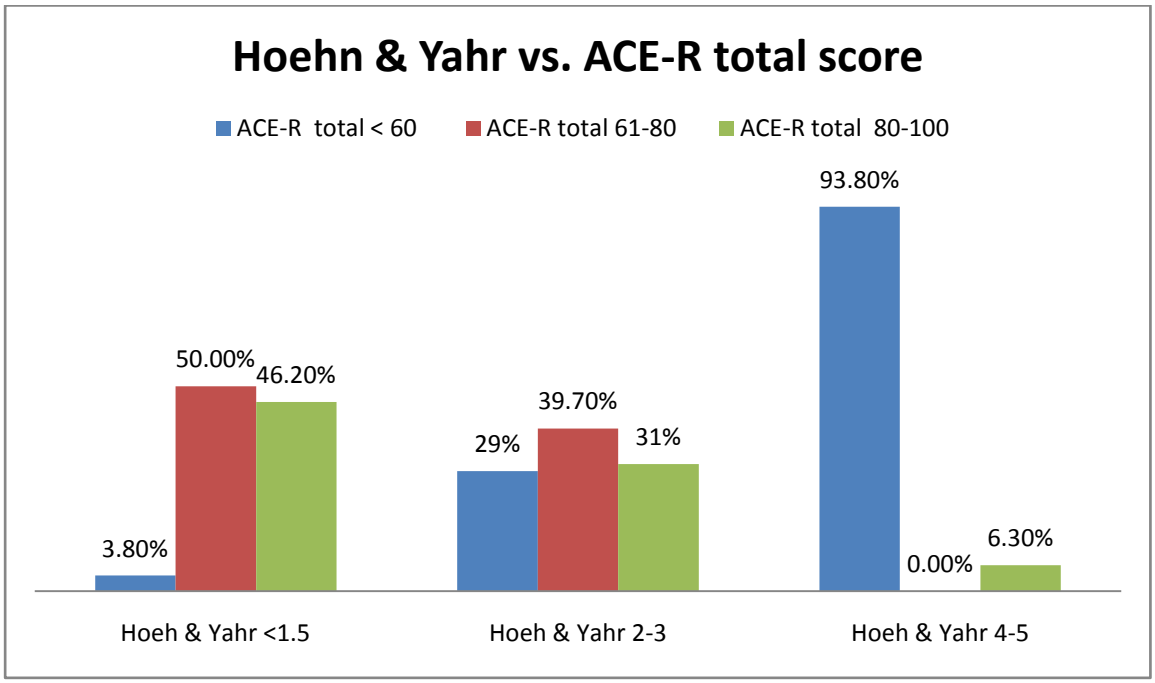
Chi-square value: 28.2; P=0.001, (P<0.05) **Significant**

The MMSE score was higher in more abled patients with PD (lesser score on Hoehn & Yahr) and lower MMSE score was found in less abled (higher score on Hoehn & Yahr scale)

Hoehn and Yahr scale and ACE-R total score

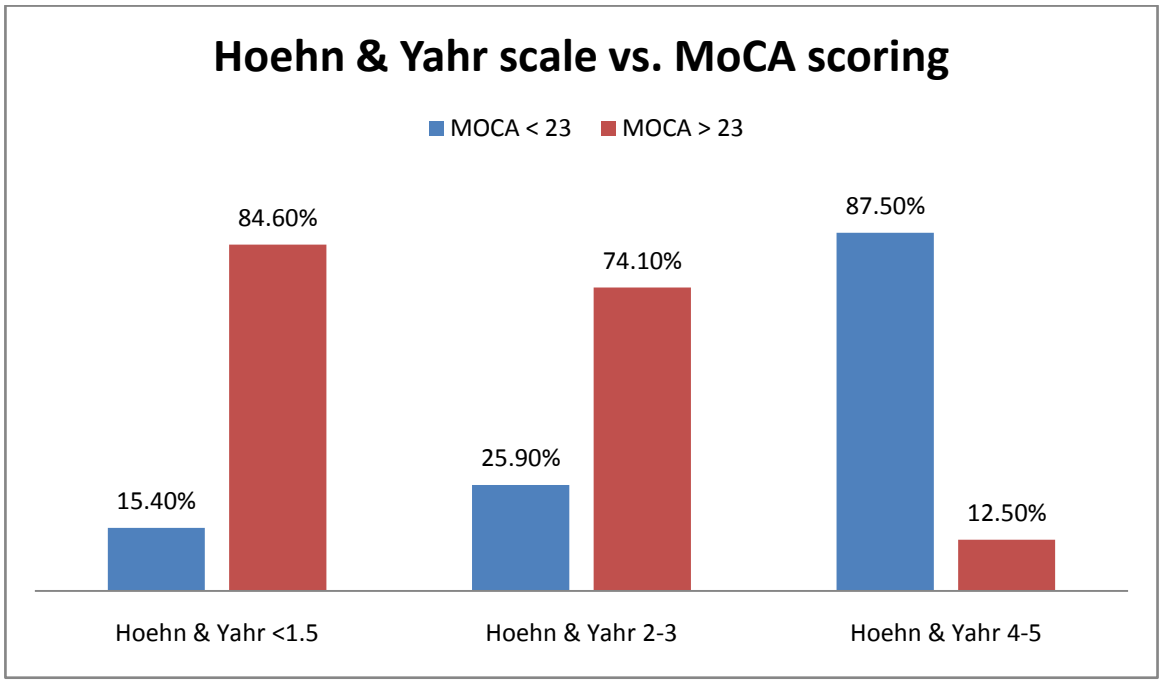
In the Figure 24, it is shown that the ACE-R cognitive score is higher in more abled (low Hoehn and Yahr score) patients and lower cognitive score seen in less abled patients (high Hoehn andYahr score)

Figure 24. Hoehn and Yahr and ACE_R total score



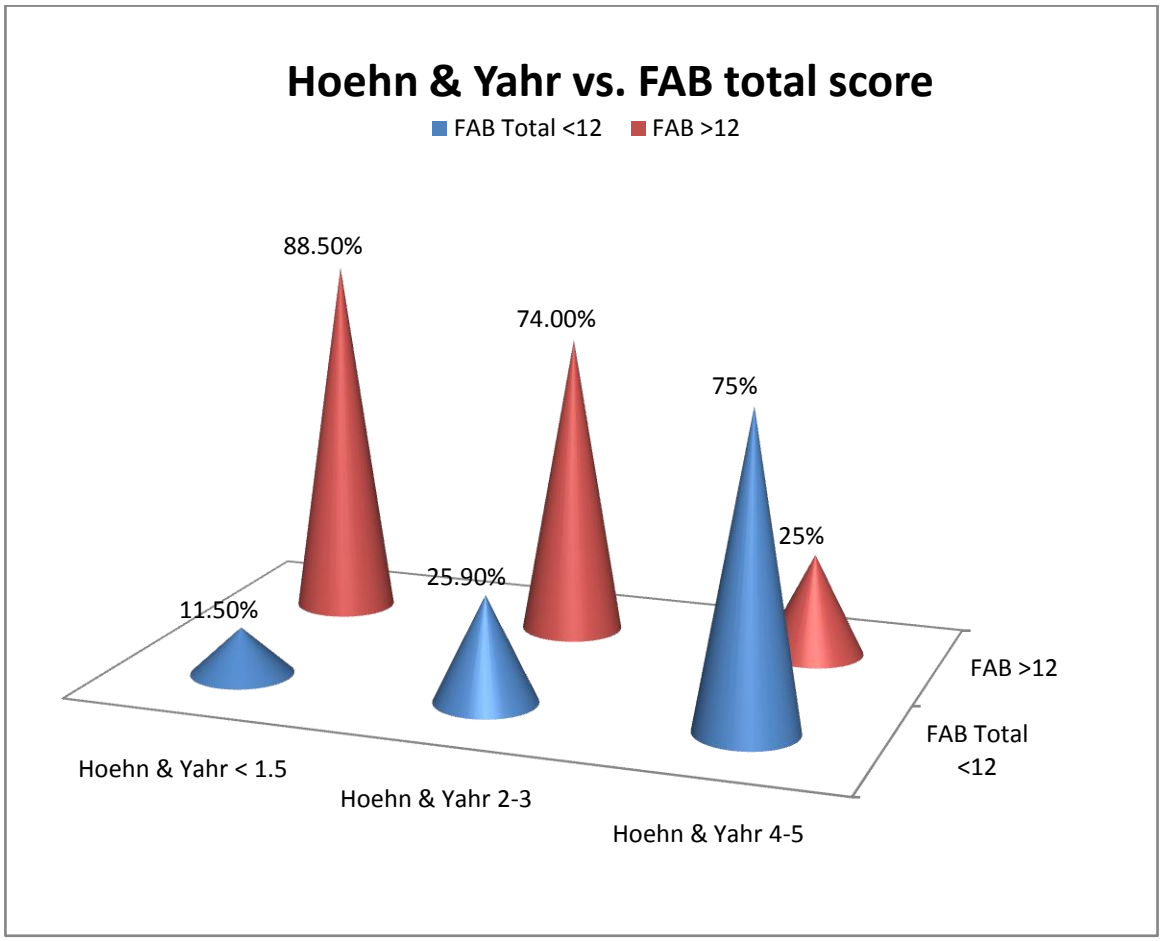
Chi square 37.308, P value= 0.001 ($p < 0.05$), significant

Figure 25:Hoehn & Yahr scale and MoCA scoring



Chi-square value: 26.48. P=0.001 (P<0.05) **Significant**

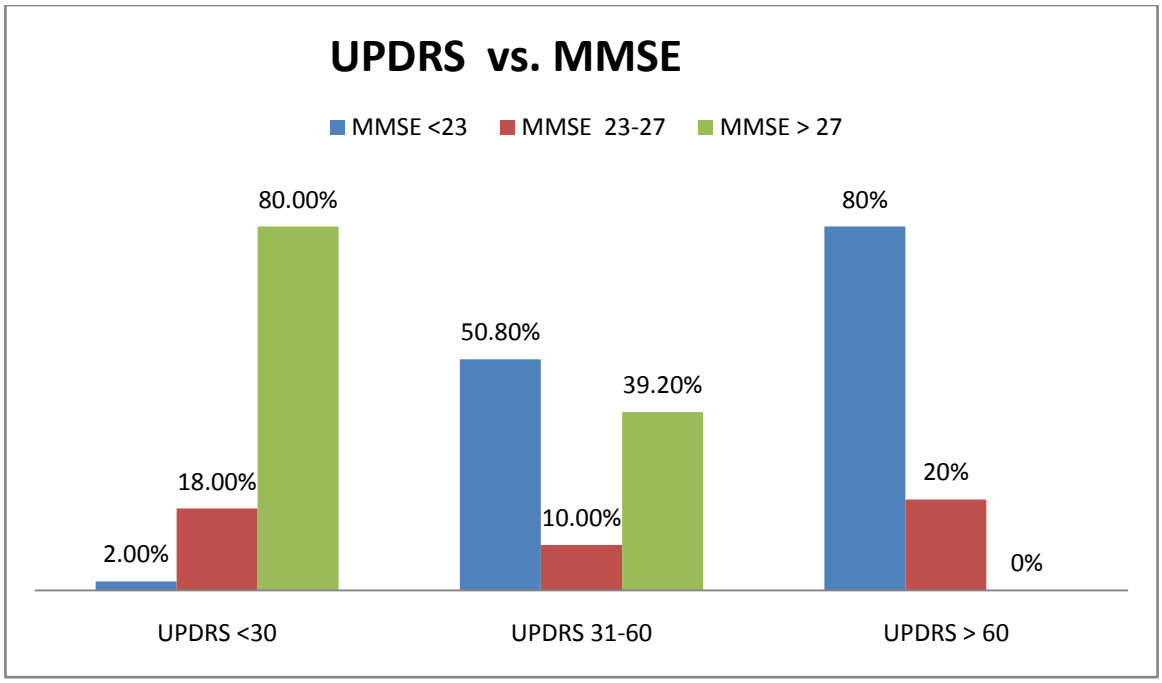
Figure 26: Hoehn & Yahr vs. FAB total score



Chi-square value: 7.704; P=0.021 (P<0.05) **Significant**

PARAMETER 4: UPDRS

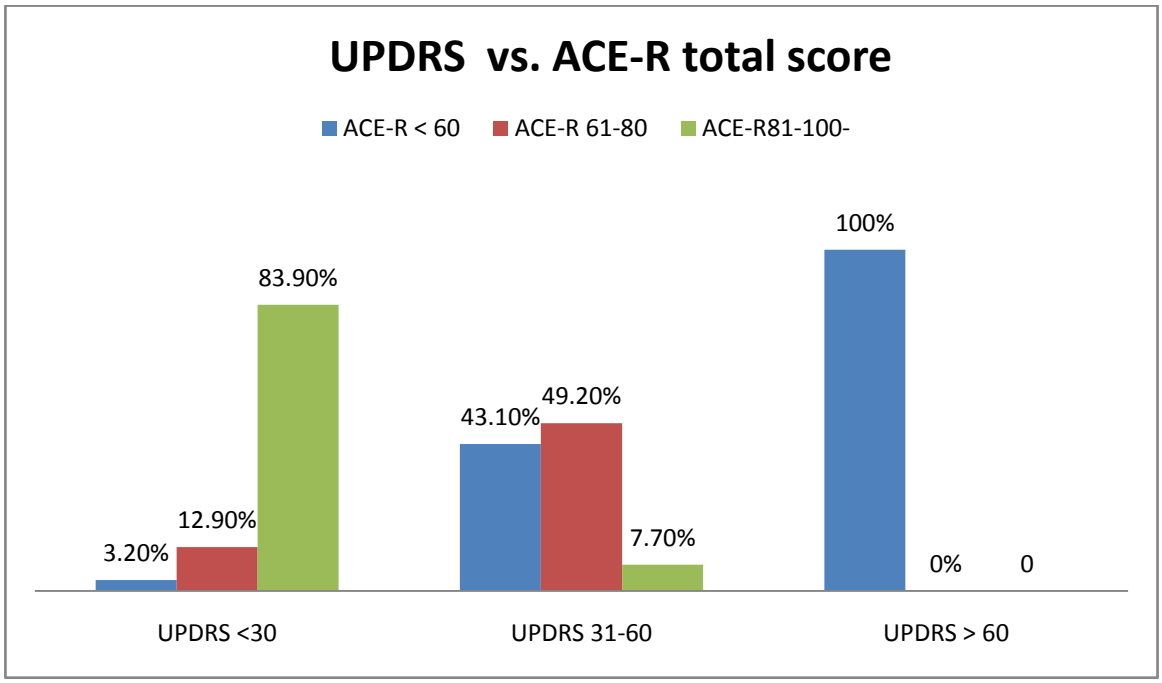
Figure 27: UPDRS and MMSE



Chi-square value: 30.304, P=0.001 (P<0.05) **Significant**

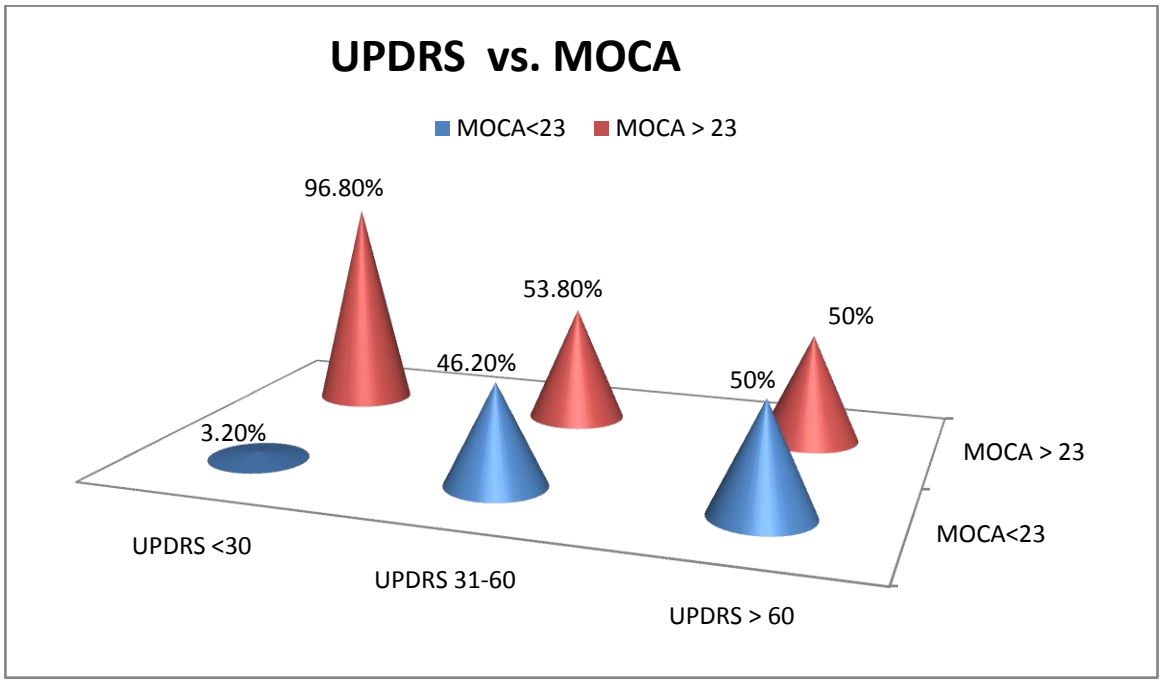
In above table the UPDRS score is inversely proportional to MMSE score

Figure 28: UPDRS and ACE-R total score



Chi-square value: 65.548, P=0.001 (P<0.05) **Significant**

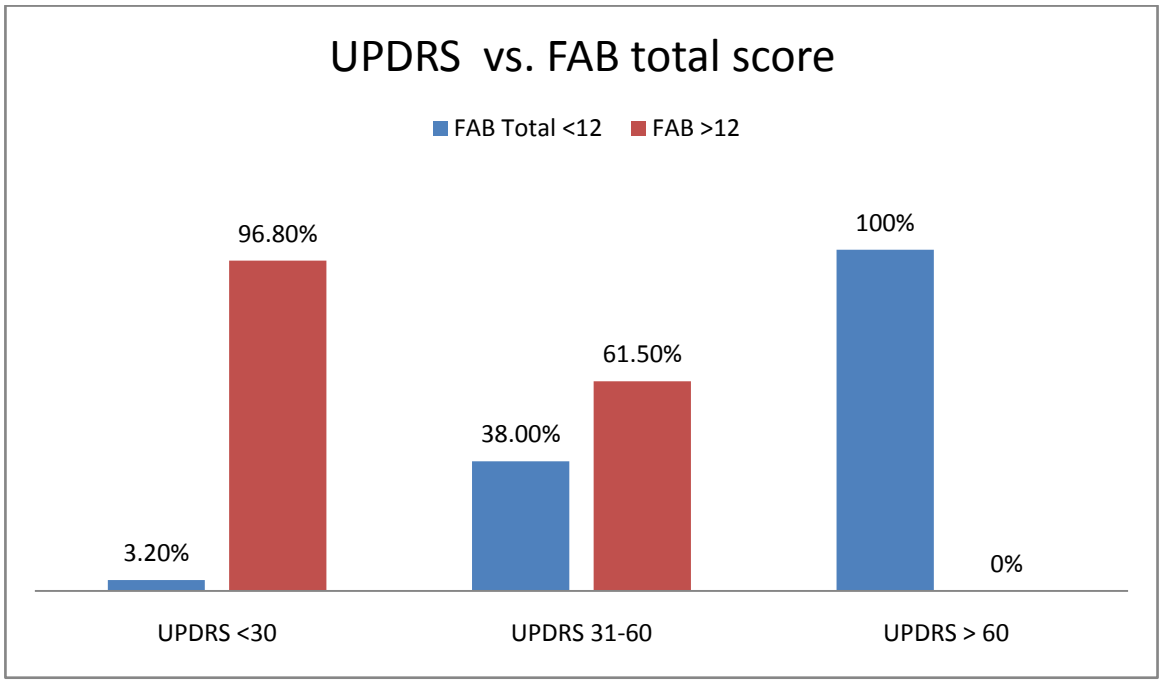
Figure 29: UPDRS and MOCA



Chi-square value: 18.039, P=0.001 (P<0.05) **Significant**

UPDRS vs FAB total score: As illustrated in the figure below, patients with higher score on UPDRS indicating more severe illness have performed with lower FAB total score

Figure 30: UPDRS vs. FAB total score



Chi-square value: 22.132, P=0.001 (P<0.05) **Significant**

Table: 3 UPDRS * all cognitive tests

UPDRS score	MMSE			ACE-R			MoCA		FAB	
	< 23	**23-27**	**28- 30**	**< 60**	**61 - 80**	**81- 100**	**<23**	**>23**	**< 12**	**>12**
< 30	2.0%	18%	80%	3.2%	12.9%	83.9%	3.2%	96%	3.2%	96%
31-60	50.85	10.%	39.2%	43.1%	49.2%	7.7%	46.2%	53.8%	38%	61.5%
>60	80%	20%	0%	100%	0%	0%	50%	50%	100%	0 %

UPDRS score was analyzed with the cognitive tests viz. MMSE, ACE-R, MOCA and FAB test. In patients with low UPDRS (< 30), it was found that more patients had higher score. This was particularly so with FAB test (96%) and MoCA (96%) followed by ACE-R (83.9%) and finally MMSE (80%). Conversely in patients with UPDRS score > 60, more patients had lower score and once again it was marked for FAB test with none getting score more than 12 in this group.

DISCUSSSION

The total number of patients included in this study was 100. Majority of patients were males (61%) and the male/female ratio was 2.2: 1 which is more than in previous studies,[31] where it ranged from 1.4:1 to 1.6:1. One of the possible reasons for this could be that women of the social group attending this hospital may not seek medical help as much as men, as they have to leave behind household activities to come to hospital. The mean age of patients with PD was 64.

Out of the total 100 patients 20% were illiterate or studied only up to elementary school. The majority (76%) studied up to secondary school and few (4%) were degree holders.

It was reported by Caviness JN et al [5] that 21% of the 86 patients with PD had MCI. Prevalence of dementia in PD population was found by various population studies to be 40% to 80%.[3, 4, 5, 8] Similar to these observations in our study too76% of PD patients had cognitive deficits; the remaining 24% had no cognitive deficits. Out of 76% patients with cognitive deficits 44% had MCI and 30 % patients had dementia (PDD).

The MMSE score was less than 23 in 63% of patients with PD and more than 23 in 37% of studied population. The mean MMSE score was 24%.

Effect of age on the cognitive testing:

There is inverse relationship between age and cognitive decline as illustrated in Table 1. with more subjects in age group of 71-75 showing score less than 23 on MMSE compared to age group of 55- 60

On comparing the age group with that of total ACE-R score (Fig.2), it is clear that the ACE- R cognitive score is better in younger age group of PD patients (47% having score more than 80) and worsens with increasing age (12.5% having score more than 80). This is consistent with Pillon Bet al study, [16] where 45% of patients aged less than 60 scored more than 80 on ACE-R score. In Addenbrooke's cognitive exam for attention and orientation, in the age group of 55- 60 years, 72% scored more than 12 points when compared to only 27.8% in age group 71-75 years. Our study is similar to that of Pillon B et al study in this aspect. [16]Mohr et al's study however did not show disturbance of attention and concentration.[44]

When taking memory component of ACE-R, with increasing age, more patients scored less than 18 which is the cut off for cognitive impairment on this test, and this was statistically significant. In the verbal fluency component of ACE-R, with total possible score of 14, 50 % the patients younger than 55 scored above 8, whereas 48% of age group 71- 75 years score more than 8. This particular domain does not have big difference compare to other components of ACE-R.

In the language front of ACE-R, although there is decline in ACE-R score with increasing age, this is smooth and marginal and not as marked as in other cognitive domains. This is consistent with previous studies [30] by Dudas B et al. Similarly older age groups had progressively fewer score for visuospatial component for ACE-R cognitive examination (fig.12) which had statistical significance.

The FAB test has total score of 18, testing frontal lobe functions. With cut off 12 being kept for cognitive impairment, only 22% showed evidence of cognitive impairment in patients less than 60 years of age, while 50% in the older age group of 71to 75 years had that score, inferring the frontal lobe functions are particularly compromised in the Parkinson's disease patients more than language or fluency. This is similar to the study by Mohr et al. [44]

Like other cognitive tests done in this study, the MoCA test too showed decline in cognitive score in the older age group, with score less than 23 increasing with age and score more than 23 decreasing with age (fig. 13). This correlates well with previous study by Zadikoff C et al. [31]

Duration of illness and PD cognition:

The duration of illness varied from 1½ to 13 years. The majority of patients (52%) fell in the category of duration 5 to 10 years.

While more than 90% of patients with illness less than 5 years scored more than 23 on MMSE (Fig.19), exactly opposite effect was seen in patients with duration more than 10 years (i.e. more than 90% scored less than 23 in this group). This clearly suggests that cognitive impairment is much more prevalent with longer duration of illness. These findings are comparable to the longitudinal studies by Reid WG et al,[36] where62% of patients had dementia in the 5 year follow up. Our study is also consistent with the prospective study by Aarsland D et al [37] in whose study the cumulative incidence of dementia varied from 28% at baseline to 78% at 8 years follow up was observed.

When ACE-R total score was considered, in patients with duration of illness less than 5 years, only 4.5% had ACE-R score less than 60(can be taken as cut off for dementia); whereas all the patients whose illness lasted more than 10 years had score less than 60, which is highly significant. Similarly, significant but less dramatic difference was seen with MoCA cognitive testing when it was compared with the duration of illness. FAB score also showed more cognitive decline in patients with longer duration of illness.

Education and cognition in patients with PD:

Majority (76%) of patients in this study had completed secondary school.One fifth (20%) were either illiterate or studied only up to elementary

school, and only 4%were degree holders. When MMSE score was usednone of graduates scored less than 23, while 60% of illiterate/elementary school educated patients had this score of less than 23 and this was statistically significant. Education had very similar effect on cognition using ACE-R memory scoring. The FAB testalso showed almost similar results with none of the graduates scoring less than 12 (Fig.18). This is consistent with study by Guedj et al. [34]Similar trends is seen when the MoCA test was used, as is seen in earlier study [31] and this was statistically significant. However this was less so compared to other cognitive scales used.

Effect of UPDRS (Unified Parkinson's Disease Rating Scale) on cognition

UPDRS is the most commonly used rating scale in PD.[1] It tests the motor functions, activities of daily living, and non-motor functions of PD including cognition. Since it includes cognition, it is expected that patients with higher score of UPDRS will fare worse on other cognitive tests. Giving allowance for this, there was statistically significant effect of UPDRS on MMSE. All patients scoring less than 30 on UPDRS (less severely affected) had MMSE score of more than 23, while all of those with UPDRS score more than 60 had MMSE score of less than 23.

All patients with UPDRS scale of more than 60 (more affected individuals) had ACE-R total cognitive scoring of less than 60 which could be taken as cut off for dementia. UPDRS had similar effect on MoCA which

is another cognitive tool, with more affected PD (UPDRS > 60) individuals scoring less the 23 on MoCA.

Hoehn & Yahr scale and cognition:

In patients with advanced disease with Hoehn& Yahr scale 4 to 5, none had ACE-R score of more than 80. Majority (93%) of this category of PD patients had MMSE less than 23 consistent with PDD (Parkinson's disease dementia). Similar trend was seen when Hoehn & Yahr scale was used to compare MoCA cognitive scale**.** Here 87% in the Hoehn and Yahr category of 4 to 5 (advanced disease), the MoCA score was less than 23 indicating significant cognitive decline. Similar effect was seen when Hoehn and Yahr scaling was compared to FAB cognitive test. Thus there is greater prevalence of cognitive impairment in patients with more advanced disease as assessed by Hoehn and Yahr staging. This is consistent with previous studies of Janven et al, [4] where 90% of patients with Hoehn and Yahr of 4 to 5 scored less than 23 on MMSE.

CONCLUSION

1) Patients with Parkinson's disease were found to have cognitive impairment on formal neuropsychological testing, though they do not show functional restriction in activities of daily living.
2) There is clear linear relationship between age of patients and duration of illness in developing cognitive impairment.
3) Mild cognitive impairment is seen in early stages of Parkinson's disease. This is observed even in patients with low score for UPDRS and Hoehn and Yahr scales. This trend is reflected across all domains of cognitive testing used. This is particularly so with the frontal lobe functions and less so with testing for fluency and language.
4) Frank dementia however, was found only in proportion of patients especially those with more advanced disease.
5) This study highlights the importance of screening of cognition in patients with Parkinson's disease. If cognitive impairment is found, it will help to intervene in the early stages of the illness.

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ABBREVIATIONS

AD - Alzheimer's Disease

DLB - Dementia with Lewy Body disease

FAB - Frontal Assessment Battery

HYS - Hoehn and Yahr Staging

MCI - Minimal Cognitive Impairment

MMSE - Mini Mental State Examination

MoCA - Montreal Cognitive Assessment

PD - Parkinson's Disease

PDD - Parkinson's Disease Dementia

UPDRS - Unified Parkinson's disease Rating Scale

PROFORMA

Name Age Sex

Education Occupation

Address

OP No. MIN No.

Duration of illness;

Presenting complaints

Family history

Past history

Diabetes: Y/N Hypertension Y/N CAD Y/N

Tuberculosis Y/N CKD: Y/N CVA: Y/N

Personal History

Social history: Married Y/N Living with

Alcohol Smoking

CLINICAL FEATURES

PR: BP: CVS RS

HMF:

MMSE Score:

Executive dysfunction: Y/N Apathy Y/N

Memory:Y/N (working, recent, remote)

Speech: dysarthria: Y/N

Language: motor/ sensory

Reading/writing/ copying

Apraxia

Ideational Y/N	Ideomotor Y/N
Dressing Y/N	Constructional Y/N
R/L confusion Y/N	Hemineglect Y/N
Hemianopia/ Quadrantanopia Y/N	Delusion / hallucination

UPDRS scale

Modified Hoehn and Yahr staging (0-5)

Cognitive assessment scales:

- ACE-R (Addenbrookes' cognitive assessment)
- MoCA (Montreal cognitive assessment)

CRANIAL NERVES

Spinomotor system

Exrapyramidal system

Cerebellar system

Sensory system

Gait

Spine and cranium

INVETIGATIONS

Hematology TC: DC: P L E B Hb ESR

Sugar Urea Creatinine Na K

ECG: CXR

Cardiac evaluation

CT BRAIN:

MRI BRAIN;

Other investigations:

PATIENT CONSENT FORM

Study Details: To undergo Cognitive function assessment in patients with Parkinson's disease.

Study Centre: Rajiv Gandhi Govt. GeneralHospital, Madras Medical College, Chennai-600003

Patient may check✓ these boxes

I confirm that I have understood the purpose of procedure for the above study ☐

I have the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arisefrom the study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or wellbeing or any unexpected or unusual symptoms. ☐

I hereby give permission to undergo complete clinical examination including tests for cognitive function and diagnostic tests. ☐

I hereby consent to participate in this study. ☐

Signature/ thumb impression

Patient name and address: Place

Date:

Signature of investigator: Plaice

Study investigator's name Date

UKPDS BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA

STEP 1: Diagnosis of Parkinsonian syndrome

- Bradykinesia [slowness of initiation of voluntary with progressive reduction in speed and amplitude of repetitive action]
- And at least one of the following

  Muscular rigidity

  4-6 Hz rest tremors

  Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.

STEP 2: Exclusion criteria for Parkinson's disease

- h/o repeated strokes: stepwise progression of Parkinsonian features
- h/o repeated head injury
- h/o definite encephalitis
- oculogyric crisis
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language and praxis
- Babinski sign

- presence of cerebraltumor or communicating hydrocephalus of CT scan
- negative response of large doses of L-Dopa[if malabsorption excluded]
- MPTP exposure

STEP 3: supportive prospective positive criteria for PD

[3 or more required for diagnosis of definite PD]

- Unilateral onset
- Rest tremor
- Progressive disorder
- Persistent disorder
- Persistent asymmetry ,affecting side of onset most
- Excellent response to L-dopa
- Severe L-dopa induced chorea
- L-dopa response for 5 years or more
- Clinical course of 10 years or more.

MODIFIED HOEHN AND YAHR STAGING

Stage 0 no signs of disease

Stage 1 unilateral disease

Stage 1.5 unilateral plus axial involvement

Stage 2 bilateral disease, without impairment of balance

Stage 2.5 mild bilateral disease with recovery on pull test

Stage 3 mild to moderate bilateral disease; some postural instability; physically challenged

Stage 4 severe disability; still able to walk or stand unassisted

Stage 5 wheel chair bound or bedridden unless aided

CLINICAL DIAGNOSTIC CRITERIA FOR PDD BY MOVEMENT DISORDER SOCIETY TASK FORCE

Features of dementia associated with Parkinson's disease

I. Core features

1. Diagnosis of Parkinson's disease based on UKPDS Brain Bank clinical criteria

2. A dementia syndrome, which is insidious onset and slowly progressive, developing in the context of established Parkinson's disease and diagnosed by history taking, clinical examination, and neuropsychological testing, defined as:

• Impairment in more than one cognitive domain

• A decline from premorbid level

• Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment attributable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:

• Attention: Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day

• Executive functions: Impairment in tasks requiring initiation, planning, and concept formation, set shifting or set maintenance; impaired mental speed (bradyphrenia)

• Visuo-spatial functions: Impairment in tasks requiring visual-spatial orientation, perception, or construction

• Memory: Impairment in free recall of recent events or in tasks requiring learning new material, and memory usually improves with cues.

• Language: Word finding difficulties and impaired comprehension of complex sentences. But Core language functions are largely preserved.

2. Behavioral features:

• Apathy: loss of motivation, decreased spontaneity, interest, and effortful behavior

• Changes in mood and personality including depressive features and anxiety

• Hallucinations: usually complex and visual in the form of formed images of people, animals or objects

• Delusions: usually paranoid delusions, such as infidelity, Capgras syndrome.

• Excessive daytime sleepiness

III. Features which do not exclude PD-D, but make the diagnosis uncertain

• Co-existence of other abnormalities, which may itself cause cognitive impairment, but not to be the cause of dementia such as presence of periventricular hyperintensities in imaging.

• Exact time interval between the development of motor and cognitive symptoms is not known.

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D

• Behavioral and Cognitive symptoms appearing solely in the context of other conditions such as, acute confusion due to

a. Systemic causes

b. Drug intoxication

C. Major Depression according to DSM IV

Criteria for the diagnosis of probable and possible PD-D

Probable PD-D

A. Both core features must be present

B. Associated clinical features:

• Cognitive deficits in at least two of the four core cognitive domains (impaired attention which may fluctuate, impairment in visuo-spatial functions impaired executive functions, and impaired free recall memory which usually improves with cues)

• The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis

C. None of the group III features present

D. None of the group IV features present

Possible PD-D

A. Both core features must be present

B. Associated clinical features:

• Atypical cognitive deficits in the form of impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention

• Behavioral symptoms may or may not be present

OR

C. One or more of the group III features present

D. None of the group IV features present

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment

0 = None.

1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.

2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems.

Mild but definite impairment of function at home with need of occasional prompting.

3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.

4 = Severe memory loss with orientation preserved to person only. Unable to make judgements

or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

0 = None.

1 = Vivid dreaming.

2 = "Benign" hallucinations with insight retained.

3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.

4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.

3. Depression

0 = None.

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.

2 = Sustained depression (1 week or more).

3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).

4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

0 = Normal.

1 = Less assertive than usual; more passive.

2 = Loss of initiative or disinterest in elective (nonroutine) activities.

3 = Loss of initiative or disinterest in day to day (routine) activities.

4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING *(for both "on" and "off")*

5. Speech

0 = Normal.

1 = Mildly affected. No difficulty being understood.

2 = Moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.

4 = Unintelligible most of the time.

6. Salivation

0 = Normal.

1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

0 = Normal.

1 = Rare choking.

2 = Occasional choking.

3 = Requires soft food.

4 = Requires NG tube or gastrotomy feeding.

8. Handwriting

0 = Normal.

1 = Slightly slow or small.

2 = Moderately slow or small; all words are legible.

3 = Severely affected; not all words are legible.

4 = The majority of words are not legible.

9. Cutting food and handling utensils

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can cut most foods, although clumsy and slow; some help needed.

3 = Food must be cut by someone, but can still feed slowly.

4 = Needs to be fed.

10. Dressing

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Occasional assistance with buttoning, getting arms in sleeves.

3 = Considerable help required, but can do some things alone.

4 = Helpless.

11. Hygiene

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Needs help to shower or bathe; or very slow in hygienic care.

3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.

4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can turn alone or adjust sheets, but with great difficulty.

3 = Can initiate, but not turn or adjust sheets alone.

4 = Helpless.

13. Falling (unrelated to freezing)

0 = None.

1 = Rare falling.

2 = Occasionally falls, less than once per day.

3 = Falls an average of once daily.

4 = Falls more than once daily.

14. Freezing when walking

0 = None.

1 = Rare freezing when walking; may have starthesitation.

2 = Occasional freezing when walking.

3 = Frequent freezing. Occasionally falls from freezing.

4 = Frequent falls from freezing.

15. Walking

0 = Normal.

1 = Mild difficulty. May not swing arms or may tend to drag leg.

2 = Moderate difficulty, but requires little or no assistance.

3 = Severe disturbance of walking, requiring assistance.

4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)

0 = Absent.

1 = Slight and infrequently present.

2 = Moderate; bothersome to patient.

3 = Severe; interferes with many activities.

4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism

0 = None.

1 = Occasionally has numbness, tingling, or mild aching.

2 = Frequently has numbness, tingling, or aching; not distressing.

3 = Frequent painful sensations.

4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech

0 = Normal.

1 = Slight loss of expression, diction and/or volume.

2 = Monotone, slurred but understandable; moderately impaired.

3 = Marked impairment, difficult to understand.

4 = Unintelligible.

19. Facial Expression

0 = Normal.

1 = Minimal hypomimia, could be normal "Poker Face".

2 = Slight but definitely abnormal diminution of facial expression.

3 = Moderate hypomimia; lips parted some of the time.

4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

0 = Absent.

1 = Slight and infrequently present.

2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.

3 = Moderate in amplitude and present most of the time.

4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

0 = Absent.

1 = Slight; present with action.

2 = Moderate in amplitude, present with action.

3 = Moderate in amplitude with posture holding as well as action.

4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position.

Cogwheeling to be ignored.)

0 = Absent.

1 = Slight or detectable only when activated by mirror or other movements.

2 = Mild to moderate.

3 = Marked, but full range of motion easily achieved.

4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and
horizontally, with as large an amplitude as possible, both hands simultaneously.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude
should be at least 3 inches.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

27. Arising from Chair

(Patient attempts to rise from a straightbacked chair, with arms folded across chest.)

0 = Normal.

1 = Slow; or may need more than one attempt.

2 = Pushes self up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to arise without help.

28. Posture

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal.

1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps,

or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders
while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small
amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons.
Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal.
Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY *(In the past week)*

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present?

(Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias?

(Historical information; may be modified by office examination.)

0 = Not disabling.

1 = Mildly disabling.

2 = Moderately disabling.

3 = Severely disabling.

4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?

0 = No painful dyskinesias.

1 = Slight.

2 = Moderate.

3 = Severe.

4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)

0 = No

1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?

0 = No

1 = Yes

37. Are "off" periods unpredictable?

0 = No

1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?

0 = No

1 = Yes

39. What proportion of the waking day is the patient "off" on average?

0 = None

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?

0 = No

1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?

0 = No

1 = Yes

42. Does the patient have symptomatic orthostasis?

(Record the patient's blood pressure, height and weight on the scoring form)

0 = No

1 = Yes

V. MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment.

Essentially normal. Unaware of any difficulty.

90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and

impairment. Might take twice as long. Beginning to be aware of difficulty.

80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and

slowness.

70% = Not completely independent. More difficulty with some chores. Three to four times as long in

some. Must spend a large part of the day with chores.

60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort.

Errors; some impossible.

50% = More dependent. Help with half, slower, etc. Difficulty with everything.

40% = Very dependent. Can assist with all chores, but few alone.

30% = With effort, now and then does a few chores alone or begins alone. Much help needed.

20% = Nothing alone. Can be a slight help with some chores. Severe invalid.

10% = Totally dependent, helpless. Complete invalid.

0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning.

Bedridden.

MASTER CHART

S.No.	Age	Age	SEX	Education	Durartion of illness	UPDRS	Hoehn & Yahr scale	MMSE	ACE=R attention	ACE-R memory	ACER-fluency	ACER-language	ACER visuospatial	ACE- R total score	MOCA	FAB GO-NO-GO	FAB Lurias Test	FAB total score
1.	57	1	M	2	1	1	3	2	2	2	1	2	2	3	2	3	3	2
2.	58	1	F	1	3	2	2	1	1	1	1	2	1	1	1	1	1	1
3.	56	1	M	3	1	1	2	2	2	2	2	2	2	3	2	3	3	2
4.	55	1	F	2	2	1	2	2	2	2	2	2	2	1	2	1	3	2
5.	58	1	F	1	3	2	3	1	1	1	2	2	1	1	1	2	1	1
6.	60	1	M	2	1	1	2	2	2	2	1	2	2	3	2	3	3	2
7.	57	1	M	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
8.	55	1	M	3	1	1	1	2	2	2	2	2	2	3	2	3	3	2
9.	59	1	M	2	1	1	1	2	2	2	2	2	2	3	2	3	3	2
10.	70	2	M	1	3	2	3	1	1	1	1	1	1	1	1	1	2	1
11.	56	1	M	2	1	2	2	1	1	1	1	1	1	1	1	1	1	1
12.	57	1	M	3	2	2	1	2	2	2	2	2	2	2	2	2	2	2
13.	58	1	F	2	1	1	1	2	2	2	2	2	2	3	2	3	3	2
14.	59	1	M	2	1	1	1	2	2	2	2	2	2	3	2	3	3	2
15.	65	2	M	2	2	2	2	2	2	2	1	2	2	3	2	3	3	2
16.	70	2	M	1	2	2	3	1	1	1	1	2	1	1	1	1	0	1
17.	74	3	M	2	2	2	2	1	1	1	1	2	1	2	2	3	3	2
18.	60	1	M	1	2	2	2	2	2	1	1	2	1	3	2	3	2	2
19.	57	1	M	2	1	2	2	2	2	2	2	1	2	3	1	2	3	2
20.	63	2	M	1	3	2	1	1	1	1	1	2	2	1	1	1	2	1
21.	65	2	M	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2
22.	58	1	M	3	2	1	1	2	2	2	1	2	2	3	2	3	3	2
23.	65	2	M	2	2	1	2	2	2	2	1	2	2	3	2	3	3	2
24.	56	1	M	2	2	2	1	2	2	2	1	2	2	3	2	2	2	2

S.No.	Age	Age	SEX	Education	Durartion of illness	UPDRS	Hoehn & Yahr scale	MMSE	ACE=R attention	ACE-R memory	ACER-fluency	ACER-language	ACER visuospatial	ACE- R total score	MOCA	FAB GO-NO-GO	FAB Lurias Test	FAB total score
25.	62	2	M	2	2	1	2	2	2	1	1	2	1	3	2	3	3	2
26.	75	3	F	2	3	2	2	1	1	1	1	2	1	1	1	1	1	1
27.	72	3	F	1	3	2	3	1	1	1	1	2	1	1	1	1	2	2
28.	66	2	M	2	2	2	2	2	2	2	1	1	2	2	2	2	3	2
29.	65	2	M	2	2	2	2	1	1	1	1	2	1	1	1	1	1	1
30.	66	2	M	2	2	1	2	2	2	2	1	2	2	2	2	2	2	2
31.	65	2	M	2	1	1	2	2	2	2	1	2	2	3	2	3	3	2
32.	57	1	M	2	1	2	1	2	2	2	1	2	2	2	2	3	3	2
33.	74	3	M	2	3	2	3	1	1	1	1	2	1	1	1	1	1	1
34.	61	2	M	2	2	2	2	2	2	2	2	1	1	2	2	3	3	2
35.	55	1	M	2	2	2	3	1	1	1	1	1	1	1	1	2	1	1
36.	60	1	F	2	2	1	2	2	2	2	1	1	2	3	2	3	3	2
37.	66	2	F	2	3	3	3	1	1	1	1	1	1	1	1	1	1	1
38.	58	1	F	2	1	1	1	2	2	2	1	2	2	3	2	3	3	2
39.	65	2	M	1	2	2	1	2	1	1	1	2	1	2	2	2	3	1
40.	64	2	F	2	2	2	2	1	1	1	1	1	1	2	2	2	3	2
41.	66	2	F	2	2	2	1	1	2	2	1	1	2	2	1	2	3	2
42.	59	1	M	2	2	1	2	2	2	2	1	2	2	2	2	3	2	2
43.	78	3	M	2	3	2	3	1	1	1	1	1	1	1	1	1	1	1
44.	60	2	F	2	2	1	1	2	2	2	2	2	1	2	1	3	2	1
45.	67	2	M	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2
46.	74	3	F	2	3	2	2	1	1	1	2	1	2	1	1	1	2	1
47.	65	2	M	1	3	2	2	1	1	1	2	2	1	1	1	1	2	1
48.	64	2	F	1	3	2	2	1	1	1	1	1	2	1	1	1	1	1
49.	63	2	M	1	2	2	2	1	1	1	1	1	1	1	1	2	3	2
50.	75	3	M	2	3	2	2	1	1	1	1	1	1	1	1	1	1	1

S.No.	Age	Age	SEX	Education	Durartion of illness	UPDRS	Hoehn & Yahr scale	MMSE	ACE=R attention	ACE-R memory	ACER-fluency	ACER-language	ACER visuospatial	ACE- R total score	MOCA	FAB GO-NO-GO	FAB Lurias Test	FAB total score
51.	64	2	M	2	3	2	2	1	1	2	2	2	1	1	1	1	1	1
52.	64	2	F	2	1	1	1	2	2	2	2	2	2	3	2	3	3	2
53.	59	1	F	2		2	2	1	1	2	2	2	1	2	2	2	3	2
54.	55	1	F	2	1	1	2	2	2	2	1	2	2	3	2	3	3	2
55.	70	2	M	2	3	2	3	1	1	1	1	1	1	1	1	2	1	2
56.	74	3	M	2	2	2	2	1	1	1	1	1	1	1	1	2	1	1
57.	73	3	F	2	2	2	1	2	2	2	2	2	2	2	2	2	3	2
58.	62	2	M	2	2	1	2	2	2	2	2	2	2	3	2	3	3	2
59.	60	1	F	2	2	1	2	2	2	2	2	2	2	3	2	3	3	2
60.	55	1	M	2	3	3	2	1	1	1	1	2	1	1	1	1	1	1
61.	68	2	F	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2
62.	58	1	F	1	2	1	1	2	2	1	1	2	1	2	2	2	2	2
63.	61	2	F	1	3	2	3	1	1	1	1	1	2	1	1	2	2	1
64.	70	2	M	2	3	2	3	1	1	2	2	2	2	1	1	3	1	2
65.	76	3	M	1	3	3	2	1	1	2	2	2	2	1	2	2	1	1
66.	67	2	M	2	2	1	2	2	1	1	1	2	1	3	2	2	2	2
67.	65	2	M	2	1	1	1	2	2	2	2	2	2	3	2	3	3	2
68.	72	3	F	2	1	1	1	2	2	2	2	2	2	3	2	3	3	2
69.	73	3	M	2	2	1	2	2	2	2	2	2	2	2	2	2	3	2
70.	66	2	F	2	3	2	3	1	1	2	2	1	2	1	1	1	1	1
71.	56	1	F	2	3	2	2	1	1	2	2	1	2	1	2	1	1	1
72.	60	1	M	2	3	2	2	1	1	1	1	2	1	1	1	1	2	1
73.	59	1	F	2	3	2	2	1	1	2	2	1	2	1	1	1	1	1
74.	63	2	F	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2
75.	67	2	F	2	2	2	1	2	2	2	1	2	2	2	2	2	3	2
76.	68	2	F	2	3	2	2	1	1	1	1	2	1	1	1	1	1	1

S.No.	Age	Age	SEX	Education	Durartion of illness	UPDRS	Hoehn & Yahr scale	MMSE	ACE=R attention	ACE-R memory	ACER-fluency	ACER-language	ACER visuospatial	ACE- R total score	MOCA	FAB GO-NO-GO	FAB Lurias Test	FAB total score
77.	63	2	M	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2
78.	55	1	F	2	2	2	1	2	2	2	2	2	2	2	2	2	3	2
79.	73	3	M	2	2	2	2	2	1	1	1	2	1	2	2	2	3	2
80.	67	2	F	2	1	2	1	1	1	1	1	1	1	2	1	2	3	2
81.	65	2	M	2	1	2	2	2	1	1	1	1	1	2	2	2	3	2
82.	54	1	M	2	2	2	2	2	1	1	1	1	1	2	2	3	3	2
83.	67	2	F	2	2	2	1	1	1	1	1	1	1	2	2	2	3	2
84.	59	1	F	2	1	2	1	2	2	2	2	2	2	2	2	2	2	2
85.	58	1	F	2	1	1	1	2	2	2	2	2	2	3	2	3	3	2
86.	73	2	F	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2
87.	72	2	M	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
88.	65	1	F	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2
89.	65	2	M	2	2	1	2	2	2	2	2	2	2	3	2	3	3	2
90.	67	2	F	2	2	1	2	2	2	2	2	2	2	3	2	3	3	2
91.	72	3	M	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2
92.	65	2	M	2	2	1	2	2	2	2	2	2	2	3	2	2	3	2
93.	66	2	M	1	2	2	1	2	2	2	2	2	1	2	2	3	3	2
94.	62	2	M	1	3	2	2	2	2	2	2	2	2	1	2	1	1	1
95.	71	3	M	1	1	1	2	2	2	2	2	2	1	3	2	3	3	2
96.	79	3	M	1	3	3	3	1	1	1	1	1	1	1	2	1	1	1
97.	66	2	M	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2
98.	68	2	F	1	2	2	2	2	2	2	1	2	2	2	2	2	2	2
99.	60	1	M	1	2	2	1	2	2	2	1	1	2	3	2	2	3	2
100.	61	2	F	2	1	1	2	2	2	2	2	2	2	3	2	3	3	2

KEY TO MASTER CHART

Age

1= 55-60 years
2=61-70 years
3= 71-75 years

Sex

M= Male
F= Female

Education

1=Illiterate and studied up to elementary school
2= Studied up to secondary school
3= degree holder

Duration of the illness

1= less than 5 years
2= 5 to 10 years
3= more than 10 years

UPDRS

1= < 30
2= 31 to 60
3= > 60

Hoehn & Yahr score

1= < 1.5
2= 2 to 3
3= 4 to 5

MMSE= Mini Mental State Examination score

1=<23
2=>23

ACE-R- ADDENBROOKES COGNITION SCALE

ACE-R Attention and orientation

1= <12
2= 13 to 18

ACE-R Memory

1= <18
2=18to 26

ACE-R Fluency

1= <8

2= 9 to 14

ACE-R Language

1=<18

2=18 to 24

ACE-R Visuospatial

1=<10

2= 11 TO 16

ACE-R Total score

1=<60

2=61 to 80

3=81 to 100

MOCA

1= < 23

2= > 23

FAB Lurias test

3 =Patient performs six correct consecutive series alone:

2= Patient performs at least three correct consecutive series alone:

1= Patient fails alone, but performs three correct consecutive series with the examiner:

0=Patient cannot perform three correct consecutive series even with the examiner:

FAB Go-no-Go test

3=No errors

2= 1 -2 errors

1= > 2 errors

FAB Total score

1= <12,

2= 13 to 18

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.S.Rajendran
PG in Neurology
Madras Medical College,Chennai -3

Dear Dr.S.Rajendran,

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " Study of cognitive profile in parkinson's disease" No.19112012.

The following members of Ethics Committee were present in the meeting held on 01.11.2012 conducted at Madras Medical College, Chennai -3.

1. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
2. Prof. Reghu MD -- Member
   Director , Inst. Of Internal Medicine, MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. G.Muralidharan MS -- Member
   Prof of Surgery, MMC, Ch-3
6. Thiru. S. Govindsamy. BA,BL -- Lawyer

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

19/11/12
Member Secretary, Ethics Committee

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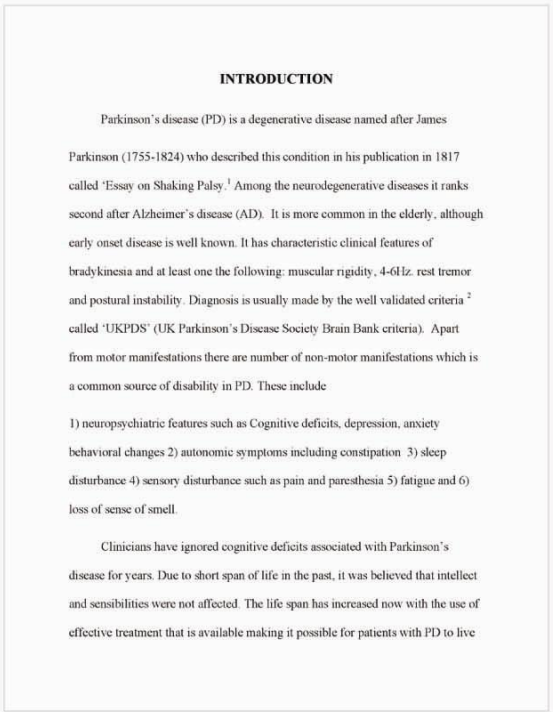
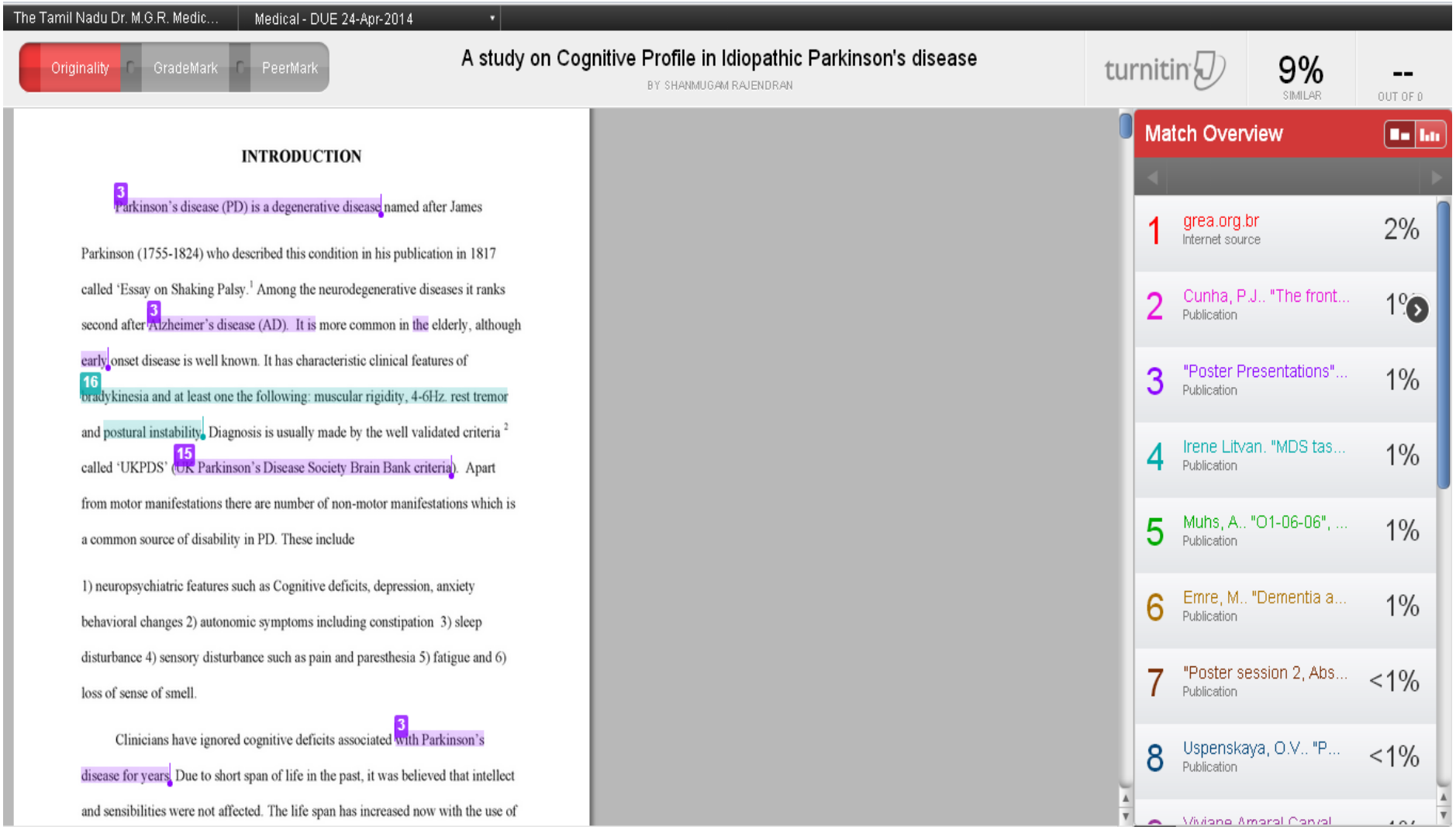


INTRODUCTION

Parkinson's disease (PD) is a degenerative disease named after James Parkinson (1755-1824) who described this condition in his publication in 1817 called 'Essay on Shaking Palsy.[1] Among the neurodegenerative diseases it ranks second after Alzheimer's disease (AD). It is more common in the elderly, although early onset disease is well known. It has characteristic clinical features of bradykinesia and at least one the following: muscular rigidity, 4-6Hz. rest tremor and postural instability. Diagnosis is usually made by the well validated criteria [2] called 'UKPDS' (UK Parkinson's Disease Society Brain Bank criteria). Apart from motor manifestations there are number of non-motor manifestations which is a common source of disability in PD. These include

1) neuropsychiatric features such as Cognitive deficits, depression, anxiety behavioral changes 2) autonomic symptoms including constipation 3) sleep disturbance 4) sensory disturbance such as pain and paresthesia 5) fatigue and 6) loss of sense of smell.

Clinicians have ignored cognitive deficits associated with Parkinson's disease for years. Due to short span of life in the past, it was believed that intellect and sensibilities were not affected. The life span has increased now with the use of effective treatment that is available making it possible for patients with PD to live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A study on Cognitive Profile in Idiopathic Parkinson's disease
BY SHANMUGAM RAJENDRAN
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Clinicians have ignored cognitive deficits associated with Parkinson's disease for years. Due to short span of life in the past, it was believed that intellect and sensibilities were not affected. The life span has increased now with the use of
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