Neurocognitive Profile and Depression in Obstructive Sleep Apnea

Rajasekhar Varma, Narendra Kumar Narahari, Paramjyothi Kruparao Gongati, Afshan Jabeen Shaik¹, Bhaskar Kakarla, Padmaja Gaddamanugu¹, Ravi Charan Avala²

Departments of Pulmonary Medicine and ¹Neurology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, ²Department of Pulmonary Medicine, Apollo Hospitals, Vishakapatnam, Andhra Pradesh, India

Abstract

Background: Neurocognitive decline and depression are the most common unaddressed but noticeable adverse consequences linked with obstructive sleep apnea (OSA) which can affect work performance, social functioning, and quality of life. It is significant to explore both cognition and mood disorders in OSA, as there is adequate evidence in the literature supporting the efficacy of continuous positive airway pressure (CPAP) in the management. **Aims and Objectives:** The aim was to assess the neurocognitive profile and depression in patients with OSA in our center. **Patients and Methods:** This was a cross-sectional observational study conducted in a tertiary care center between January 2017 and January 2018. A total of 92 patients with an established diagnosis of OSA (by polysomnography) were included in the study. All patients were given questionnaires for the assessment of neurocognitive function and depression scoring. **Results:** Out of 92 OSA patients, 29 (31.5%) had normal cognition, 43 (46.7%) had mild cognitive impairment (CI), and 20 (21.7%) had major CI. Out of twenty patients with major CI, major attention deficit was observed in 17 (85%), memory impairment in 16 (80%), verbal fluency was affected in 13 (65%), deficit in language skills was observed in 7 (35%), and visuospatial abilities were affected in 17 patients (85%). Out of 92 OSA patients, 21 (22.8%) had depression and 71.4% of them were females. **Conclusions:** OSA is an independent risk factor for both depression and neurocognitive decline. It is highly recommended that patients with OSA should be screened for both, so as to provide better clinical outcomes.

Keywords: Apnea hypopnea index, continuous positive airway pressure, depression, neurocognitive decline, obstructive sleep apnea, sleep disordered breathing

INTRODUCTION

Obstructive sleep apnea (OSA) is described by repetitive events of partial or complete upper airway collapse during sleep which is highly prevalent condition but still underdiagnosed.^[1] Complete airway collapse during sleep is identified as apnea (cessation of airflow for ten or more seconds), and partial airway collapse as hypopneas (when airflow decreases by 30% or more and a drop in oxygen saturation by $\geq 3\%$ or an arousal).^[2] Untreated OSA may cause fragmentation of sleep, which has many dangerous health consequences, leading to serious morbidity and mortality.^[1]

OSA is linked with neurocognitive dysfunction, depression, and mood disorders.^[3] Neurocognitive decline is one of the noticeable adverse consequences associated with OSA, which can affect work performance, social functioning, and quality of life.^[4] A high prevalence of depression is seen in patients with OSA when

compared to those not having OSA.^[5] It is still speculative whether depression is a primary consequence of OSA or it is secondary to sleep problems and irritability associated with OSA. In addition, there are many confounding and shared risk factors such as obesity, hypertension (HTN), diabetes, hypothyroidism, and cardiovascular disease which can strongly affect the association of OSA with depression and neurocognitive decline.^[5]

Intermittent hypoxia caused by repetitive opening and closure of airways during sleep, systemic inflammation, and endothelial

Address for correspondence: Dr. Narendra Kumar Narahari, Department of Pulmonary Medicine, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad - 500 082, Telangana, India. E-mail: drnarendrajipmer@gmail.com

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dysfunction altering brain structure and function are most likely pathogenic mechanisms responsible for neurocognitive decline in OSA.^[6] It was also observed that severe OSA can be a risk factor for dementia in the elderly.^[7] A recent meta-analysis by Leng *et al.*^[6] which included 212,943 patients concluded that adults with OSA are 26% more susceptible to dementia and neurocognitive decline over the period of 3–15 years follow-up. It is important to address and explore both cognition and mood disorders in OSA, as there is adequate evidence in the literature supporting the efficacy of continuous positive airway pressure (CPAP) in the management.^[1] It is also relevant to look up for OSA in patients with depression and mood disorders. The current study is aimed to assess the neurocognitive profile and depression in patients with OSA in our center.

MATERIALS AND METHODS

The study was carried out in the department of pulmonary medicine at a tertiary care hospital for both Telangana and Andhra Pradesh states. It was a prospective, observational study conducted between January 2017 and January 2018. Institutional ethics committee approval was obtained. A total of 92 patients with an established diagnosis of OSA (by polysomnography) were included in the study. All patients were given questionnaires for the assessment of neurocognitive function and depression scoring. The following eligibility criteria were observed in the study.

Eligibility criteria

Inclusion criteria

1. Age >18 years
2. Diagnosed cases of OSA by polysomnography
3. Individuals having a minimum of average intelligence
4. Informed consent.

Exclusion criteria

1. Persons whose literacy level does not allow administration of neuropsychological tests
2. Patients with known neuropsychiatric disorders or neurosurgical condition
3. Patients with sleep disorders other than OSA
4. Patients who are unable to communicate due to blindness and deafness
5. Patients with a history of drug abuse (psychoactive medications).

According to 2014 INOSA guidelines, prevalence of OSA is about 2%–4%, so with assumed precision of 10% and 95% confidence level, minimum required sample taken for the study was 92 ($n = 92$). A detailed history was taken, and all patients were given questionnaires for assessment of neurocognitive function and depression scoring. The questionnaires used in this study were Addenbrook's Cognitive Examination (ACE-III),^[8] an authorized questionnaire available in local languages (Hindi and Telugu)

for neurocognitive assessment [Supplementary Data 1], and Hamilton Depression rating scale^[9] [Supplementary Data 2]. The ACE-III is a brief cognitive test that assesses five cognitive domains, namely, attention (18 points), memory (26 points), verbal fluency (14 points), language (26 points), and visuospatial abilities (16 points). Total score is 100, higher scores indicate better cognitive functioning, and scores <100 indicate worse cognitive functioning.^[10]

Statistical analysis

Data were collected and stored in excel sheets with password protection. A copy of collected data was also updated to co-investigators. Thus, collected data were analyzed at the end of the study for descriptive statistics, and Chi-square test was used wherever necessary. *P* values were calculated with the help of statistician using SPSS software (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp., USA). A *P* < 0.05 was considered statistically significant.

RESULTS

Demographic data

The mean age of the study population was 53.35 ± 11.6 . Maximum patients were in the age group of 50–60 years (41%). Out of 92 patients in the present study, 63 were males (68.47%) and 29 were females (31.53%). The comorbidities in the present study were HTN (58.69%), diabetes mellitus (DM) (29.3%), hypothyroidism (17.32%), and coronary artery disease (10.86%).

Prevalence of neurocognitive impairment in obstructive sleep apnea

Out of 92 OSA patients in the present study, 29 patients (31.5%) had normal cognition, 43 (46.7%) had mild cognitive impairment (CI), and 20 (21.7%) had major CI. Of the 20 OSA patients with major CI, 13 (65%) were females and 7 (35%) were males and most of the patients, 14 (70%), were in the age group of 50–70 years. Out of the twenty patients with major CI, 18 patients were known hypertensive, 10 of them were diabetic, and 5 were hypothyroid. In the present study based on the Chi-square test, we conclude that there was a statistically significant association between HTN and neurocognitive impairment with a *P* = 0.0001. However, there was no significant association between DM or hypothyroidism and neurocognitive impairment with a *P* = 0.55.

Profile of neurocognitive decline in cases of obstructive sleep apnea

Out of twenty patients with major CI in our study, major attention deficit was observed in 17 patients (85%), memory impairment in 16 (80%), verbal fluency was affected in 13 (65%), deficit in language skills was observed in 7 (35%), and visuospatial abilities were affected in 17 patients (85%). Out of the twenty patients with major CI, 15 patients had education of <12 years and 5 patients had more than 12 years of education. In the present study based on the Chi-square

test, we conclude that there was a significant statistical association between education years and neurocognitive impairment indicating that patients with a lesser number of years of education had more chances of having major CI with a $P = 0.0007$.

Association between neurocognitive impairment and severity of obstructive sleep apnea

Out of the 92 OSA patients in the study, 13 patients (14.1%) had mild OSA, of these three patients had normal cognition and ten patients had mild CI. Thirty-two patients (34.8%) had moderate OSA, of these seven patients had normal cognition, 16 patients had mild CI, and nine patients had major CI. Forty-seven patients (51.1%) had severe OSA, of these 19 patients had normal cognition, 17 patients had mild CI, and 11 patients had major CI. There was a significant statistical association between the severity of apnea hypopnea index (AHI) and neurocognitive impairment with a $P = 0.047$.

Prevalence of depression in cases of obstructive sleep apnea

Out of 92 OSA patients in the present study, 21 patients (22.8%) had depression, of which nine patients (9.7%) had mild depression, seven (7.6%) had moderate depression, and five (5.4%) had severe depression. Of the 21 OSA patients with depression in our study, 14 (71.4%) were females and 6 (28.5%) were males, and most of the patients 13 (61.9%) were in the age group of 50–70 years.

Association between depression and severity of obstructive sleep apnea

Out of the 92 OSA patients in the study, 13 patients (14.1%) had mild OSA, of these one patient had severe depression. 32 patients (34.8%) had moderate OSA, of these eight patients had depression (1 – mild depression, 4 – moderate depression, and 3 – severe depression). Forty-seven patients (51.1%) had severe OSA, of these 12 patients had depression (mild – 8, moderate – 3, and severe – 1). We conclude that there was no significant association between the severity of AHI and severity of depression with a $P = 0.13$. In the present study, there was a significant statistical association between the severity of body mass index and severity of depression with a $P = 0.0017$. Furthermore, there was a significant statistical association between the severity of depression and education levels, indicating that patients with a less number of education years had more chances of having major depression with a $P = 0.04$.

DISCUSSION

The present study assessed the neurocognitive profile and depression in patients with OSA in our center. Out of 92 patients in the present study, 63 were males (68.47%) and 29 were females (31.53%). Out of 92 OSA patients, 29 (31.5%) had normal cognition, 43 (46.7%) had mild CI, 20 (21.7%) had major CI, and 21 patients (22.8%) had depression. The present study shows 21.7% prevalence of major neurocognitive impairment in patients with OSA. This is in concordance

with a recent meta-analysis which showed that patients with sleep-disordered breathing (SDB) are 26% more prone to develop CI.^[6] A multicenter cohort study by Yaffe *et al.*^[11] in 228 elderly women showed that OSA patients had high rate of mild degree of CI (44.8%) with odds ratio of 1.85, when compared to those not having OSA, whereas our study reported that 46.7% of patients had mild degree of neurocognitive impairment. The prevalence of depression in majority of studies ranged from 7% to 63%;^[12] however, in our study, it was 22.8%. There was no association between severity of OSA and severity of depression in our study.

It is a known fact that neurocognitive deficits occur in OSA, but the exact prevalence in adult patients with OSA is still unknown.^[3] This could be explained by variability in study design, various shared risk factors, and comorbidities independently affecting cognitive decline irrespective of severity of OSA.^[3,13] It was observed that increasing age, male sex, current cigarette smoking, obesity, HTN, DM, metabolic syndrome, hypothyroidism, and alcohol consumption are the common shared risk factors for both OSA and cognitive decline.^[13] Our study had twenty OSA patients with major neurocognitive deficit, of which 70% were in the age group of 50–70 years. This supports the fact that middle and elderly aged are at a higher risk for developing cognitive deficits when compared to the younger age with the same severity of OSA.^[14] The comorbidities observed in the present study were HTN (58.69%), DM (29.3%), hypothyroidism (17.32%), and coronary artery disease (10.86%).

OSA leads to intermittent hypoxia and systemic inflammation. This along with changes in sleep micro- and macroarchitecture causing micro infarcts, stroke, reduced neurogenesis, changes in brain gray, and white matter and abnormal levels of Alzheimer's disease biomarkers can lead to progressive cognitive decline and dementia.^[15] Thus, OSA through intermittent hypoxia can predispose and further amplify the pathologic mechanisms, resulting in the progression and worsening of depressive symptoms and cognitive deficits.^[1,6]

The domains of the neurocognition such as attention, memory, verbal fluency, and visuospatial abilities were affected in most of the patients with major neurocognitive deficit.^[16-18] However, language skills were preserved.^[19] In our study, twenty patients with OSA had major neurocognitive deficit, and in these patients, attention (85%), memory (80%), verbal fluency (65%), and visuospatial abilities (85%) were affected sparing language skills (35%) which was intact in most of the affected patients. A meta-analysis by Bucks *et al.*^[20] including 33 studies concluded that deficits of attention, memory, and executive functions are the most affected cognitive domains in OSA. A systematic review and meta-analysis by Leng *et al.*^[6] concluded that SDB is linked with a higher risk of CI and a small worsening in executive function.

Results of our study showed that an increase in severity of OSA can aggravate the neuropsychological deficit ($P < 0.047$). A study by Bédard *et al.*^[18] showed

that OSA not only worsens the neuropsychological deficits present in moderately affected patients but also produces new deficits. Several studies examined the strength of association between OSA severity as measured by AHI and the cognitive deficits. A few studies reported that more severe the OSA (AHI >30), more likely the cognitive deficits when compared to mild or moderate OSA,^[4] while there was no association seen in some studies.^[21-23] Heterogeneous studies with different study designs and methods of assessing SDB are limiting factors to make firm conclusions on the strength of association.

Various studies^[5,12] reported a much higher prevalence of depression among patients with OSA than the current study. In a study conducted by Mosko *et al.*,^[24] 58% of patients with OSA met the Diagnostic and Statistical Manual criteria for depression and a study by Millman *et al.*^[25] revealed that 45% of patients with OSA had depressive symptoms. A study by Aloia *et al.*^[26] in 2005 which included 93 patients showed that 24% of the patients had mild depression, 5% moderate depression, and 4% had severe depression. In the present study, 21 patients (22.8%) had depression, out of which 9.7% had mild depression, 7.6% had moderate depression, and 5.4% had severe depression. Diverse definitions and instruments used in assessing depression in these studies can partially explain the variances in the prevalence of depression among patients with OSA. The present study did not show any significant association between severity of depression and AHI severity, which was concurrent with the available literature^[27,28] but that does not prove the fact that there is no link between the two conditions.

OSA can be a risk factor for depression and both commonly share risk factors such as obesity, increasing age, and adverse lifestyles and symptoms such as daytime sleepiness, insomnia, fatigue, and poor quality of life.^[29] Similar to previous studies,^[29,30] our study showed that depression was more common among women (71.4%). In a study by Smith *et al.*^[31] in 2002 which included 773 participants, 14% of patients had diagnosis of depression. Female patients with OSA were twice as likely as male to have depression.

In a systematic review and meta-analysis by Gupta *et al.*,^[32] it was concluded that CPAP improves depressive symptoms in patients with OSA, and the positive effect is more in patients with severe depression. Another systematic review by Zheng *et al.*,^[33] which included twenty randomized trials and 4255 participants, confirmed the same benefit of CPAP. The ADIPOSA study (anxiety and depression in patients with OSA before and after CPAP) concluded that 12-week CPAP therapy was highly favorable at improving the lack of positive affect, and stresses to use more precise depression and anxiety scales.^[34] Similarly, a study by Edwards *et al.*^[35] reported the beneficial effect of 3 months of CPAP in 228 subjects with OSA and depression. In this study, 3 months of CPAP treatment resulted in decrease in percentage of depression at baseline from 74.6 to 3.9 stressing the fact that prolonged treatment with CPAP may be beneficial.

Research also showed that long-term CPAP adherence can improve the cognition and slow the 1-year cognitive decline in older OSA patients.^[36] The PROOF Study (protective effect of long-term CPAP therapy on cognitive performance in elderly patients with severe OSA) concluded that CPAP therapy may protect and maintain cognitive performance and functions in patients with OSA.^[37] In a multicenter, double-blind, randomized study, Apnea Positive Pressure Long-term Efficacy Study, which studied the effects of CPAP versus SHAM concluded that cognitive function in severe OSA improved better than milder OSA patients. However, long-term follow-up did not show any improvement in attention/psychomotor and learning/memory functions.^[38]

Clinical studies have demonstrated that successful treatment of OSA with CPAP improves cerebral microvascular perfusion and oxygenation, reduces vascular inflammatory responses, and thus may further inhibit cerebral and neurovascular damage.^[1,6] As symptoms of cognition and depression overlap with that of OSA, there is a tendency to overlook these factors which may hinder the diagnosis and management of these conditions.^[1]

Limitations

In the present study, a relatively small number of patients were evaluated ($n = 92$). The number of patients required to evaluate the prevalence of neurocognitive impairment and depression has to be prospectively determined by larger studies. The response to the treatment was not checked in these patients. The questionnaires that were administered were unblinded. The other risk factors such as smoking and alcoholism were not considered in present study.

CONCLUSIONS

OSA is identified as an independent risk factor for both depression and neurocognitive decline. It is highly recommended that OSA patients should be screened for neurocognition and depression. CPAP therapy is shown to have a positive effect on improving and maintaining cognitive performance and depressive symptoms. However, long-term prospective studies, randomized controlled trials, standardized methodology with uniform assessment scores, and definitions can overcome the hurdles and address the limitations in making firm future recommendations. This may better help to augment the diagnostic accuracy as well as to provide better clinical outcomes. Clinicians should closely monitor patients with OSA for cognitive dysfunction and depression as effective treatment of both the conditions can improve the overall quality of life.

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY DATA 1

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-III Indian English																								
Name: _____ Date of Birth: _____ Hospital No. or Address: _____ Languages Known: _____ Native Language: _____			Date of testing: ____/____/____ Tester's name: _____ Age at leaving full-time education: _____ Occupation: _____ Handedness: _____																					
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➤ Tell: "I'm going to give you three words and I'd like you to repeat them after me: lemon, key and ball." After subject repeats, say "Try to remember them because I'm going to ask you later". ➤ Score <i>only</i> the first trial (repeat 3 times if necessary). ➤ Register number of trials: _____						Attention [Score 0-3] <input style="width: 40px;" type="text"/>																		
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➤ Ask the subject: "Could you take 7 away from 100? I'd like you to keep taking 7 away from each new number until I tell you to stop." ➤ If subject makes a mistake, do not stop them. Let the subject carry on and check subsequent answers (e.g., 93, 84, 77, 70, 63 - score 4). ➤ Stop after five subtractions (93, 86, 79, 72, 65): _____						Attention [Score 0-5] <input style="width: 40px;" type="text"/>																		
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➤ Ask: "Which 3 words did I ask you to repeat and remember?" _____						Memory [Score 0-3] <input style="width: 40px;" type="text"/>																		
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➤ Letters Say: "I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. For example, if I give you the letter "C", you could give me words like "cat, cry, clock" and so on. But, you can't give me words like Catherine or Canada. Do you understand? Are you ready? You have one minute. The letter I want you to use is the letter "P".						Fluency [Score 0 - 7] <input style="width: 40px;" type="text"/>																		
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2	2																							
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0	0																							
Total	Correct																							
➤ Animals Say: "Now can you name as many animals as possible. It can begin with any letter."						Fluency [Score 0 - 7] <input style="width: 40px;" type="text"/>																		
						<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr><td>>16</td><td>7</td></tr> <tr><td>14-16</td><td>6</td></tr> <tr><td>11-13</td><td>5</td></tr> <tr><td>8-10</td><td>4</td></tr> <tr><td>6-7</td><td>3</td></tr> <tr><td>3-5</td><td>2</td></tr> <tr><td>1-2</td><td>1</td></tr> <tr><td>0</td><td>0</td></tr> <tr><td>Total</td><td>Correct</td></tr> </table>	>16	7	14-16	6	11-13	5	8-10	4	6-7	3	3-5	2	1-2	1	0	0	Total	Correct
>16	7																							
14-16	6																							
11-13	5																							
8-10	4																							
6-7	3																							
3-5	2																							
1-2	1																							
0	0																							
Total	Correct																							

MEMORY			
<p>➤ Tell: "I'm going to give you a name and address and I'd like you to repeat the name and address after me. So you have a chance to learn, we'll be doing that 3 times. I'll ask you the name and address later."</p> <p>Score only the third trial.</p>			<p>Memory [Score 0 - 7]</p> <div></div>
	1st Trial	2nd Trial	3rd Trial
Sunil Kumar Singh 52, Station Road, Gandhinagar, Allahabad.	_____	_____	_____
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____
MEMORY			
<p>➤ Name the current Chief Minister.....</p> <p>➤ Name the Prime Minister of India</p> <p>➤ Name the actor who was hero in the film 'Mera Naam Joker'.....</p> <p>➤ Name the Father of our Nation.....</p>			<p>Memory [Score 0 - 4]</p> <div></div>
LANGUAGE			
<p>➤ Place a pencil and a piece of paper in front of the subject. As a practice trial, ask the subject to "Pick up the pencil and then the paper." If incorrect, score 0 and do not continue further.</p> <p>➤ If the subject is correct on the practice trial, continue with the following three commands below.</p> <ul style="list-style-type: none"> Ask the subject to "Place the paper on top of the pencil" Ask the subject to "Pick up the pencil but not the paper" Ask the subject to "Pass me the pencil after touching the paper" <p>Note: Place the pencil and paper in front of the subject before each command.</p>			<p>Language [Score 0-3]</p> <div></div>
LANGUAGE			
<p>➤ Ask the subject to write two (or more) complete sentences about his/her last holiday/weekend/festival. Write in complete sentences and do not use abbreviations. Give 1 point if there are two (or more) complete sentences about the one topic; and give another 1 point if grammar and spelling are correct.</p>			<p>Language [Score 0-2]</p> <div></div>
LANGUAGE			
<p>➤ Ask the subject to repeat: 'caterpillar'; 'eccentricity'; 'unintelligible'; 'statistician' Score 2 if all are correct; score 1 if 3 are correct; and score 0 if 2 or less are correct.</p>			<p>Language [Score 0-2]</p> <div></div>

LANGUAGE	
➤ Ask the subject to repeat: 'All that glitters is not gold'	Language [Score 0-1] <input type="text"/>
➤ Ask the subject to repeat: 'A stitch in time saves nine'	Language [Score 0-1] <input type="text"/>
LANGUAGE	
<p>➤ Ask the subject to name the following pictures:</p> <div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> <div style="width: 33%; text-align: center;"> <p>_____ <input type="text"/></p> </div> </div>	<p>Language [Score 0-12] <input type="text"/></p>
LANGUAGE	
<p>➤ Using the pictures above, ask the subject to:</p> <ul style="list-style-type: none"> Point to the one which is used in rain Point to the one which emits light Point to the one which is associated with farming Point to the one which is found in desserts 	<p>Language [Score 0-4] <input type="text"/></p>

VISUOSPATIAL ABILITIES	
<p>➤ Ask the subject to count the dots without pointing to them</p>	<p>Visuospatial [Score 0-4]</p> <div></div>
<div></div> <div> </div> <div></div>	<div></div> <div> </div> <div></div>
<div></div> <div> </div> <div></div>	<div></div> <div> </div> <div></div>

VISUOSPATIAL ABILITIES					
➤ Ask the subject to identify the letters					Visuospatial [Score 0-4] <input style="width: 40px;" type="text"/>
				<input style="width: 40px; height: 20px;" type="text"/> <input style="width: 40px; height: 20px;" type="text"/>	
				<input style="width: 40px; height: 20px;" type="text"/> <input style="width: 40px; height: 20px;" type="text"/>	
MEMORY					
➤ Ask "Now tell me what you remember about that name and address we were repeating at the beginning"					
Sunil Kumar Singh 52, Station Road, Gandhinagar, Allahabad.				Memory [Score 0-7] <input style="width: 40px;" type="text"/>	
MEMORY					
➤ This test should be done if the subject failed to recall one or more items above. If all items were recalled, skip the test and score 5. If only part was recalled start by ticking items recalled in the shadowed column on the right hand side; and then test not recalled items by telling the subject "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point, which is added to the point gained by recalling.					Memory [Score 0-5] <input style="width: 40px;" type="text"/>
Sunil Kumar Sharma	Sunil kumar Singh	Rakesh Yadav	recalled		
25	52	37	recalled		
Market Road	Sastri Marg	Station Road	recalled		
Prakash Nagar	Gandhi Nagar	Patel Nagar	recalled		
Allahabad	Gwalior	Indore	recalled		
SCORES					
TOTAL ACE-III SCORE			/100		
Attention			/18		
Memory			/26		
Fluency			/14		
Language			/26		
Visuospatial			/16		

SUPPLEMENTARY DATA 2

HAMILTON DEPRESSION RATING SCALE (HAM-D)

(To be administered by a health care professional)

Patient Name _____

Today's Date _____

The HAM-D is designed to rate the severity of depression in patients. Although it contains 21 areas, calculate the patient's score on the first 17 answers.

☐

1. DEPRESSED MOOD

(Gloomy attitude, pessimism about the future, feeling of sadness, tendency to weep)

0 = Absent

1 = Sadness, etc.

2 = Occasional weeping

3 = Frequent weeping

4 = Extreme symptoms

☐

2. FEELINGS OF GUILT

0 = Absent

1 = Self-reproach, feels he/she has let people down

2 = Ideas of guilt

3 = Present illness is a punishment; delusions of guilt

4 = Hallucinations of guilt

☐

3. SUICIDE

0 = Absent

1 = Feels life is not worth living

2 = Wishes he/she were dead

3 = Suicidal ideas or gestures

4 = Attempts at suicide

☐

4. INSOMNIA - Initial

(Difficulty in falling asleep)

0 = Absent

1 = Occasional

2 = Frequent

☐

5. INSOMNIA - Middle

(Complains of being restless and disturbed during the night. Waking during the night.)

0 = Absent

1 = Occasional

2 = Frequent

☐

6. INSOMNIA - Delayed

(Waking in early hours of the morning and unable to fall asleep again)

0 = Absent

1 = Occasional

2 = Frequent

☐

7. WORK AND INTERESTS

0 = No difficulty

1 = Feelings of incapacity, listlessness, indecision and vacillation

2 = Loss of interest in hobbies, decreased social activities

3 = Productivity decreased

4 = Unable to work. Stopped working because of present illness only. (Absence from work after treatment or recovery may rate a lower score).

☐

8. RETARDATION

(Slowness of thought, speech, and activity; apathy; stupor.)

0 = Absent

1 = Slight retardation at interview

2 = Obvious retardation at interview

3 = Interview difficult

4 = Complete stupor

☐

9. AGITATION

(Restlessness associated with anxiety.)

0 = Absent

1 = Occasional

2 = Frequent

☐

10. ANXIETY - PSYCHIC

0 = No difficulty

1 = Tension and irritability

2 = Worrying about minor matters

3 = Apprehensive attitude

4 = Fears

HAMILTON DEPRESSION RATING SCALE (HAM-D)

(To be administered by a health care professional)

- ☐ **11. ANXIETY - SOMATIC**
Gastrointestinal, indigestion
Cardiovascular, palpitation, Headaches
Respiratory, Genito-urinary, etc.
0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

- ☐ **12. SOMATIC SYMPTOMS - GASTROINTESTINAL**
(Loss of appetite, heavy feeling in abdomen; constipation)
0 = Absent
1 = Mild
2 = Severe

- ☐ **13. SOMATIC SYMPTOMS - GENERAL**
(Heaviness in limbs, back or head; diffuse backache; loss of energy and fatigability)
0 = Absent
1 = Mild
2 = Severe

- ☐ **14. GENITAL SYMPTOMS**
(Loss of libido, menstrual disturbances)
0 = Absent
1 = Mild
2 = Severe

- ☐ **15. HYPOCHONDRIASIS**
0 = Not present
1 = Self-absorption (bodily)
2 = Preoccupation with health
3 = Querulous attitude
4 = Hypochondriacal delusions

- ☐ **16. WEIGHT LOSS**
0 = No weight loss
1 = Slight
2 = Obvious or severe

- ☐ **17. INSIGHT**
(Insight must be interpreted in terms of patient's understanding and background.)
0 = No loss
1 = Partial or doubtful loss
2 = Loss of insight

TOTAL ITEMS 1 TO 17: _____

0 - 7 = Normal
8 - 13 = Mild Depression
14 - 18 = Moderate Depression
19 - 22 = Severe Depression
≥ 23 = Very Severe Depression

- ☐ **18. DIURNAL VARIATION**
(Symptoms worse in morning or evening. Note which it is.)
0 = No variation
1 = Mild variation; AM () PM ()
2 = Severe variation; AM () PM ()

- ☐ **19. DEPERSONALIZATION AND DEREALIZATION**
(feelings of unreality, nihilistic ideas)
0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

- ☐ **20. PARANOID SYMPTOMS**
(Not with a depressive quality)
0 = None
1 = Suspicious
2 = Ideas of reference
3 = Delusions of reference and persecution
4 = Hallucinations, persecutory

- ☐ **21. OBSESSIVE SYMPTOMS**
(Obsessive thoughts and compulsions against which the patient struggles)
0 = Absent
1 = Mild
2 = Severe