Original Article

A comparison of cognitive functions in non-hypoxemic chronic obstructive pulmonary disease (COPD) patients and age-matched healthy volunteers using mini-mental state examination questionnaire and event-related potential, P300 analysis

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ABSTRACT

Objective: To assess sub-clinical cognitive dysfunctions in stable chronic obstructive pulmonary disease (COPD) patients having no hypoxemia vs. age-matched healthy volunteers using (i) an electrophysiological test: Auditory event related potential, P300 test and (ii) a questionnaire tool: Mini-mental state examination (MMSE) questionnaire. **Materials and Methods:** Eighty male subjects were included: 40 stable COPD patients (smoking history >20 pack years) and 40 healthy volunteers (HVs). Age, duration of illness, smoking pack years, and spirometric indices were assessed. MMSE scores were evaluated in these groups. Latency of P300 wave and amplitude of P300 wave were studied in both groups to detect P300 abnormalities in COPD group. Correlations of P300 abnormalities with patient characteristic parameters and MMSE scores were assessed. In addition, individual COPD patients having significant cognitive dysfunctions beyond cut-off value of 99th percentile of HVs were analyzed. **Results:** We observed significantly prolonged P300 latency ($P < 0.001$) and decreased P300 amplitude ($P < 0.001$) in COPD group. MMSE scores were significantly reduced in COPD group ($P < 0.001$). 10/40 COPD patients had prolongation of P300 latency, and 27/40 COPD patients had reduced MMSE scores beyond 99th percentile of HV. However, we did not observe any statistically significant correlation between P300 abnormalities and patients' characteristics or MMSE scores ($P > 0.05$ for all). **Conclusions:** Our study explores cognitive dysfunctions in stable COPD patients with no hypoxemia. This study highlights the relative importance of using MMSE and P300. Cognitive dysfunctions were detected both by MMSE and P300; however, MMSE abnormalities were more frequent compared to P300 abnormalities (27/40 vs. 10/40) in COPD patients.

KEY WORDS: Chronic obstructive pulmonary disease, cognitive functions, event-related potential, mini-mental state examination, P300

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) continues to be a significant disease worldwide and, presently, it is the fourth leading cause of death. Further increases in its prevalence and mortality are predicted for coming decades.[1] COPD is a preventable and treatable disease; its pulmonary components are characterized by airflow limitation that is not fully reversible. Frequently, COPD has significant extrapulmonary effects that contribute to its severity in individual patients. The mechanisms linking COPD to systemic manifestations and co-morbidities are not yet fully understood, but the potential ones include systemic inflammation. Several inflammatory cytokines are increased in the circulation of COPD patients; these cytokines are increased in sputum and bronchioalveolar

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lavage fluid as well, suggesting the role of overspill of inflammatory mediators from the lung.[2] Other possible mechanisms include shared genetic predispositions, physical inactivity secondary to airway obstruction and chronic hypoxia.[2] The associated peripheral neuropathy is well illustrated in medical literature.[3,4] Impairment of brainstem auditory-evoked potentials in stable COPD patents has also been described.[5] Visual-evoked potentials are also affected in many of these patients.[6] In addition, motor neuron involvement and encephalopathy have been observed in patients with chronic respiratory insufficiency.

Association of cognitive dysfunctions in hypoxemic patients with severe COPD has been recognized for few decades.[7] Cognitive functions are comprised of thought processes related to remembering, thinking, learning and using language skills. Higher cognitive functions (abstracting ability, complex perceptual-motor integration) are more severely affected. Previous studies have suggested a strong relationship between decline in cognitive functions and COPD severity.[8] Moreover, severe COPD is found to be associated with lower cognitive performance on standardized measurements over time.[9] In a more recent study, a pattern of cognitive dysfunction specific to COPD has been suggested; the incidence being significant in COPD patients with hypoxemia.[10] Majority of previous publications included COPD subjects with hypoxemia and concluded that cognitive impairments are related to hypoxemia. Whereas the existence of cognitive dysfunctions in severe COPD patients with hypoxemia has been beyond doubts, that in stable COPD patients with no significant hypoxemia remains to be investigated.[11]

In present study, we included stable COPD patients with no hypoxemia/hypercapnia along with healthy volunteer (HV) as controls; all COPD patients were smokers/ex-smokers with well-documented COPD for years. We adopted two tools to assess cognitive functions: (i) P300, event-related brain potential (ERP) that is known to reflect neuro-electric activities related to cognitive processes such as attention allocation and activation of immediate memory,[12,13] and (ii) Mini-mental state examination (MMSE), described by Folstein *et al.*, widely used to screen for cognitive impairment.[14] We assessed cognitive functions using both of these tools simultaneously to see their relative relevance in clinical setup and under electrophysiological setup.

MATERIALS AND METHODS

The present study was conducted at the Departments of Respiratory Medicine and Physiology at our Institute and was approved by Institutional Board of Studies. We enrolled 80 male subjects with age 40 year or more, including 40 COPD patients and an equal number of HVs. All subjects had given explicit written consent for this study prior to inclusion. The diagnosis of COPD was based on modified criteria defined in Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[15] All COPD patients had duration of symptoms for 5 years or more. They had regular follow-up in 'COPD Clinic' at our institute for previous one year or more before inclusion to this study. None of them was admitted to indoors due to COPD-related illness for at least preceding six months. Out of 40 COPD patients, 28 were smokers and 12 were ex-smokers; however each patient was having a history of smoking not less than 20 pack years. The assessment of smoking pack years in COPD patients was based on (i) mode of smoking (bidi, cigarette or hookah), (ii) daily consumption and (iii) total years smoked. One pack year comprised of 20 cigarettes smoked every day for one year.[16] For bidi, cigarette equivalents were calculated by applying a weight of 0.5 to bidis;[17] and for hookah, 12.5 g of loose tobacco was considered as equivalent to one packet of 20 cigarettes.[18] The current smokers were required to abstain from smoking for at least 48 h before the assessment of study variables. The COPD patients had post-bronchodilator (20 min after inhalation of 2 puffs of salbutamol given via a metered dose inhaler through a spacer) FEV_1 less than 80% of the predicted value along with an FEV_1/FVC % not more than 70%. Post-bronchodilator increase in FEV_1 was less than 200 ml and not more than 12% of baseline value. The classification of airflow limitation severity in COPD patients was based on post-bronchodilator FEV_1 as described in GOLD guidelines:

1. Mild: Post-bronchodilator $FEV_1 \geq 80\%$ predicted
2. Moderate: Post-bronchodilator $FEV_1 \geq 50\%$ but <80% predicted
3. Severe: Post-bronchodilator $FEV_1 \geq 30\%$ but <50% predicted
4. Very Severe: Post-bronchodilator $FEV_1 < 30\%$ predicted.

Arterial blood gases analysis was done in all patients after taking blood sample from radial artery. None of the patient had any resting hypoxemia/hypercapnia at the time of inclusion to study or during prior visits; all of them had PaO_2 above 60 mm Hg (8.0 kPa) and oxygen saturation SaO_2 above 90%. None of the subject had any concomitant auditory dysfunction. There was no clinical symptom of any cognitive impairment/neurological deficit/neuropathy in any subject. Patients having concomitant diabetes mellitus, chronic alcoholism, uremia, cystic fibrosis, sarcoidosis, leprosy, malignancy, any hereditary disorders involving peripheral nerves, history of intake of any neurotoxic drug or history of any traumatic lesion possibly affecting auditory functions or central nervous system were excluded from the study. None of included subjects had any cardiovascular or other systemic disease during follow-up visits or after inclusion to the study. All HVs were non-smokers. They were selected out of healthy attendants of patients and comprised the control group. Both patients as well as control subjects were drawn from the same socio-economical, cultural and educational background.

The spirometry was carried out using a dry rolling seal spirometer, Transfer Test Model 'C', P K Morgan, Kent, UK. Inhaled short acting bronchodilators were withheld for 6 h prior to test, long acting β-2 agonists for 12 hours

before test, and sustained release theophylline for 24 hours ahead of test. Spirometric indices were calculated using best out of three technically satisfactory performances as per recommendations of American Thoracic Society.[19] The following spirometry parameters were used for statistical analyses: Peak expiratory flow rate (PEFR), forced expiratory volume in first second (FEV_1), forced vital capacity (FVC) and the ratio: FEV_1/FVC%.

Electrophysiological study for assessment of P300 variables was done over microprocessors-based neurophysiological testing equipment along with dedicated software: RMS EMG EP MARK II, Recorders and Medicare Systems Pvt. Ltd., Chandigarh, India. A standard setting was used while carrying out the electrophysiological study. The volume conducted evoked responses were picked up from scalp using disc type of Ag/AgCl electrodes.[20] Two reference electrodes, A1 and A2, were attached to left and right mastoid, respectively; the active electrode on vertex was labeled as Cz. The ground electrode attached to forehead was termed as Fz. All electrodes were plugged to a junction box. Skin to electrode impedance' was monitored and was kept below 5 K ohms.

Procedure for event related potential, P300

The study subjects were made to relax in a soundproof climate controlled room. Event-related potential wave pattern was recorded in context of a standard auditory oddball paradigm.[20] There were two varieties of stimuli: Target [rare tone] stimuli and non-target [frequent tone] stimuli. Each type was of 85 dB and the stimuli were applied to both ears simultaneously in random sequence through headphones. Rare tone and frequent tone stimuli were of 2 KHz and 1 KHz, respectively. The frequency of rare tone stimuli was 20% and that of frequent tone stimuli was 80%. Stimuli frequency was 1 stimulus/s. Total numbers of stimuli given were 300. Band pass filter was of 0.2-100 Hz. The subjects were asked to identify the rare stimuli, counting in loud voice. The signals were picked by electrodes, and then filtered, amplified, averaged, displayed on the screen and printouts were taken.

Patterns of event-related potentials

Many different components of event-related potentials (ERP) wave pattern including P65, Nd, N2, P3a, P3 (also described as P300), P4, and N400 have been identified. With the exception of P300, various components have not been consistently observed in different recording situations;[21] primarily (i) because of their small amplitude, these are difficult to separate from background noise when only a few trials are averaged, and (ii) they occur with short latencies and overlap considerably with somatosensory-evoked potentials that take place simultaneously. The wave patterns seen with frequent tone stimuli and those with rare tone stimuli are different. With the frequent tone stimuli, a negative N1 → positive P2 vertex potentials are seen [Figure 1]. With rare tone stimuli, a negative N1 → positive P2 → negative N2 → positive P3 complex potentials are seen[21] [Figure 2]. Latencies and

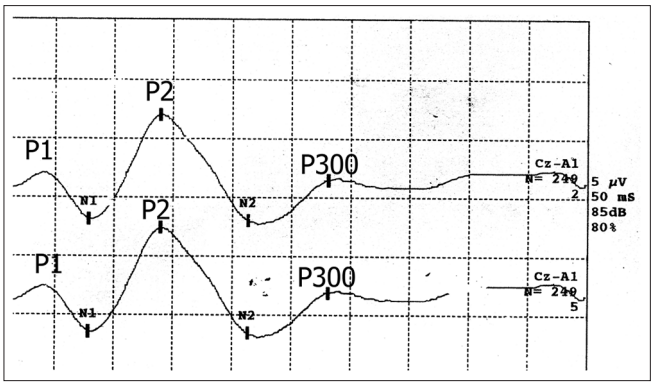

Figure 1: The electrophysiological assessment was done in response to auditory stimuli given with a frequency of 1 stimulus/s. They were of two types: Frequent tone stimuli [80% of total stimuli] and rare tone stimuli [20% of total stimuli]. Event-related potential wave pattern observed with a frequent tone stimulus is shown here: A negative N1 wave is followed by positive P2 vertex potential

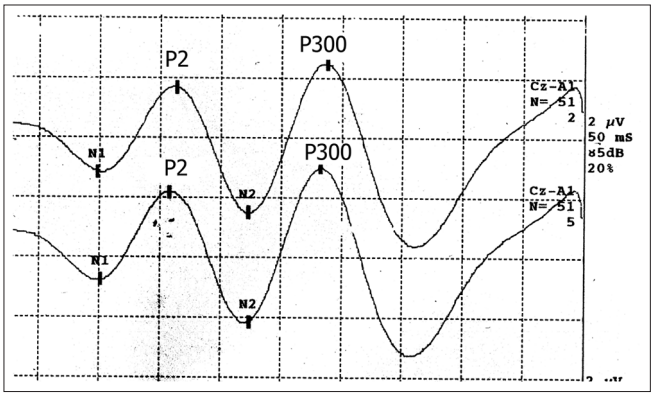

Figure 2: Event-related potential pattern with a rare tone stimulus: A negative N1, followed by positive apparent P2, again followed by negative N2–positive P300 complex (representing, in part, the event-related response) is seen. The latency of N2–P300 and amplitude of P300 wave is used for analysis purpose.

amplitude of P3 (P300) wave were measured in present study. P300 itself is known to be influenced by various biological processes like fluctuations in the arousal state of subjects. The factors affecting P300 recordings include natural (circadian, ultradian, seasonal, menstrual) variables and environmentally induced state (exercise, fatigue, drugs) variables.[12,13]

Mini-mental state examination

The mini-mental state examination (MMSE) is a questionnaire comprising of 11 questions intended to evaluate cognitive functions of an adult. It was introduced in 1975 by Folstein and co-workers[14] and was designed for use with elderly patients who are able to cooperate at an optimum level with an examiner for only a brief period of time. The benefits of the MMSE include its brevity and the fact that it is a global assessment of many domains including: Orientation to time and place, registration, attention and calculation, recall, language and visual construction. MMSE has been reported to be influenced by age,[22] education level,[23,24] cultural settings,[25] severe

functional limitations,[26] marital status and immigration status,[27] presence of frontal-executive dysfunction and visuospatial deficits.[28]

MMSE is a widely used questionnaire in India and used routinely by Psychiatry department at our Institute to assess cognitive functions of rural as well as urban subjects. This has been previously validated and used by us also in prior studies.[5,6] In present study, MMSE was administered by same qualified pulmonary resident doctor for all subjects including COPD patients and HVs. The subjects were asked in their native language [Hindi] by exact conversion of the questions of MMSE International Version in English.

Statistical analyses

The data of HVs and COPD patients was analyzed by including the same in two different groups. The statistical significance of difference between group means of various parameters between HVs group and COPD group was analyzed by using independent sample test, "*t*" test. Individual COPD patients having increase in latency of P300 wave or decrease in its amplitude beyond the range of mean ±3 standard deviation (99th percentile) of HVs were considered as having significant P300 abnormalities. The P300 abnormalities were correlated with patient characteristics including age, duration of illness, quantum of smoking, spirometric indices (FEV_1, FEV_1/FVC% and PEFR) and MMSE scores. The data obtained was statistically analyzed using Pearson's correlation. All statistical analyses were carried out with the help of SPSS (version 14.0), Chicago, software.

RESULTS

We included only male subjects in both COPD and HVs' groups; there were 40 patients in COPD group and 40 subjects in HVs' groups. All COPD patients belonged to stage II (moderate airflow obstruction severity) as per GOLD classification. The subjects included in COPD group and HVs group had matched age and height [Table 1]. COPD patients had a mean duration of illness for 10.67 ± 4.89 years and mean smoking 39.95 ± 20.94 pack-years. All HVs were non-smokers and asymptomatic.

For electrophysiological evaluation of P300, *rare tone stimuli* wave patterns were used in all subjects. The mean latency of P300 (rare tone stimuli) in HVs group was 265.69 ± 15.49 ms and the same in COPD group was 300.06 ± 22.57 ms. The mean amplitude of P300 (rare tone stimuli) in HVs group was 5.19 ± 2.66 μv and the same in COPD group was 3.76 ± 1.94 μv. The statistical analyses revealed that mean latency of P300 was significantly prolonged ($P < 0.001$) and mean amplitude of P300 was significantly decreased ($P < 0.001$) in COPD patients as compared to HVs [Table 2]. MMSE scores in COPD group were significantly reduced ($P < 0.001$) compared to those in HVs group. These findings clearly show that COPD patients` group had impaired cognitive functions detected both over P300 as well as MMSE evaluation.

Table 1: Characteristics of subjects in chronic obstructive pulmonary disease (COPD) group (*n*=40) and healthy volunteers group (*n*=40)

Characteristics	COPD group Mean±S.D	Healthy volunteers group Mean±S.D	Significance of difference between two groups (*P* value)
Age (years)	57.25±9.07	56.9±9.21	>0.05
Education Level			
Graduation and more	2	3	>0.05
Up to high school	7	6	>0.05
Up to middle	1	3	>0.05
Up to primary	15	14	>0.05
No formal education	15	14	>0.05
Duration of illness (years)	10.67±4.89	Nil	–
Smoking (Pack years)	39.95±20.94	Nil	–
Height (m)	1.677±0.004	1.66±0.005	>0.05
BMI	19.30±2.22	23.40±0.80	>0.05
PEFR (L/min)	3.42±1.27	7.59±0.30	<0.001
FEV_1 (L)	1.48±0.50	2.90±0.12	<0.001
FVC (L)	2.77±0.66	3.48±0.14	<0.001

Table 2: Comparison of event-related potential P300 variables and mini-mental state examination (MMSE) scores between subjects in chronic obstructive pulmonary disease (COPD) group and healthy volunteers group

Study variable	COPD group *n*=40 Mean±S.D	Healthy volunteers group *n*=40 Mean±S.D	Significance of difference between two groups (*P* value)
Event related potential P300: Rare tone stimuli wave parameters			
Latency P300 (ms)	300.06±22.57	265.69±15.49	<0.001
Amp P300 (P3–N2) (μv)	3.76±1.94	5.19±2.66	<0.001
MMSE scores			
MMSE score (maximum score=30)	22.48±2.42	27.85±1.51	<0.001

In addition, we analyzed for individual COPD patients who had prolongation of P300 latency and/or a decrease in P300 amplitude beyond 99th percentile of HVs. Prolongation of latency of P300 wave was seen in 10/40 COPD patients (25%) but none of the patient had decreased in amplitude beyond 99th percentile of HVs. 27/40 COPD patients (67.5%) had significantly reduced MMSE scores beyond 99th percentile of HVs. Interestingly, all subjects with P300 abnormality in term of increased P300 latency also had MMSE abnormality.

The correlations between P300 variables and the characteristics of COPD patients were analyzed. P300 latency had inverse correlation with age, PEFR, FEV_1, FEV_1/FVC ratio and MMSE scores, and a positive correlation with duration of illness and quantum of smoking; however, none of these correlations was statistically significant. P300 amplitude had positive correlation with age, duration of illness, quantum of smoking and MMSE scores, and an inverse correlation with PEFR, FEV_1, FEV_1/FVC ratio; again none of these correlation was statistically significant. Despite the

presence of cognitive dysfunctions in terms of both P300 abnormalities and reduced MMSE scores, no significant correlation between them was observed.

DISCUSSION

Cognitive functions in human beings are known to decline with advancing age, particularly evident beyond the age of 60 year.[29] One of the suggested hypotheses for this decline is a decrease in oxygen transport to brain that leads to hypoxemic changes.[30] Some neuroimaging studies have found that adults with severe COPD may develop alterations in brain perfusion due to hypoxemia leading to cognitive impairment.[31] Additionally, COPD patients are more inclined to avoid the physical activities due to increase in dyspnea during activity.[32] Thus, COPD patients are affected in more than one way that may be responsible for the decline in cognitive functions.

Prior studies have primarily evaluated cognitive functions in severe COPD patients with hypoxemia/hypercapnia. As early as in 1982, higher cognitive functions impairment was observed in hypoxemic COPD patients.[7] Various studies observed increased latencies of P300 and found decline in cognitive functions was related to severity of the disease.[33-35] Many studies used MMSE to assess cognitive dysfunctions with variable results. The studies found significant MMSE impairment in severe COPD patients,[8,36] but not in COPD patients with mild hypoxemia.[37] Liesker *et al*. using a different study tool found[38] that even non-hypoxemic COPD patients had significant cognitive impairment. Klein and coworkers found global impairment in cognitive functions in COPD patients.[39]

Majority of earlier studies have included severe COPD patients with hypoxemia. However, in present study, we assessed a unique COPD patient population. The study population in our study was comparatively younger; all patients had significant history of smoking and belonged to stage II of GOLD classification with no coexisting resting hypoxemia or hypercarbia. We also included the age-matched HVs to take care of age co-factor. In present study we have used two different tools, P300 and MMSE, simultaneously to assess cognitive functions; the utility of each one of them for assessment of cognitive functions has been established in prior studies. Some workers have found MMSE alone an insensitive tool and recommended P300 latency to assess cognitive dysfunctions.[40] For these reasons, we used P300 in addition to MMSE for cognitive assessment.

Invariably, all studies have reported increased latency of P300 wave; the probable cause being demyelinating dysfunction of the cerebral cortex. In our study, P300 abnormalities were seen in fewer COPD patients compared to MMSE abnormalities. MMSE has been reported to be influenced by age, education level, cultural settings, severe functional limitations, marital status and immigration status, presence of frontal-executive dysfunction and visuospatial deficits. We have taken age-matched controls belonging to similar socio-economical, cultural and educational background. None of our patient had any frontal-executive dysfunction and visuospatial deficits. However, immigration status and marital status were not specifically analyzed in our study. To our knowledge, this is perhaps first study that assessed cognitive dysfunctions in stable COPD patients using both tools simultaneously.

As none of our patient had any hypoxemia or hypercarbia, whether the chronicity of COPD disease contributes to cognitive dysfunctions needs to be evaluated. Also, the possibility of cigarette smoke contents leading to cognitive dysfunctions over a period of time remains. Though, our patients had no resting desaturation at the time of investigations, many of them might be having desaturation during moderate to severe activities. Frequent oxygen desaturation during everyday activity has been described as an important mechanism leading to damage to brain tissue.[41]

We observed no significant correlation of P300 variables with patients' characteristics, probably due to the narrow range of patients' characteristics in our study as we included only stable COPD patients [GOLD stage II]. It is well known that P300 latency has a large spectrum of distribution (250–600 ms), so perhaps increasing the number of study subjects will make the correlations significant. It is also known that sensitivity of P300 test might be reduced due to large differences between frequencies of target and non-target stimuli.

Cognitive impairment is frequent and clinically important in COPD, but their association with COPD is often not fully recognized.[42] A recent meta-analysis included 15 studies over this subject involving 655 COPD patients and 394 controls; cognitive functions were impaired in COPD patients as compared to healthy controls and there was a significant association between severity of COPD and cognitive dysfunction, but only in patients with severe COPD.[43] Cognitive dysfunctions do have significant impact on self-management and adherence to therapy.[9] The identification of existence of subclinical cognitive dysfunctions in COPD patients is of practical use: (i) while planning management strategies for these patients, the unpredictable effect of cognitive dysfunctions may put some of these patients at risk; (ii) for medico-legal litigations in some of these patients, impaired cognitive functions may be wrongly attributed to work place related factors rather than to COPD disease itself. Cognitive dysfunctions have significant impact over the disease as COPD patients with untreated cognitive difficulties may deteriorate with faster rates and have worse health outcomes than cognitively intact patients.[9] Moreover, the cognitive dysfunctions are also recognized to be associated with increased mortality and disability.[44] The influence of COPD on cognitive performance is partially reversible

using oxygen therapy and physical activity, which is often not appreciated enough.[11] Our study has raised a concept of cognitive impairment in stable COPD patients with no hypoxemia which has not received due attention in past.

Finally, we were not able to remove certain limitations in our study like: Small sample size, institute-based sample subjects that were primarily medical care seekers or their willing attendants rather than planned sample collection from community for a pre-defined purpose, lack of quantification of their hypoxemia/hypercapnia during severe/strenuous work or exercise, uncertainty regarding their compliance to medications prescribed in past, history-based assessment of quantum of smoking etc., Due to these limitations, we cannot make sweeping conclusions but we do feel this study highlights the relative relevance of these two tests, P300 and MMSE in COPD patient populations like in the present study. MMSE does not fit the criteria to be a gold standard test because of its own limitations and its susceptibility to various confounding factors but still we feel we are left to use MMSE at the end to screen the COPD patients cognitive dysfunctions because MMSE is a questionnaire-based tool that can be applied in any setting and does not require huge investment by a peripheral medical setup. If we are providing referral services then we should definitely adopt P300 method in addition. This study definitely explores cognitive dysfunctions in stable COPD patients with no hypoxemia that may lead to search for mechanisms coexisting with/alternative to hypoxemia as a cause of cognitive impairment in these patients.

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