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Study of cognitive functions in major idiopathic interstitial pneumonias

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Abstract

Background: Cognitive dysfunction in idiopathic interstitial pneumonia (IIP) is an important clinical co-morbidity that is associated with impaired lung function. *The aim of the work* is to assess cognitive function in major IIP and to find out the relation between cognitive dysfunction and the oxygenation parameters.

Results: Fifty individuals were involved in the study; 30 patients with major IIP and 20 healthy individuals. Patients with IIP had significantly lower mini mental state examination (MMSE) score compared to the control group ($P <$ 0.001). Wechsler Deterioration Index (WDI) revealed that 33.3% ($n = 10$) of the patients with IIP had sure cognitive impairment and 26.6% ($n = 8$) had ongoing cognitive deterioration. Patients with idiopathic pulmonary fibrosis (IPF) had lower cognitive function than other IIP.

Conclusion: There is an impairment of cognitive function in patients with major IIP, particularly in IPF, as measured by WDI and MMSE. Further large studies are needed to assess the possible predictors of cognitive impairment and their effects on the patients' outcome.

Keywords: Cognition, Idiopathic interstitial pneumonia, MMSE, WDI

Background

Idiopathic interstitial pneumonias are interstitial lung diseases of unknown aetiology that have similar clinical and radiological features. They differ primarily by the histological patterns on lung biopsy that is characterized by variable degrees of inflammation and fibrosis [1].

Major idiopathic interstitial pneumonias (IIP$_S$) include the entities of idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), and desquamative interstitial pneumonia (DIP) [2].

IIP$_S$ have been associated with several co-morbidities, including gastro-esophageal reflux disease, coronary artery disease, pulmonary hypertension, and venous thromboembolic disease. In addition to that, cognitive

dysfunction is considered an important clinical co-morbidity which is associated with impaired lung functions that suggest a systemic disease [3]. It is well known also that cerebral oxygen desaturation is significantly associated with decrease in cognitive functions [4].

Assessments of cognitive functions include wide range of capabilities, including attention, memory, problem solving, and intellectual functions. It is a process of detection of a patient cognitive strength and weakness via qualitative and quantitative approach [5].

The aim of the study was to assess the cognitive functions in patients with major IIP$_S$. The secondry goal was to find out the relation between cognitive function and the oxygenation parameters.

Methods

A prospective case control study that was conducted at the Chest Department, Kasr Al-Ainy Hospital, Cairo University, in collaboration with the Psychiatry Department during the period between February 2016 and April 2017. It was carried out on 50 individuals; 30

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patients with major idiopathic interstitial pneumonias who were diagnosed based on multidisciplinary review of the clinical, radiological, and pathological data according to the guidelines of the international consensus statement produced as a collaborative effort from the American Thoracic Society and European Respiratory Society Guidelines 201 3[2], and 20 healthy individuals.

This human study was performed in accordance with the Declaration of Helsinki and was approved by the ethical committee of the Faculty of Medicine, Cairo University. All adult participants provided written informed consent to participate in the study.

All patients were subjected to the following:

1. Thorough history taking and clinical examination including age, sex, smoking status, and modified Medical Research Council scale (mMRC) for dyspnea.
2. Six minute walk test (6MWT): Every patient was instructed to wear his/her comfortable footwear. The patient's usual medication should be continued and the patient should not have exercised vigorously within 2 h before the beginning of the test. The objective of this test is to measure the distance walked as far as possible for 6 min [6].
3. Spirometry: It was performed using master screen Jager-D 97204 Hochberg Germany. Measurement of the forced expiratory volume in the first second (FEV1% predicted), forced vital capacity (FVC% predicted), FEV1/FVC %, forced expiratory flow (FEF25–75% predicted) were obtained. The presence of an FEV1/FVC > 0.70 together with FVC < 80% predicated confirm the presence of restriction. The severity of restriction was determined according to the results of FVC as follows [7]: mild restriction: FVC 60–80%, moderate: FVC 40–59%, and severe restriction: FVC less than 40%.
4. High-resolution computed tomography (HRCT) of the chest.
5. Echocardiography: Assessment of pulmonary artery systolic pressure.
6. Measurement of arterial blood gases (ABG): One ml of arterial blood was obtained from the radial artery in a heparinized needle and then taken immediately to a blood gas analyzer (pHOx plus C) to assess the PH, PaO_2, $PaCO_2$, and SaO_2. Calculation of alveolar-arterial oxygen pressure difference (PA-a O_2) was carried out.

The two groups; the patients, and the control group were subjected to Cognitive assessment tests, which included the following:

1. Wechsler Adult Intelligent Scale (WAIS).

2. Mini Mental State Examination (MMSE) test.

Cognitive function assessment
Wechsler Adult Intelligent Scale (WAIS)
Wechsler adult intelligent scale (WAIS) is an intelligent IQ test that measures the intelligence and cognitive function in adults and older adolescents (Fig. 1) [8].

WAIS score
The WAIS is an IQ test that is given by psychologists and measures global intellectual function, it includes both verbal and non-verbal components. The WAIS report subtests score are labeled; extremely low for 4 and below, borderline for 5–6, low average for 7, average for 8–11, high average for 12–13, superior for 14–15, and very superior for 16 and up.

The average score for all test and subtest is 100; thus, a score above 100 is above average and below 100 is below average [9]. The examinee is given three basic scores: verbal IQ, performance IQ, and full IQ.

Analyzing WAIS score
The first step in analyzing score is to look at the WAIS composite score and the IQ, where the average score is 100. Anything from 90 to 109 is considered average. Score from 110 to 119 is considered high average, from 120 to 129 is superior, and from 130 and up is very superior. On the other end of the spectrum, from 80 to 89 is considered below average, 70 to 79 is borderline and from 69 and below is extremely low. Once the scores are interpreted, the next step is to check for strength and weakness of each test and subtest.

Calculation of Wechsler Deterioration Index (WDI)
This is a ratio between two groups of subtests:

The first group of subsets includes four subtests that are little affected with age:

- Comprehension.
- Picture completion.
- Information (or vocabulary).
- Object assembly.

The second group of subsets includes those that show more rapid decline with age:

- Arithmetic.
- Digit span.
- Block design.
- Digit symbol.

A ratio derived from the two groups of subtest; provides the deterioration index or estimate of mental
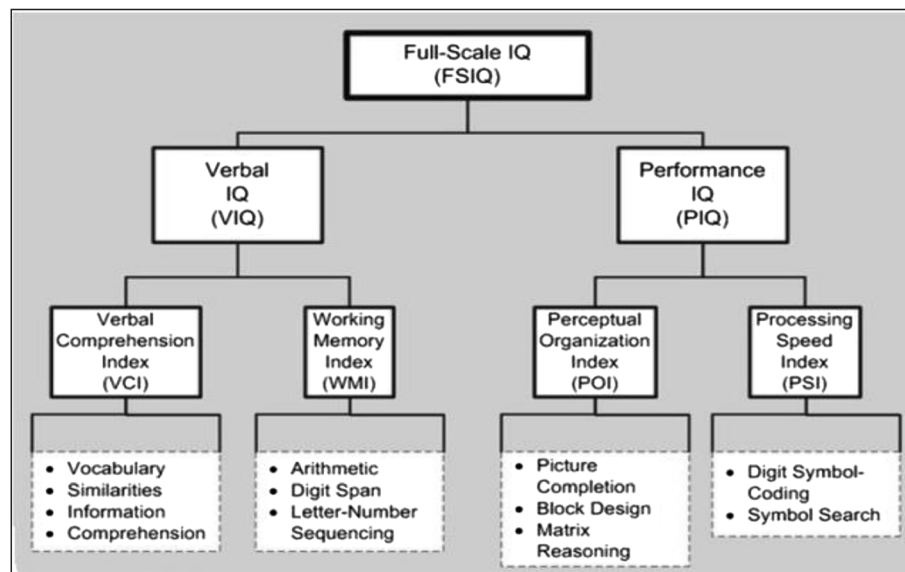
Fig. 1 WAIS major components

decline. This index can be compared for the average or normal decline with age.

Significant deviation from the normal pattern for a specific age group is then considered indicative of deterioration [10].

The interpretation of the test is as the following:

- < 10: no deterioration.
- 10–< 18: deterioration may be present.
- ≥ 18: Sure deterioration.

Mini-Mental State Examination (MMSE)

Administration of MMSE takes between 5 and 10 min; it consists of 11 questions that measure 5 areas of cognitive function which include registration, attention and calculation, recall, and language, ability to follow simple command, and orientation. The maximum score is 30, a score of 23 or lower is indicative of cognitive impairment [11].

A copy of mini-mental state examination questionnaire is attached at the end.

Statistical analysis

Sample size was calculated and data were coded and entered using the statistical package SPSS version 25. Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparison between both groups was done using independent sample t test or Mann-Whitney rank sum test or chi-square when appropriate. Correlation between quantitative variables was done using Pearson

correlation coefficient, P values less than 0.05 were considered as statistically significant.

Results

Patients' characteristics

In total, 30 patients with a diagnosis of IIP and 20 healthy individuals were involved in the study. Patients' characteristics are shown in Table 1.

The median age of the patients with IIP was 44 years whereas the median age of the control group was 41.5. Also, there was no statistical difference between both groups as regards the sex and smoking habit.

Idiopathic pulmonary fibrosis represented 50% (n = 15) of the involved patients followed by non-specific interstitial pneumonia (40%, n = 12) and most of the patients had severe restrictive function. Advanced grade of dyspnea was present in seventeen patients.

Oxygenation parameters

The mean arterial oxygen pressure (P_aO_2) was 46.53 mmHg, the mean alveolar-arterial oxygen pressure (PA-a O_2) difference was 51.07 mmHg, and room air arterial oxygen saturation (SaO_2) was 82%.

Cognitive function of the studied groups

The patients' group was significantly associated with mental state disability (P = 0.03), also they had significantly lower MMSE score in comparison to the control group (P < 0.001) (Table 2).

The verbal IQ of the patients' groups was not significantly lower than the control one, (P = 0.07), even though some of its subscales (similarities, information, vocabulary, and comprehension) were significantly lower

Table 1 The clinical characteristic of the study population

Parameter	IIP$_S$ group (N = 30)	Control group (N = 20)	P value
Age (years)	44 (40–57)	41.5 (39.25–55.25)	0.38[^^]
Sex (female)	17 (56.67%)	10 (50%)	0.82[#]
Smoking (no)	21 (70%)	10 (50%)	0.25[#]
Pulmonary hypertension	14 (46.67%)		
IIP$_S$ types:			
DIP	2 (6.67)		
IPF	15 (50%)		
NSIP	12 (40%)		
RB-ILD	1 (3.33%)		
Severity of restriction:			
Mild	3 (10%)		
Moderate	10 (33.33%)		
Severe	17 (56.67%)		
Dyspnea score (mMRC):			
1	4 (13.33%)		
2	7 (23.33%)		
3	9 (30)		
4	10 (33.33)		
6MWD(meter)	148.67 ± 116.49		

Abbreviations: *IIP$_S$* idiopathic interstitial pneumonias, *DIP* desquamative interstitial pneumonia, *IPF* idiopathic pulmonary fibrosis, *NSIP* non-specific interstitial pneumonia, *RB-ILD* respiratory bronchiolitis-associated interstitial lung disease, *6MWD* 6 minute walk distance
Numerical data normally distributed represented as mean ± SD and data not normally distributed represented as median (Q1–Q3), categorical data as number (%)
^^Mann-Whitney rank sum test
[#]Chi-square; *N* number, significant *P* value < 0.05

with P = 0.003, 0.007, 0.01, and 0.002, respectively. In the same way, the performance IQ was not significantly decreased in the patients in comparison with the control subjects, and in spite of that, some of its subscales were significantly lower in the patients' group; block design, matrix design, and digit symbol (P = 0.002, 0.024, and 0.03), respectively. At the end, the total WAIS IQ score was not lower enough to be significant in patients' group (P = 0.14) (Table 3).

According to the Wechsler Deterioration Index, it was found that 33.3% (n = 10) of the patients with IIP had sure cognitive impairment and 26.6% (n = 8) had ongoing cognitive deterioration.

Correlation between cognitive functions and the oxygenation parameters

There was statistical significant positive correlation between PaO_2 and performance IQ while a non-significant positive correlation between performance IQ and SaO_2, and negative correlation with $PA\text{-}aO_2$ difference (Table 4).

Comparison between IPF and other IIP$_S$

Table 5 shows that MMSE score was significantly lower in IPF patients, also the cognitive disability significantly affecting IPF patients [(P = 0.01 and 0.05), respectively]. Besides, the verbal IQ was significantly affected (P = 0.05).

Discussion

In the current study, the UIP/IPF accounts for almost 50% (n = 15) of the all cases followed by NSIP which accounts for 40% (n = 12), while all other patterns accounts for almost 10% (DIP 6.6% &RB-ILD 3.3%) (Table 1). This matches with Raghu and co-workers [12] who named IPF as the most common form of IIP$_S$, and Kim and colleagues [13] who stated that UIP/IPF ranges between 47 and 64% from the whole populations in

Table 2 Mini Mental State Examination of the studied groups

Parameter	IIP$_S$ group		Control group		P value
MMSE (number of affected patients)	10	33.33%	1	5%	0.03[#]
MMSE score	25	(22–28)	29.5	(28–30)	< 0.001[^^]

Numerical not normally distributed data represented as median (Q1–Q3), categorical data as number (%)
^^Mann-Whitney rank sum test
[#]Chi-square; significant *P* value < 0.05

Table 3 Wechsler Adult Intelligent Scale (WAIS) in both groups

Parameter	IIP$_S$ group		Control group		P value
Total IQ	86.17	11.42	90.6	8.62	0.14
Verbal IQ	85.93	12.39	92.4	11.95	0.07
Arithmetic	5	(3–7)	6	(5.25–8)	0.1
Digit span	7	(4–8.25)	7	(7–8)	0.3^^
Similarities	7.37	1.92	9	1.622	0.003^
Information	5	(5–7)	7	(6–7)	0.007^^
Vocabulary	6.5	(5–8)	8	7–9	0.01
Comprehension	9.03	2.98	11.75	2.92	0.002^
Performance IQ	91.3	12.73	92.85	10.21	0.65
Block design	5.73	1.70	7.25	1.52	0.002^
Matrix design	7	(5–8)	7	(7–9)	0.024^^
Visual puzzle	7.83	2.42	9.10	2.36	0.07^
Picture completion	6.5	(5–7)	7	(7-8)	0.08^^
Digit symbol	6.63	1.65	7.85	2.30	0.03^

Normal numerical data represented as mean (SD) and abnormal one as median (Q1–Q3), categorical data as number (%)
^Independent sample *t* test
^^Mann-Whitney rank sum test, significant *P* value < 0.05

different studies, and RB-ILD/DIP ranges between 10 and 17%. While Belloli and co-workers [14] stated that idiopathic NSIP incidence is almost half the incidence of IPF.

There was a female predominance in IIP patients (female:male ratio = 1.3:1), while in Lee et al. 2011 [15], there was a reverse in the ratio female:male = 1:1.58.

It has been stated that UIP/IPF is more prevalent in males and mortality is higher too [16] that was attributed to more deterioration in exercise desaturation over time in comparison to females and a suggestion of uncharacterized sex related effect [17]. However, in our study, the female:male ratio in this pathological entity was 11:4.

In the USA, from 1992 to 2003, the age adjusted mortality rate increased 28.4% in men and 41.13% in women,

Table 4 Correlation of oxygenation parameters, with MMSE and WAIS (total IQ, verbal IQ, and performance IQ)*

		MMSE	Total IQ	Verbal IQ	Performance IQ
PaO$_2$,	*r*	0.207	0.266	0.116	0.396
	P value	0.273	0.156	0.542	0.030
SaO$_2$	*r*	0.185	0.140	0.010	0.311
	P value	0.327	0.460	0.959	0.095
PA-aO$_2$	*r*	− 0.250-	− 0.276	− 0.207	− 0.315
	P value	0.182	0.140	0.273	0.090

Abbreviations: *PaO$_2$* arterial oxygen tension, *SaO$_2$* arterial oxygen saturation, *PA-aO$_2$* alveolar-arterial oxygen pressure difference, *MMSE* Mini Mental State Examination, *WAIS* Wechsler Adult Intelligent Score
*Pearson correlation, the sign before (*r*) represent the direction of correlation, while *P* represents the significant of correlation, significant *P* value < 0.05

with significant increase all years in both sexes especially females [18].

Almost all patients were presented with moderate to severe restriction pattern by spirometry (Table 1). A picture which by itself may reflect the presence of concomitant cognitive dysfunction as was mentioned by Lutsey and co-workers [19], who studied 14,184 participants with spirometry and found that midlife lung disease and reduced lung functions were associated with modestly increase odds of mild cognitive dysfunction. Almost 33% of the patients had dyspnea grade 4, a very distressing symptom associated with increased rate of depression and decrease functional status [20]. This late presentation is proved by presence of respiratory failure type 1, where the mean PaO$_2$ was 46.5 + 11.85 mmHg, and arterial oxygen saturation was 82%. The mean alveolar-arterial oxygen pressure difference was 51.07 + 14.63 mmHg. It was suggested that hypoxia may cause gradual prefrontal deoxygenation which leads to alternating short term memory and executive functions at earlier stages followed by cognitive dysfunctions at later stages [21].

Almost half of the patients (46.67%) presented with echo-cardiographic picture suggestive of pulmonary hypertension as a complication of the disease. Despite that Anderson and co-workers, 2012 [22] stated that the incidence of pulmonary hypertension was 14%. Subsequent studies have increased this percentage to be between 32 and 50% [23].

As regards IPF, Collum and colleagues [24] highlighted the difficulty in defining the prevalence of pulmonary hypertension due to differences in the underlying disease severity, diagnostic modality, and patient population.

The late presentation of the patients was seen reflected on the exercise capacity of the patients, which showed 6-MWT distance 148.67 ± 116.49 meters. This late presentation also affects the intellectual and cognitive functions of the patients. The importance of this test lies in being an independent predictor of mortality in IPF patients, where the presence of 6 MWD < 250 meters carries two fold increase in the risk of mortality as stated by du Bois and co-workers [25].

Interstitial lung disease (ILD) is a chronic condition with distressing dyspnea, progressive worsening of exercise tolerance, and decreased life expectancy. Many researchers studied depression and anxiety in ILDs being prevalent [20]. However, very few researchers tackled the cognitive impairment. Soliman and colleagues [26] studied cognitive auditory functions in IIP$_S$ patients and proved the presence of cognitive dysfunction in these patients.

In this study, cognitive function was assessed using Wechsler Adult Intelligent Scale (WAIS). There was a significant difference between both groups in terms of verbal

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Table 5 Comparison between IPF patients and other IIP$_S$ patients

Parameter	IPF (N = 15)		Other IIP$_S$ (N = 15)		P value
MMSE score	23.66	2.82	26.4	2.80	0.01^
MMSE (number of affected patients)	8	53.33	2	13.33	0.05#
Total IQ	82	(27–90)	91	(89–94)	0.06
Verbal IQ	81.66	13.91	90.2	9.26	0.05
Performance IQ	88.60	14.05	94.00	11.07	0.25

Abbreviations: *IPF* idiopathic pulmonary fibrosis, *IIP$_S$* idiopathic interstitial pneumonias, *MMSE* Mini Mental State Examination, *N* number
Normal numerical data represented as mean (SD) and abnormal one as median (Q1–Q3), categorical data as number (%)
^Independent sample *t* test
#Chi-square; significant *P* value < 0.05

IQ subclasses (similarities, information, vocabulary, and comprehension) and some of items of the performance IQ subclasses (block design, matrix design, and digit symbol) (Table 3). Also, when performing MMSE, there was a statistical significant difference between both groups also (Table 2), which proves the presence of lower level of cognitive function in patients with idiopathic interstitial pneumonias in comparison with the healthy control group.

Furthermore, we calculated the deterioration index which is a pattern of subtest score on WAIS. It was attributed to David Wechsler, (Wechsler Deterioration Index (WDI)).

WDI is viewed as a suggestive of decline from the baseline function [27]. It was found that IIP had evident effect on 33.3% of cases and the process was ongoing in 26.6% of the cases which proves the presence of deterioration in general cognitive status of patients with IIP$_S$.

Bors and colleagues [28] studied cognitive function in IPF patients using five neurophysiological tests and concluded that there was significant affection suggesting inferior performance on tasks requiring speed divided attention and memory. The outcome has shown that participants with severe IPF had worse cognitive function than mild IPF or control subjects.

When classifying the patients' group into IPF and other IIP$_S$ group; the IPF patients showed significant decrease of the verbal IQ (*P* = 0.05). On the other hand, the performance IQ was not significantly decreased in IPF patients in comparison with other IIPs patients (Table 5). At the end, the total WAIS IQ score was not significantly lower enough in IPF patients in comparison with other IIPs (*P* = 0.06). These findings reflect that verbal concept formation, knowledge, as well as visual intelligence and perceptual organization were affected.

Up till now, no study was done to compare cognitive disability between IPF and other IIPs types. However, the difference could be attributed to the common prevalence of IPF, compared to other types of IIPs. IPF also advances more rapidly in some individuals and may slowly progress in others [4].

It is worth to mention that the correlation between both WAIS with its subclasses and MMSE with the oxygenation parameters showed positive significant correlation between the PaO$_2$ and the performance subscale of WAIS, and positive non-significant correlation with SaO$_2$, and this carry a hope for performance improvement with improvement of oxygenation.

Conclusion
There is an impairment of cognitive function in patients with major IIP, particularly in IPF, as measured by WDI and MMSE. Further large studies are needed to assess the possible predictors of cognitive impairment and their effects on the patients' outcome.

Supplementary Information

> **Additional file 1: Table S1.** Mini mental state examination.

Abbreviations
IIP: Idiopathic interstitial pneumonia; WAIS: Wechsler Adult Intelligent Scale; MMSE: Mini Mental State Examination; WDI: Wechsler Deterioration Index; IPF: Idiopathic pulmonary fibrosis; NSIP: Non-specific interstitial pneumonia; COP: Cryptogenic organizing pneumonia; AIP: Acute interstitial pneumonia; RB-ILD: Respiratory bronchiolitis-associated interstitial lung disease; DIP: Desquamative interstitial pneumonia; mMRC: Modified Medical Research Council scale; 6-MWT: Six minute walk test; FEV1: Forced expiratory volume in the first second; FVC: Forced vital capacity; FEF: Forced expiratory flow; HRCT: High-resolution computed tomography; ABG: Arterial blood gases; PaO$_2$: Arterial oxygen pressure; PaCO$_2$: Arterial carbon dioxide pressure; SaO$_2$: Arterial oxygen saturation; PA-aO$_2$: Alveolar-arterial oxygen pressure difference; UIP: Usual interstitial pneumonia; ILD: Interstitial lung disease

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