PERSISTENT FATIGUE POST COVID-19 INFECTION: A GROWING DILEMMA IN EGYPTIAN CHILDREN

By

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ABSTRACT

Background: Fatigue represents high incidence among the children with long Covid illness, multiple consequences are associated with disease including deteriorated school performance and social family burden, in this study we aimed to detect the pattern of chronic fatigue in children post COVID -19 infection and the possible risk factors.

Patients and methods: A cross section study included 140 patients with confirmed COVID-19 infection recruited from Cairo university pediatric hospital during the period from September 2020 to September 2021, they were selected by simple random method. All patients were interviewed with the fatigue scale (CFQ-11) to assess the degree of fatigue and relate it to multiple predisposing factors.

Results: The study included 140 patients 3-18 years old, they were 86 (61.4%) males, and 54 (38.6%) females, the incidence of fatigue was 67.9% according to the fatigue scale, the severity of the fatigue increased with the severity of the symptoms, hospital admission, and the presence of underlying diseases.

Conclusion: chronic fatigue post Covid-19 infection is a growing dilemma in Egyptian children. It is related to different clinical and radiological factors. Proper history taking with specified scales and regular follow up are important to reduce the hazards of this growing problem.

Keywords: Fatigue, Covid-19, children.

INTRODUCTION

Long COVID illness is defined as the ongoing, reappearing, or the new symptoms that develop during or after COVID-19 infection lasting for four or more weeks **(Chen et al, 2022)**.

Long COVID illness is associated with numerous symptoms including fatigue, headache, muscle and joint pain, insomnia, respiratory manifestations, palpitations of the heart, and gastrointestinal problems. Recent studies describe more than the half of the affected children complained of at least one symptom for more than 120 days **(Buonsenso et al, 2021)**. Easy fatigability, learning and memory affection are among the primary characteristics of this syndrome especially in adolescents. The illness is characterized by the uniqueness and unpredictability of its symptoms in the youngsters **(Jason et al, 2006)**. In the current work we aimed to study the epidemiological pattern of chronic fatigue after COVID-19 infection in Egyptian children. To date, this is the first study to assess the incidence of chronic fatigue post COVID- 19 infection and detect its relationships with multiple risk factors. Better understanding of the disease improves the management and help to advance school achievement of the children and lessen the burden on the family.

Ethical considerations:

- The study was approved from the Scientific Research and Ethical Committee of pediatrics department, faculty of medicine, Cairo University.

- The patients had the right to withdraw from the study at any time.

- The researcher explained to the patients the aim of the study before participating.

- Consents were taken from the guardians to participate in the questionnaire.

- The authors declared no potential conflict of interest with respect to authorship, research, and /or publication of this article.

- All the data of the patients and results of the study are confidential; the patients have the right to keep it.

- The authors received no financial support for the research and/or publication of the article

Calculation of sample size:

Using EPI INFO sample size calculator; with 0.05 alpha error,

confidence interval of 0.95 and power of the study 0.80. The minimum sample size calculated to detect post COVID-19 fatigue in children is 134 confirmed Covid cases.

Inclusion criteria:

The study included all children 3-18 years with confirmed history of COVID-19 based on the criteria of the Egyptian practical Protocol for Covid-19 (**Mostafa et al, 2020**).

Exclusion criteria:

The study excluded:

- Patients >18 years

- Unconfirmed diagnosis of COVID-19

- History of any debilitating chronic diseases.

Patients and methods

This is a cross section study that included 140 children and adolescents who were diagnosed with COVID-19 during the pandemic period. They were recruited from Cairo University Pediatric Hospital over one year from September 2020 to September 2021. For all patients the following was done:

1. Medical history including:

- Demographic data,

- History of underlying diseases e.g., chronic respiratory disease (bronchial asthma, allergic rhinitis), diabetes, malnutrition, anaemia.

- Symptoms related to COVID-19 and duration of symptoms/days.

- History of hospital admission and history of subsequent complications (respiratory failure, bleeding, and thromboembolic manifestations)

- Post COVID-19 symptoms (persistent for 4-6 weeks after acute disease) e.g., post viral cough, fatigue, both cough and fatigue, and fatigue related history (insomnia, attention problems, inability of doing usual exercise, and prolonged sleep).

2. Medical examination including vital signs, cardiac, chest, abdominal, and neurological examination.

3. Validated Chalder Fatigue Scale (CFQ-11) was used to assess fatigue in our patients (**Chalder, 1993**), where the participants are asked to answer specific questions with reference to the past month in comparison to their pre-COVID-19 baseline, with responses measured on a Likert scale (0–3). The sum is calculated and those with a

total score of four or greater considered to meet the criteria for fatigue (**Jackson, 2015**). They are classified to normal (score <4), moderate fatigue (score 4-15), and sever fatigue (score 16- 33).

4. **The patients' files were reviewed for laboratory results** (complete blood picture, C reactive protein, ferritin, D dimer) and radiological results of Chest x-ray and computed tomography (CT).

Statistical analysis:

Statistical analysis was conducted using SPSS (Statistical Package for Social Sciences), version 22 (SPSS Inc., Chicago, IL). Numerical data were described as mean and standard deviation or median and interquartile range after normality testing. Categorical variables were compared using chi square. Logistic regression model was conducted to assess risk factors for orthostatic intolerance. A p-value $\leq$ 0.05 will be considered statistically significant.

RESULTS

Our results will be demonstrated in the following tables:

Table (1): Demographic data of the studied patients

Demographic data	N (%)
Age (years)	
<12	50 (35.7%)
12-15	69 (49.3%)
>15	21(15%)
Gender	
Male	86 (61.4%)
Female	54 (38.6%)
Residence	
Urban	82 (58.6%)
Rural	58 (41.4%)

The commonest age of our patients was 12-15 years

Table (2): Clinical characteristics of the studied group

Clinical parameter		N (%)
History of underlying disease	Yes	32(22.9%)
	No	108 (77.1%)
Type of underlying disease	Chronic respiratory	12 (8.5%)
	Malnutrition	9 (6.4%)
	Anemia	9(6.4%)
	Diabetes	2(1.4%)
Duration of symptoms/days	<10	36 (25.7%)
	10-15	49 (35%)
	>15	27(19.3%)
Severity of Covid symptoms	Asymptomatic	28 (20%)
	mild	60(42.9%)
	Moderate	30(21.4%0
	Sever	22(15.7%)
History of hospital admission	Yes	24 (17.1%)
	No	116(82.9%)
History of critical illness and PICU admission	Yes	19(13.6%)
	No	121 (86.4%)
History of complications	Yes	21 (15%))
	No	119(85%)

As seen in the **table (2)**, the most common underlying disease in our patients was the chronic respiratory diseases (bronchial asthma, allergic rhinitis) in 12(8.5%) patients. 24 of our patients needed hospital admission for observation and fluid replacement.

Table (3): Clinical presentations in studied group during Covid-19 illness

Clinical symptoms	N (%)
Asymptomatic	28(20%)
Dyspnea/tachypnea	63(45%)
Fever	62(44.3%)
Fatigue	60(42.9%)
Cough	56(40%)
Headache	56(40%)
Nasal congestion/rhinorrhea	55(39.3%)
Vomiting/diarrhea/abdominal pain	54(38.6%)

The most common presentations were dyspnea/ tachypnea in 63 (45%) patients followed by fever in 62 (44.3%) patients. The least presentation was the gastrointestinal manifestations in 54 (38.6%) patients.

Table (4): Distribution of the studied patients' group regarding radiological findings

Radiological finding	N (%)
Chest x-ray	
Normal	67(47.9%)
Positive findings	73(52.1%)
CT chest	
Normal	113(80.7%)
Pneumonic patches	15(10.7%)
Ground glass	12(8.6%)

As shown in **table 4** most of our patients (80.7%) showed no abnormality in chest CT, while 52.1% of our patients had positive radiological finding in the chest X ray

Table (5): Frequency of post viral symptoms among the studied group

Post viral symptoms	N (%)
Post viral cough	
No	83(59.3%)
Yes	57(40.7%)
Fatigue	
No	78(55.7%)
Yes	62(44.3%)
Cough and fatigue	
No	93(66.4%)
Yes	47(33.6%)
Fatigue related history	
No	75(53.6%)
Insomnia	15(10.7%)
Attention problems	13(9.3%)
Inability of doing usual exercise	17(12.1%)
Prolonged sleep	20(14.3%)

As shown in **table (5)** fatigue and fatigue related symptoms were the most frequent complains post viral infection among our patients (44.3, 64.3% respectively).

Table (6): Relation between results of fatigue scale (CFQ-11) and the clinico-demographic characteristics of the patients

Parameter		Results of fatigue score N (%)			P value
		Normal (<4) 45(32.1%)	**Moderate (4-15) 60(42.9%)**	**Severe (16-33) 35 (25%)**	
Gender	male	26(57.8%)	43(71.7%)	17(48.6%)	0.069
	female	19 (42.2%)	17(28.3%)	18(51.4%)	
Residence	Urban	23(51.1%)	36(60%)	23(65.7%)	0.403
	Rural	22(48.9%)	24 (40%)	12(34.3%)	
History of underlying disease	Yes	32 (71.1%)	0	0	**0.001**
	No	13 (28.9%)	60 (100%)	35 (100%)	
Duration of illness	<10	13(29.4%)	18(30%)	13(37.1%)	0.151
	10-15	24(52.9%)	31(51.6%)	9 (25.8%)	
	>15	8(17.7%)	11(18.4%)	13(37.1%)	
Severity of the symptoms	Asymptomatic	28(62.2%)	0	0	**0.001**
	mild	17(37.8%)	43(71.7%)	0	
	moderate	0	17(28.3%)	13(37.1%)	
	sever	0	0	22(62.9%)	
Hospital admission	Yes	0	0	24(68.6%)	**0.001**
	No	45(100%)	60 (100%)	11(31.4%)	
History of PICU admission	Yes	0	0	19(54.3%)	**0.001**
	No	45 (100%)	60(100%)	16(45.7%)	
Complications	Yes	0	17(28.4%)	4 (11.4%)	**0.001**
	No	45(100%)	43(71.6%)	31(88.6%)	

As shown in the previous table the degree of fatigue assessed according to the questionnaire had statistically significant relations with the presence of underlying disease, history of hospital admission, the severity of the symptoms, and the presence of complications (p=0.001).

Table (7): Relation between score for fatigue regarding radiological findings

Radiological findings	Normal N (%)	Moderate N (%)	sever N (%)	P value
Chest x-ray				
Normal	23(51.1%)	26(43.3%)	18(51.4%)	0.65
Positive findings	22(48.9%)	34(56.7%)	17(48.6%)	
CT chest				
normal	45(100%)	54(90%)	14(40%)	**0.001***
Pneumonic patches	0	6(10%)	9(25.7%)	
Ground glass	0	0	12(34.3%)	

As shown in **table 7**, there was statistically significant relation between the degree of fatigue and the CT findings of the patients (p=0.001).

DISCUSSION

Corona virus disease (COVID-19), which was brought on by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), has resulted in a pandemic that has spread over the whole world (**Valdez & Infante, 2021**). Individuals who have previously been infected with SARS-CoV-2 are known to report feelings of fatigue more frequently than any other long-term symptom (**Ceban et al, 2022**). Post-COVID-19 fatigue is defined as a reduction in the individual performance physically and/or mentally as a result of abnormalities in central, psychological and/or peripheral factors resulting from COVID-19 infection (**Rudruff et al, 2020**). Even though a lot of work has been put into trying to understand what causes weariness, our present understanding is still somewhat restricted (**Joli et al, 2022**). The precipitating pathophysiology may be due to widespread activation of the glial cells which is perhaps related to metabolic dysfunction or to the enormous immune activation in the periphery (**Nath, 2020**).

We conducted a cross section study aiming to evaluate children and adolescents with confirmed COVID-19 illness for chronic fatigue syndrome (CFS). To our knowledge this is the first study to assess fatigue post COVID-19 infection among Egyptian children. We included 140 children, their age ranges from 3

to18 years, the commonest age was 12-15 years old, males outnumbered the females accounting for 61.4% of our patients, more of our patients (58.6%) were from urban areas.

These findings were similar to ones reported by Say et al., who assessed 171 children, they reported that males outnumbered females as the study included 90 (53%) boys and 81 (47%) girls, however they reported commonly younger age of their patients (0-2 years) **(Say et al, 2021)**.

In a more recent study, **Osmanov et al, 2022** reported higher median age of 10.4 years, however, they reported nearly similar sex distribution of cases with slightly higher percentage in females (52%).

In the present study 28 (20%) patients were asymptomatic, 60 (24.9%) were having mild symptoms, which were lower than similar study done in Australia and reported rate of 36% asymptomatic children, and 58% with mild disease **(Say et al, 2021)**, this is perhaps due to different socioeconomic level with its effect on the general health and availability of medical services. The most common presenting symptoms in our patients were dyspnea/ tachypnea present in 63 (45%) patients followed by fever

in 62 (44.3%) patients, different presentations were reported by another study in Russia, they reported fever as the most common presentation (83.6%) followed by cough (55.7%) **(Osmanov et al, 2022)**. In the current study 24 (17.1%) patients required admission to the hospital mainly for observation and rehydration, this ratio was higher than the Australian study which reported 8% hospital admissions, possibly due to early seeking of medical care and the known strict control measures applied in Australia, their admissions were generally brief and for mild causes like ours **(Say et al, 2021)**.

History of persistent fatigue and its related symptoms (4-6 weeks after acute illness) were found in 65 (46.4%) patients, they complained mostly from prolonged sleep and inability to do usual exercise. Nearly similar fatigue rate (32%) was reported by another study done on Italian children, their patients complained of persistent symptoms which was mainly fatigue, muscle and joint pain, and sleep disturbances **(Buonsenso et al, 2022)**. A similar study done on Russian children reported fatigue as the most common persistent symptom after COVID-19 infection but with a lower ratio (10.2%) than ours **(Osmanov et al, 2022)**. These

different rates possibly because fatigue is a multifactorial problem. It may be attributed to the degree of inflammation, the presence of psychiatric disorders or cognitive dysfunction or simply due to the inaccuracy in case of self-reporting symptoms. Similar study on Bangladeshi adults assessed 1,002 patients who were diagnosed with mild to severe COVID-19 found that chronic fatigue was experienced by around 12% of their patients **(Islam et al, 2021)**. Several studies on adults found that fatigue remained one of the primary long-term symptoms even after a longer follow-up period **(Townsend et al, 2020)**, **(Rosalis-Castello et al, 2021)**, **(Mahmud et al, 2021)**.

After interrogating our patients and their parents according to the fatigue questionnaire (CFQ-11), 45 (32.1%) patients were found to have insignificant complaints (normal chart results), and 95 (67.9%) patients had moderate to severe score of fatigue according to the scale, there was no similar studies on children using the same fatigue scale to compare our results but a study done on adult population reported rate of (52.3%) on the same fatigue scale **(Townsend et al, 2020)**.

In the current study we didn't establish significant relation between the severity of the fatigue and the gender of the patients (p= 0.069), which contrasted a study done on a large cohort of 355 patients with mild to severe COVID-19, they found that fatigue being the main long-term symptom was significantly higher in females **(Mahmud et al, 2021)**. Hormonal changes are the suggested trigger of this gender prevalence. We didn't establish a relation between the degree of fatigue and socioeconomic level of the patients (rural or urban residence) (p=0.403) which was parallel to the results of other study where they found that chronic fatigue post Covid-19 infection affect all socioeconomic levels **(Sudre et al, 2021)**.

On linking the results of the fatigue scale and the clinical features of our patients we found that the severity of fatigue is increased with the presence of underlying disease, with history of hospital admission, the severity of the symptoms, the presence of complications, and the presence of abnormality in the chest CT (p=0.001), yet it is not related to the duration of illness (p=0.151). Our findings were comparable to other study stated that the presence of comorbidities increases the risk of developing post COVID syndrome, even with mild symptoms at initial presentation **(Sudre et al, 2021)**.

Furthermore a study on Egyptian adults showed that female sex, the presence of comorbidities, lower degree of education, longer disease duration, as well as severe and critical forms of the disease were significantly associated with the presence of post-COVID fatigue (**Abdellhafiz et al, 2022**). Our findings disagree with one study on adults showed that more than 50% of patients were suffering from fatigue, yet there was no association between development of fatigue, and the severity of infection, and hospital admission (**Townsend et al, 2020**).

CONCLUSION

Egyptian children with persistent fatigue post COVID-19 infection are a growing dilemma. The severity of fatigue is related to the presence of underlying disease, history of hospital admission, the severity of the symptoms, the presence of complications, and radiological finding in chest CT. The severity of the fatigue is not affected by the gender of the patients nor the socioeconomic level.

RECOMMENDATIONS

- Proper history taking with specified fatigue scales is required for accurate diagnosis.

- Regular follow up of those patients in specific fatigue clinic is highly recommended to lessen the social burden on the family and advance school performance.

LIMITATIONS OF STUDY

This study was limited by relatively small number of patients as it was done in a single center, lack of follow up visits of the COVID-19 patients after the recovery from the acute illness, Missing of some clinical and laboratory data in the files.

Authors' contributions:

LAI: Concept and design of the study, manuscript preparation and drafting of the article. **EEM:** collection of cases, analysis, interpretation of data. **RII:** concept, and design of the study, analysis of data, and final approval of the version to be published. **EFF** shared in design of the study, interpretation, analysis of data, and review the literature. All authors had full access to the data (including statistical results and tables), approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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