ORIGINAL ARTICLE

POST COVID-19 POSTURAL TREMOR, A POSSIBLE NEUROLOGICAL COMPLICATION.

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ABSTRACT

Background: The COVID-19 pandemic can be considered as one of major global health disasters that massively overwhelmed the health scene in the whole world and can be compared to the scale of 1918 influenza pandemic. The neurological manifestations and the subsequent complications reported with COVID-19, have been increased recently while the pandemic still going ahead.

Methods: this study included the patients with neurological complaints presented to neurology outpatient clinic after had been infected with COVID-19 during the first wave of the current pandemic, and have been divided into two groups according to presence or absence of tremor. Their tremor has been evaluated using TETRA score.

Results: 39 patients mainly from males out of total 105 patients who were included in our study, presented mainly with tremor of essential tremor character.

Conclusion: tremor has been found as a possible post COVID-19 neurological complication without clear evidence for cerebral or cerebellar abnormalities

INTRODUCTION

Patients with COVID-19 (Coronavirus-2019) mostly present with mild clinical manifestations, initially with fever and dry cough, then with mild to moderate respiratory disease, that may resolve without specific treatment [1]. The main concern in COVID-19 patients is the development of serious complications of that infection. Acute respiratory distress syndrome (ARDS), acute renal, cardiac or other organs' involvement, sepsis, disseminated intravascular coagulation (DIC), and serious metabolic changes have all been reported in COVID-19 patients, more in those with comorbidities and/or in the elderly [2-3]. The most commonly reported neurological complications of COVID-19 are ischemic vascular insults, then encephalopathy, encephalitis, oculomotor nerve palsy, isolated sudden-onset anosmia, Guillain–Barré syndrome, and Miller–Fisher syndrome [4]. Two patients were diagnosed with tremor (physiologic and probable functional) among 50 neurological consultation requests beside myoclonus, seizures and serotonin syndrome were reported as abnormal involuntary movements in patients with COVID-19 [5].

METHODS

In this cross sectional study, we included 105 patients who visited neurology outpatient clinic, they were infected by COVID-19 during the first wave of this pandemic, in the duration from January to June 2020, with post COVID-19 neurological symptoms. They were classified into two groups: one group with tremor and another without. Patients with tremor were evaluated by The Essential Tremor Rating Assessment Scale (TETRAS) and were followed up for 3 months. Patients with chronic illnesses like chronic hepatic, renal or cardiac diseases, those on regular medications known to induce tremor, those who are alcohol consumers, those with history of tremor, parkinsonian features or other neurological disorders before the onset of COVID-19, patients with psychiatric disorders, were excluded. All patients were screened with liver, kidney and thyroid function tests. One patient with high level of free T4 was excluded. All patients were screened with plain brain MRI. Two patients with subtle basal ganglionic or cerebellar abnormalities were excluded. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

STATISTICAL ANALYSIS

The collected data were computerized and statistically analyzed using SPSS program

(Statistical Package for Social Science) version 18. Qualitative data were represented as frequencies and relative percentages. Quantitative data were expressed as mean ± standard deviation (SD). Independent T-test and Mann Whitney test were used when appropriate. Pearson correlation coefficient was used to calculate correlation between quantitative variables. The validity of data was calculated using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. A p-value ≤0.05 indicates significant results.

RESULTS

Our study included 105 patients, 7 of them were females (6.7%), and 98 were males (93.3%), their age ranged from 23 to 75 years. Patients with tremor were 39 patients (37 males and 2 females) (fig. 1), with age range from 23 to 75 years, while those without tremor were 66 patients (61 females and 5 males) with age range from 36 to 71 years. None of our patients was alcohol consumer, and 13 patients were current cigarette smokers (12.4%). Those with positive family history of tremor other than parkinsonian were only 3 patients (2.9%), while those with family history who were diagnosed with Parkinson's disease, were 5 patients. Patients who had chest symptoms as initial COVID-19 symptoms were 46 patients (43.8 %), 2 of them (5.1%) developed tremor later (table 1). Patients who had anosmia and aguesia were 69 (65.7%), and 21 of

them developed tremor (53.7 %). From all patients, 41 required intensive care unit (ICU) admission, 18 of them developed tremor. Management for COVID-19 according to WHO guidelines, was received by 16 patients, 4 of them developed tremor. Headache and fatigue were found in 13 (33.3 %) and 14 (35.9%) patients respectively in tremor group. On assessing patients with tremor by TETRAS, upper limbs were involved in all of them, while lower limbs were additionally involved in one of them. Semiologically tremor was in forward horizontal and lateral posture (100%), impaired spiral drawing was noticed in 97.4%, and failure of dot approximation in 79.5%. None of our patients had facial or head tremor (table 2). The development of tremor was highly significantly correlated with the duration of ICU admission (P ‹ 0.001) (table 3). Higher TETRAS score in patients with tremor was significantly correlated with ICU admission, lost smell and taste, and other associated post COVID-19 symptoms (table 4). The improvement of tremor was initially starting in the third week after onset of COVID-19 till eighth week with a peak at the fifth week, (fig. 2), where 34 patients recovered spontaneously, and only 5 required treatment for tremor [4 patients by propranolol (40-80mg daily), and 1 by gabapentin (300-600mg daily)] which continued for almost 4 weeks with gradual withdrawal without noticing any relapse

Table 1: Demographic & clinical data of the studied group:

Variable		Total (n=105)		Tremors (n=39)		No tremors (n=66)		Test	P
Age	Mean ± SD	52.3 ± 9.88		50.72 ± 11.64		53.24 ± 8.63		t	
	Range	23 - 75		23 − 75		36 - 71		1.27	0.21 NS
Sex	Female	7	6.7	2	5.1	61	92.4	χ^2	
	Male	98	93.3	37	94.9	5	7.6	0.24	0.63 NS
Smoking	No	92	87.6	34	87.2	58	87.9	χ^2	
	Yes	13	12.4	5	12.8	8	12.1	0.01	0.92 NS
Family history of tremors	-ve	102	97.1	38	97.4	64	97	χ^2	
	+ve	3	2.9	1	2.6	2	3	0.02	0.89 NS
Family history of PD	-ve	100	95.2	38	97.4	62	93.9	χ^2	
	+ve	5	4.8	1	2.6	4	6.1	0.66	0.42 NS
Days after onset	Mean ± SD	19.3 ± 5.03		19.1 ± 5.11		19.41 ± 5.02		t	
	Range	10 - 32		10 − 32		10 − 36		0.30	0.77 NS
Chest c	No	59	56.2	37	94.9	22	33.3	χ^2	
	Yes	46	43.8	2	5.1	44	66.7	**37.71**	**<0.001****
Smell and test loss	No	36	34.3	18	46.2	18	27.3	χ^2	
	Yes	69	65.7	21	53.8	48	72.7	**3.88**	**0.04***
GIT symptoms	No	102	97.1	38	97.4	64	97	χ^2	
	Yes	3	2.9	1	2.6	2	3	0.02	0.90 NS
ICU admission	No	64	61	21	53.8	43	65.2	χ^2	
	Yes	41	39	18	46.2	23	34.8	1.32	0.25 NS
Days of ICU	Mean ± SD	3.34 ± 1.67		2.83 ± 1.51		3.74 ± 1.71		MW	
	Median (Range)	3 (1 − 7)		2.5 (1 − 7)		3.5 (1 − 7)		1,86	0.06 NS

Variable		Total (n=105)		Tremors (n=39)		No tremors (n=66)		Test	P
COVID-19 management	No	89	84.8	35	89.7	54	81.8	χ^2 1.19	0.28 NS
	Yes	16	15.2	4	10.3	12	18.2		
Associated symptoms	No	8	7.6	8	20.5	0	0	14.66	<0.001**
	Cognitive	38	36.2	10	25.6	28	42.4	2.99	0.08 NS
	Fatigue	68	64.8	14	35.9	54	81.8	22.65	<0.001**
	Headache	67	63.8	13	33.3	54	81.8	24.96	<0.001**

Sd: Standard deviation t: Independent t test χ^2: Chi square test   MW: Mann Whitney test
NS: Non-significant (P>0.05)   *: Significant (P<0.05)   **: Highly significant (P<0.001)

Table 2: Tremors data among the studied group:

Variable		N	%
Posture	Yes	39	100
Resting	No	38	97.4
	Yes	1	2.6
		Mean ± SD	
Total Tetras	Mean ± SD Range	19.1 ± 5.11 10 - 32	
Voice	Mean ± SD Median (Range)	0.05±0.19 0 (0-1)	
Hand writing	Mean ± SD Median (Range)	0.12 ± 0.29 0 (0-1)	
Lower limb	Mean ± SD Median (Range)	0.05 ± 0.32 0 (0-2)	
Spiral	Mean ± SD Median (Range)	2.64 ± 1.27 2 (0 – 5)	
Dot approximation	Mean ± SD Median (Range)	1.54 ± 1.07 2 (0 – 5)	
Standing	Mean ± SD Median (Range)	0.04 ± 0.17 0 (0-1)	
Upper limb	Mean ± SD Median (Range)	6.21 ± 1.64 6 (4 - 8)	
Forward horizontal	Mean ± SD Median (Range)	2.97 ± 1.01 2 (2 – 4)	
Lateral posture	Mean ± SD Median (Range)	3.23 ± 0.99 4 (2 – 4)	
Finger to nose	Mean ± SD Median (Range)	0.05 ± 0.32 0 (0-2)	
Improvement (week)	Mean ± SD Range	5.56 ± 1.25 3 - 8	
		N	%
TTT of trmors	Yes	5	12.8
	Face	0	0
	Head	0	0
	Voice	3	7.7
	Hand writing	6	15.4
	Lower limb	1	2.6
	Spiral	38	97.4
Frequency	Dot approximation	31	79.5

Variable		N	%
	Standing	2	5.1
	Upper limb	39	100
	Forward horizontal	39	100
	Lateral posture	39	100
	Finger to nose	1	2.6

Table 3: Correlation between tremors score and age, days of onset, ICU and improvement among the Tremors group:

Variable		Tetras total (n=39)
Age (years)	r	0.12
	P	0.46 NS
Day after Onset	r	0.15
	P	0.35 NS
Days in ICU	r	**0.81**
	P	**<0.001****
Improvement (weeks)	r	-0.09
	P	0.58 NS

r:Pearson;s correlation coefficient   NS: Non-significant (P>0.05)   **:Highly significant (P<0.01)

Table 4: Relation between tremors score and different parameters among the tremors group:

Variable		N	Tetras score			t		P
			Mean	SD	Range			
Sex	Male	37	10.68	3.0714	5.0	18.5	0.30	0.76
	Female	2	10.00	2.8284	8.0	12.0		NS
Smoking	No	34	10.60	2.8385	5.0	17	0.20	0.84
	Yes	5	10.90	4.5332	7.0	18.5		NS
FH tremors	-ve	38	10.59	3.0533	5.0	18.5	0.62	0.54
	+ve	1	12.50	.	12.5	12.5		NS
FH of PD	-ve	38	10.74	3.0084	5.0	18.5	1.23	0.23
	+ve	1	7.0	.	7.0	7		NS
Chest c	No	37	10.45	2.8131	5.0	17	1.78	0.08
	Yes	2	14.25	6.0104	10	18.5		NS
Loss of smell & taste	No	18	8.14	1.4532	5.0	10	7.46	<0.001
	Yes	21	12.79	2.2725	10	18.5		**
GIT symptoms	No	38	10.66	3.0671	5.0	18.5	0.62	0.54
	Yes	1	10.00	.	10	10		NS
ICU admission	No	21	8.74	1.8413	5.0	12	5.67	<0.001*
	Yes	18	12.86	2.6111	8.0	18.5		*
Specific ttt	No	35	10.49	2.8114	5.0	17.0	0.95	0.35
	Yes	4	12.00	4.8819	7.0	18.5		NS
Associated symptoms	No	8	8.25	1.8898	7.0	12.5	2.71	0.01*
	Yes	31	11.26	2.9773	5.0	18.5		
Ttt of tremors	No	34	10.29	2.7856	5.0	17.0	1.93	0.06
	Yes	5	13.00	3.8891	8.0	18.5		NS

Sd: Standard deviation   t: Independent t test
NS: Non-significant (P>0.05)   *: Signific ant (P<0.05)   **: Highly significant (P<0.001)
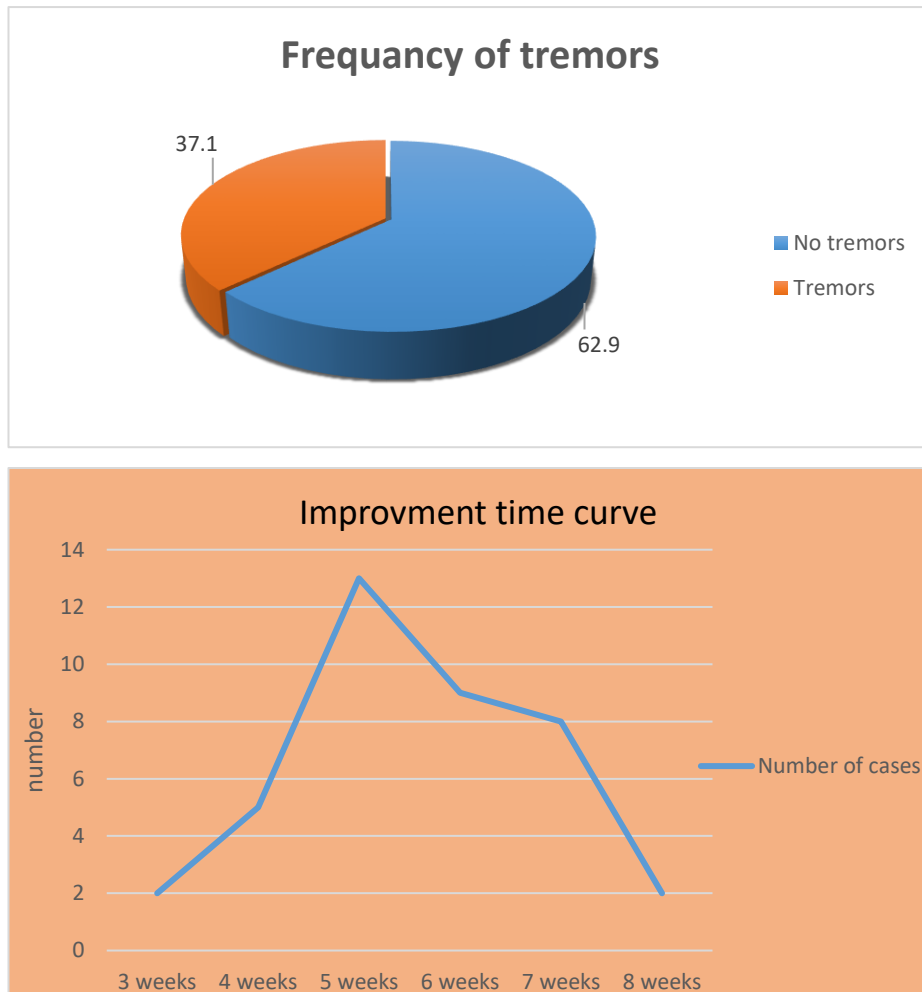
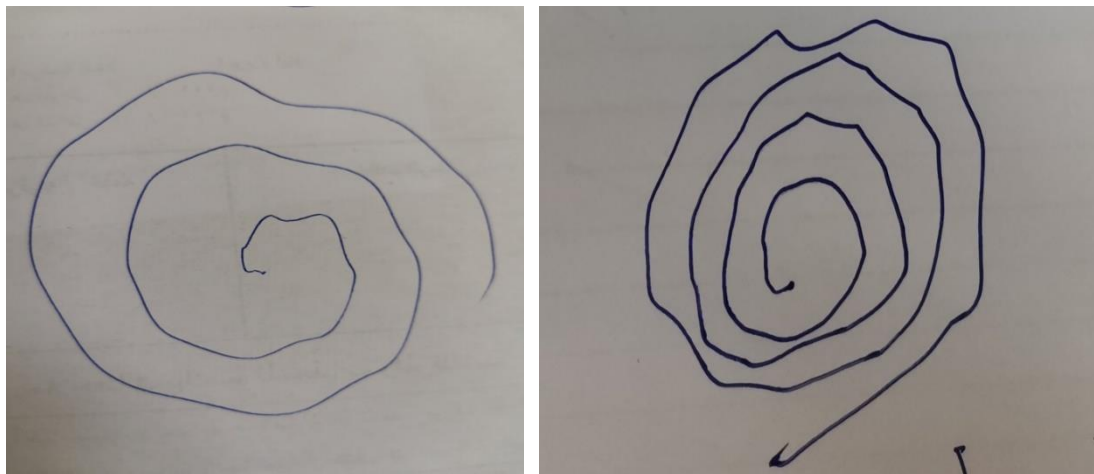**Figure (1):** Frequency of tremors among the studied group

Figure 3: example for spiral drawing in two different patients on presentation, patient A to the left the spirals are wide with more tremor initially (score 2), while in patient B to the right narrow spirals with tremor all through (score 3).

DISCUSSION

After extensive data base search, our study could be one of the first studies that reports tremor as a post COVID-19 neurological complication. In agreement with the retrospective analytic study by Clarks and colleagues, **[5],** who reported 2 cases with physiological tremors among patients with post COVID-19 abnormal involuntary movements,

we reported 39 patients who presented with tremor, correlating with exaggerated physiological and essential tremors in 38 patients, and ataxic tremor in one patient, however lacking other clinical features or radiological evidence of cerebellar abnormalities. The assessment and evaluation of thyroid function tests and the lack of other features of thyroid affection, makes our cases different from

that case reported by **Ruggeri et al.,** [6], that presented with tremor plus pain and tenderness in the anterior cervical region, fatigue, palpitations, diffuse painful goiter, and enlarged tender cervical and submandibular lymph nodes, and was diagnosed as subacute thyroiditis. In our study, the clinical characteristics of tremor, and the lack of clear evidence of both laboratory and radiological cerebral abnormalities are all suggestive of a post COVID-19 immune mediated inflammatory pathology or altered angiotensin-converting enzyme 2 (ACE2) receptor expression in endothelial, neuronal, and glial cells as suggested by Zangbar and his colleagues [7]. Based on this hypothesis it can lead to GABAergic dysfunction of the cerebellar dentate nucleus and brain stem, which may lead to tremulous activity within the cerebellothalamocortical circuit and explaining the presence of such tremor., and despite the presence of family history of tremor in 8 of our patients, but they were improved completely and this would abolish the hypothesis of being familial or with underlying genetic base.

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