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The Neurological Manifestations Of Covid-19 And Their Relationship With The Disease Severity In Hospitalized Patients: A Single-Centered, Cross-Sectional Study On Patients With Covid-19 from Basra, Iraq

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Abstract

The Coronavirus disease (COVID-19) emerged in Wuhan city, China in December 2019 and rapidly spread as a global health pandemic. The primary presentation is respiratory and cardiac symptoms, but neurological features are also being reported. A single-centered, cross-sectional study on 168 patients with COVID-19 was conducted in Al-Mawani teaching hospital, Basra, Iraq to assess the neurological manifestations of COVID-19 and their relationship with the disease severity. 60.7% of the patients involved in the study were documented to have neurological manifestations. The most common reported symptom is the headache (39%) followed by the dizziness(lightheadedness) (28.6%). The more severe neurological manifestations as the acute confusion, cranial nerve palsies, hemiplegia are more seen among those with sever desaturation, higher lung involvement as well as those with cytokine storm syndrome and mainly distributed among older age, males and in patients with comorbidities.The acute cerebrovascular accident(stroke)present in 14.3% of patient, mainly in whom are complain from sever desaturation and aggressive lung involvement.

Introduction

In December 2019, many unexplained pneumonia cases occurred in Wuhan, China, and rapidly spread worldwide, this outbreak of pneumonia causes by the novel Coronavirus [1]. Although COVID-19 preferentially affects the respiratory and cardiovascular system, several patients of COVID-19 are also likely to have neurological symptoms (such as headache, dizziness, hypogeusia, and neuralgia) and complications including encephalopathy, acute cerebrovascular diseases, impaired consciousness and skeletal muscular injury [2,3]. Corona viruses are not primarily neurotropic virus, and their primary target is respiratory epithelium. The target receptor for attachment to cell and subsequent internalization is through the angiotensin converting enzyme-2 receptor [4]. ACE 2 receptors are also present in glial cells in the brain as well as in the spinal neurons. Hence the virus can attach, then multiply and damage the neuronal tissue. There is evidence from the animal experiments in mice that coronavirus enters the brain through a retrograde transfer via the olfactory epithelium or through the cribriform bone and reaches the brain in seven days' time. Secondly, during the viremia phase of illness, disruption of blood brain barrier causes the virus to enter the brain directly [5].

The aims of the study:

1. To study the neurological manifestations among the hospitalized patients of COVID-19.
2. To assess the association between the severity of lung injury and respiratory distress as well as the cytokine storm with the development of the neurological manifestations .

Methods

This is a cross sectional observational study hold in single center in Basra governorate at the south of Iraq (in Al-Mawani teaching hospital who specialized in dealing with COVID-19 patients) and the data collected from 1st of August, 2020 to 30th of September, 2020. The study includes 168 hospitalized patients with clinical, radiological and laboratory diagnosis of COVID-19.

The consent was obtained from patients or a relative for patients who could not give consent, this study was approved by the Ministry of Health (according to the Ministry order No. 994, dated 1/10/1992) and written informed consent was waived by the Training and Human Development Centre in Basra Health Directorate.

The clinical data were collected by direct interview with the patients, neurological assessment was done by neurology resident under senior neurologist supervision, and revising the medical records for the laboratory and radiological data and plotted on organized questionnaire which include special information related to the patient as the sex (male or female), the age, the duration of illness, the patient co-morbidities (as Diabetes mellitus, hypertension, ischemic heart diseases, heart failure, atrial fibrillation, chronic kidney disease, bronchial asthma

or COPD, hemoglobinopathies, malignancy, and immunocompromised patients (on steroid, or immunotherapy) while any patient with pre-existing neurological disorder (previous stroke, epilepsy, Parkinson disease) was excluded from the study. The neurological manifestations were reviewed by history and examination and categorize into simple which includes alter smell or taste sensation, dizziness(lightheadedness), headache and complex which includes disturbances in conscious level through Glasgow coma scale, recent limb weakness by assessment of the power, seizure activity by history, facial and ocular motor nerves palsy by direct neurological examination. The degree of severity of COVID-19 was assessed depending on clinical parameters (O_2 saturation which classified into 4 categories: above 90 %, 70 %–90 %, 50 %–79 %, below 50 %) and radiological parameters by depending on CT chest and the percentage of lung involvement (less than 50 % and more than 50 %) as well as the laboratory markers which include the serum ferritin level (less 1000 ng/ml, more than 1000 ng/ml) and lactate dehydrogenase/LDH level (below 500 U/L, above 500 U/L).
The statistical analysis was done by using SPSS (Statistical package for the social sciences) version 20, the categorized variables were expressed by count and percentage, the results was expressed in form of tables, the association between the variables was asses by using qi square test and the significant threshold was set at a P value less than 0.05.

Results

The total of 168hospitalized patients with the diagnosis of COVID-19 infection was included in the study ; their mean Age was (59.9 year) with (12.91) standard deviation. The sex distribution shows (119) (70.8%) of patients were male and (49) (29.2%) were female. Regarding the co-existing medical illness, (43) (25.6%) has no comorbidities and (125) (74.4%) has any Co-Morbidities. In terms of severity of disease, the oxygen saturation of the patients was distributed as follow: (48)(28.6) their SPO2 was above 90%, in (95)(56%) of them, the SPO2 was between 70 % to 90 %, while in (25)(14.9%) the saturation was below 70. About the lung involvement with the disease from chest CT scan, there is approximately equally distribution,hence (83)(49.5%) of patients have lung involvement below 50 % and the remain (85)(50.6%) of them, the virus affect 50% and more of their lung. In relation to the parameters that give hint about the cytokine release syndrome (storm) the patients distribution according to serum ferritin level and LDH levelsshows that (82)(48.8%) of patients and (90)(53.6%), their serum ferritin was above 1000 ng/ml and serum LDH level above 500 U/L respectively .
From the total number of the patients (102) (60.7%) were documented to have neurological manifestations, (74) (44%) of patients have simple neurological complains but the complex and sever neurological manifestation was reported in (44) (26.2%) of patients. The most common reported symptoms is the headache (66) (39%), followed by the dizziness (48) (28.6%) while the least common is the abnormal body movement (3) (1.8%), the frequency of symptoms is shown in table 1.

Table 1: Neurological manifestations in patients with COVID-19

Manifestation		**Frequency**	
		No.	**%**
Simple	Alter smell &taste sensation	42	25
	Dizziness	48	28.6
	Headache	66	39
Complex	Disturb level of consciousness	32	19
	Recent limb weakness(hemiplegia)	24	14.3
	Sensory loss	16	9.5
	Abnormal body movements	3	1.8
	Facial palsy	17	10.1
	Ocular motor nerves palsy	9	5.4
	Agitation and irritability	19	11.3
	Speech disturbances	28	16.7
	Extensor planter UP/Equivocal	31	18.5
	Cerebellar signs	Not reported	

The onset of the neurological manifestation in relation to the duration of respiratory complains is expressed in the table 2 below, which shows that the majority of patients develop the simple neurological complains within the 1st week of respiratory illness, whereas the complex neurological manifestation develop mainly in the second week of illness, and during the 3rdweek of diseases progression, no more simple neurological complains were developed and this was of high statistical significant.

Table 2: Onset of the neurological manifestation

Onset	Simple neurological manifestations	Complex neurological manifestations	Total
Within 1st week	57 (83.8%)	11 (16.2%)	68
Within 2nd week	17 (42.5%)	23 (57.5%)	40
Within 3rd week	Zero	10 (100%)	10
Total	74	44	**118**
Statistical numbers	**P value: 0.001**		

The relationship between the Age, sex and comorbidities with the development of neurological manifestation, weather simple or complex is shown in table 3.

Table 3: The cross tab of the neurological manifestation with Age, sex, and comorbidities

Demographic features		Neurological manifestations		Simple neurological manifestations		Complex neurological manifestations		Total
		Absent	Present	Absent	Present	Absent	Present	
Age (years)	Less than 35	3(50%)	3(50%)	3(50%)	3(50%)	6(100%)	Zero	6
	35–65	46(46.5%)	53(53.5%)	56(56.6%)	43(43.4%)	81(81.8%)	18(18.2)	99
	Higher than 65	17(27%)	46(73%)	35(55.6%)	28(44.4%)	37(58.7%)	26(41.3%)	63
Total		66	102	94	74	124	44	**168**
Statistical numbers		**P value: 0.040**		**P value: 0.949**		**P value: 0.002**		
Sex	Female	17(34.7%)	32(65.3%)	24(49%)	25(51%)	37(75.5%)	12(24.5%)	49
	Male	49(41.2%)	70(58.8%)	70(58.8%)	49(41.2%)	87(71.1%)	32(26.9%)	119
Total		66	102	94	74	124	44	**168**
Statistical numbers		**P value: 0.434**		**P value: 0.243**		**P value: 0.748**		
Comorbidities	No	22(51.2%)	21(48.8%)	24(55.8%)	19(44.2%)	40(93%)	3(7%)	43
	Any	44(35.2%)	81(64.8%)	70(56%)	55(44%)	84(67.2%)	41(32.8%)	125
Total		66	102	94	74	124	**44**	**168**
Statistical numbers		**P value: 0.064**		**P value: 0.983**		**P value: 0.001**		

The association between the development of the neurological manifestations and the severity of illness through the Oxygen saturation by oximeter, the severity of the lung damage and the elevation of laboratory markers that reflect the cytokine storm syndrome (Serum ferritin and LDH levels) were studied and the results are shown in table 4.

Table 4: The relationship between the development of neurological features and the O_2 saturation, % of lung damage, Serum ferritin and LDH levels

The severity of illness		Neurological manifestations		Simple neurological manifestations		Complex neurological manifestations		Total
		Absent	Present	Absent	Present	Absent	Present	
Oxygen saturation	50 %–69 %	4(16%)	21(84%)	15(60%)	10(40%)	8(32%)	17(68%)	25
	70 %–90 %	37(38.9%)	58(61.1%)	52(54.7%)	43(45.3%)	74(77.9%)	21(22.1%)	95
	Above 90 %	25(52.1%)	23(47.9%)	27(56.2%)	21(43.8%)	42(87.5%)	6(12.5%)	48
Total		66	102	94	74	124	44	**168**
Statistical numbers		**P value: 0.011**		**P value: 0.894**		**P value: 0.001**		
The % of lung involvement	<50 %	38(45.8%)	45(54.2%)	49(59%)	34(41%)	67(80.7%)	16(19.3%)	83
	>50 %	28(32.9%)	57(67.1%)	54(52.9%)	40(47.1%)	57(67.1%)	28(32.9%)	85
Total		66	102	94	74	124	44	**168**
Statistical numbers		**P value: 0.088**		**P value: 0.426**		**P value: 0.044**		
Ferritin level	<1000 ng/ml	35(40.7%)	51(59.3%)	47(54.7%)	39(45.3%)	68(79.1%)	18(20.9%)	86
	>1000 ng/ml	31(37.8%)	51(62.2%)	47(57.3%)	35(42.7%)	56(68.3%)	26(31.7%)	82
Total		66	102	94	74	124	44	**168**
Statistical numbers		**P value: 0.701**		**P value: 0.728**		**P value: 0.112**		
LDH level	<500 U/L	34(43.6%)	44(56.4%)	45(57.7%)	33(42.3%)	64(82.1%)	14(17.9%)	78

	>500 U/L	32(35.6%)	58(64.4%)	49(54.4%)	41(45.6%)	60(66.7%)	30(33.3%)	90
Total		66	102	94	74	124	44	**168**
Statistical numbers		**P value: 0288**		**P value: 0.672**		**P value: 0.024**		

To emphasize on the development of cerebrovascular accident in patient with COVID-19, the data show that, (24) Patients was documented clinically and some of them by image (brain CT) to have stroke, weather ischemic or hemorrhagic. The relationship between the development of stroke and the severity of lung injury, the degree of respiratory distress as well as the cytokine storm is shown in the Table 5.

Table 5: the relationship between the development of stroke and the O_2 saturation, % of lung damage, Serum ferritin and LDH levels

The severity of illness		**Stoke**		**Total**
		Absent	Present	
Oxygen saturation	50 %–69 %	16(64%)	9(36%)	25
	70 %–90 %	83(87.4%)	12(12.6%)	95
	Above 90 %	45(93.8%)	3(6.2%)	48
Total		144	24	168
Statistical numbers		**P value: 0.002**		
The % of lung involvement	<50 %	75(90.4%)	8(9.6%)	83
	>50 %	69(81.2%)	16(18.8%)	85
Total		144	24	168
Statistical numbers		**P value: 0.08**		
Ferritin level	<1000 ng/ml	76(88.4%)	10(11.8%)	86
	>1000 ng/ml	78(82.9)	14(17.1%)	82
Total		144	24	**168**
Statistical numbers		**P value: 0.313**		
LDH level	<500 U/L	70(89.7%)	8(10.3%)	78
	>500 U/L	74(82.2%)	16(17.8%)	90
Total		144	24	**168**
Statistical numbers		**P value: 0.165**		

Discussion

To our knowledge, this is the 1st report on the neurological manifestations of the hospitalized patient with COVID-19 in Basra city, Iraq.

COVID-19 primarily affect the respiratory systems with usual respiratory feature at presentation as cough and dyspnea. However, neurological involvement occurs and can results in serious complications, especially in severely ill patients.

In January 2020,ACE2 was identified as the functional receptor for corona virus, which is present in multiple human organs, including nervous system [6,7]. The expression and distribution of ACE2 remind us that virus may cause some neurologic manifestations through direct or indirect mechanisms. Autopsy results of patients with COVID-19 showed that the brain tissue was hyperaemic and oedematous and some neurons degenerated [8].

Our results show that (60.7%) were documented to have neurological manifestations, Mao et al shows in their study who conducted in Wuhan city thatSeventy-eight patients (36.4%) had nervous system manifestations [2].

The 1st mechanism by which the COVID-19 can affect the nervous system is through hypoxia induces brain injury, Severe pneumonia can result in systemic hypoxia leading to brain damage. The contributory factors include peripheral vasodilatation, hypercarbiaand anaerobic metabolism with accumulation of toxic compounds. These can result in neuronal swelling and brain oedema which ultimately results in neurological damage [9]. According to our result, the complex neurological manifestation is higher among those with severe desaturation below 70% and this of high statistical significant and also the severe neurological damage is of higher percentage among those with lung involvement above (50%) which is again, of statistical significant as shown in table 4 above.

The 2nd mechanism of nervous system damage is through Immune mediated injury which is mainly due to the cytokine storms with increased levels of inflammatory cytokines and activation of T lymphocytes, macrophages, and endothelial cells. Further release of Interleukins 6 causes vascular leakage, activation of complement and

coagulation cascade, disseminated intravascular coagulation and end organ damage [10,11]. Unfortunately, the level of interleukin-6 cannot assess in most of the patients enrolled in this study, so the cytokine storm is suggested depending on the level of serum ferritin and LDH and the result also shows that the complex neurological manifestations are higher among those with higher ferritin and LDH levels.

According to our results, the headache which is consider as a simple neurological complains represent the most common neurological manifestation of COVID-19 and represent (39%) of the total data.A meta-analysis of 61 studies (59,254 patients) reported that headache prevalence with COVID-19 is in 12% [12], Headache was also reported in the retrospective case series from Wuhan with nearly exactly the same prevalence (13%) [2]. But in a large, multicentre, prospective European study performed on mild COVID-19 patients reported a higher prevalence of headache (70%) [13]. This difference in percentage possibly is related to the different population involve in these studies (mild vs. sever).

Many viruses may lead to olfactory dysfunction through an inflammatory reaction of the nasal mucosa and the development of rhinorrhea; the most familiar agents being rhinovirus, parainfluenza, Epstein–Barr virus, and some other coronaviruses. However, olfactory dysfunction linked to COVID-19 infection seems specific as it is not associated with rhinorrhea [14]the alteration of smell and taste sensation occurred in (25%) of our patients. There was a positive association between olfactory and gustatory dysfunctions as expected, considering that the perceived gustatory impairment is usually secondary to the true olfactory dysfunction. large, multicentre, prospective European study performed on mild COVID-19 patients confirmed a high prevalence of loss of smell (70%) and gustatory dysfunction (54%) [13].While The retrospective study from Wuhan reported a markedly lower prevalence of these symptoms (taste impairment 6% and smell impairment 5%). However, this study was done on elderly age group,with severe disease [2].

The simple symptoms as headache, dizziness and the alteration of smell or taste sensation are mainly reported within the 1st week of respiratory illness while the complex symptoms are started to appear after the 2nd or 3rd week of illness, and this association was highly significant.

COVID-19-related disturb level of consciousness and delirium are probably due to septic or toxic encephalopathy, and this type is a reversible brain dysfunction syndrome caused by factors such as systemic inflammatory response syndrome–related toxaemia and hypoxia during the process of acute pulmonary infection [15]. The confusion is reported in (19%) of our patients while the agitation is reported in (11.3%) of them. Chen and co-workers reported that altered consciousness at the time of hospital admission was (22%)which is approximately similar to our results [16] and the retrospective study from Wuhan also showed that impaired consciousness' was reported in (15%) of the most severely ill subjects [2].

The disturb level of consciousness and delirium are likely to be associated with pyramidal signs (enhanced tendon reflexes, ankle clonus, bilateral extensor plantar response) [3] and this was reported in (18.5%) of our patients.

Stroke is diagnosed clinically and radiologically in (14.3%) of our patients, and in (83 %) of them the D dimer level was high but unfortunately the association can't be assessed because the result of D dimer were not available for all of the patients included in this study. The retrospective study from Wuhan,shows five reported cases of ischemic stroke in the severely ill subjects (5%) compared with only one (1%) in the other group (moderately affected patients). It is important to know that patients with severe infection had higher D-dimer level, suggestive of consumptive coagulation system [17]. In relation to our data, the higher incidence of stroke is found among those with sever desaturation (SPO_2 below 70%) and this was of statistical significant, in addition, the percentage is higher among those with higher degree of lung involvement, LDH and Ferritin level but this was of no statistical significant .

The abnormal body movements are shown in 3 cases (1.8%) in all of them, the brain CT was done, 2 of 3 represented with fit, the brain CT in the 1st case show haemorrhagic lesion while the 2nd patient has normal brain CT with but with neck stiffness and bilateral extensor planter response with aphasia so the diagnosis of viral encephalitis was suspected. Moriguchi et al reported first confirmed case of COVID-19 associated viral encephalitis from Japan [17]. A recent retrospective study from China confirmed that seizures are rare during COVID-19. A total of 304 people were studied, of whom 108 had a severe condition. It was found that only two of them had seizure-like symptoms during the hospitalization. Therefore, there was no evidence suggesting an important additional risk of seizures in people with COVID-19 [18]in the last case of the three, the abnormal body movement was in form of hemibalsitic activity of the upper extremity, and the brain CT was normal .

The ocular motor nerves are examined thoroughly, nine patients (5.4%) documented to have either one or more nerve palsy (5.4%), one of these cases is diagnosed as rhinocerebral Mucormycosis and died within 10 days. Two of these cases are also diagnosed clinically and radiologically with venous sinus thrombosis, there is reports of patients with various neurological features during the course of COVID-19 including cerebral venous thrombosis [19]. But in the remain of our cases, the definitive diagnosis wasn't reach, a recent paper reported two Spanish cases highlighting the rare occurrence of Miller Fisher syndrome and polyneuritis cranialis during the COVID-2 pandemic [20]. Anothertwo patients who were diagnosed with COVID-19 after presenting with diplopia and ophthalmoparesis were also reported [21]

The sensory assessment was taken apart in this article, but unfortunately the detailed examination can't be done because of poor patient's cooperation due to severe illness or alter level of consciousness, the percentage of sensory deficit is (9.5%), some of them was show a pattern of hemisensory loss as a part of cerebrovascular accident, others complain from paraesthesia and numbness but further study is required for detailed assessment of sensory manifestations as well as neurophysiological diagnostic modalities may require to reach the definitive diagnosis, There are few reports of patients who experienced typical acute inflammatory demyelinating polyneuropathy during or after the course of COVID-19 [22]. A detailed case series from Northern Italy described five patients who had Guillain–Barré syndrome after the onset of COVID-19 [23].

Regarding the demographic presentation of the neurological manifestation, the result shows that the neurological complains mainly distributed among those of older age group (above 65 years) specially the complex complains as confusion, stroke and cranial nerve palsies and this of statistical significant, but regarding the simple neurological features as dizziness or headache and change smell or taste sensation were of no statistical significant among the different age categories. In relation to the sex distribution, the complex manifestation occurred more in male but also this is of no statistical significant, this picture is of some similarity to what shown in A study on 113 Chinese patients who died from COVID-19,The median age of the deceased patients was 68 years, and male sex was predominant. This Chinese study show also the presence of Hypertension and other cardiovascular comorbidities were more frequent among the deceased patients with severe neurological complains, in a comparison to our result the presence of complex neurological complains is higher among those with comorbidities as hypertension, diabetes mellitus and coronary artery disease possibly COVID-19 was not blames because all these factors consider a risk for development of cerebrovascular disease or possibly COVID-19 increase the hypercoagulability and participate to more and more thrombosis risk, further analytical study is requires to assess the causality.

During the epidemic period of COVID-19, when seeing patients with such neurological manifestations, the doctors should suspect thepossibilityof COVID-19 infection. Most neurological manifestations may occur early during the course of the illness

Conclusion

COVID-19 primarily affects the respiratory and cardiovascular system. However, neurological involvement is not uncommon and can result in serious complications if not detected and managed early. These complications are mostly seen in severely ill, In those with severe infection, the complex neurologic involvement is greater, which includes acute cerebrovascular diseases, impaired consciousness. Further analytical studies are required to assess the association, as well as we recommend to search for underlying COVID-19 in patients with neurological manifestations in this pandemic period and vice versa to be aware about the possibility of neurological complications in severely ill COVID-19 patients.

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