Frequency and Determinants of Neurological Symptoms of COVID-19 Patients

Mohammed Radhi Radeef[1], Fatimah Mustafa Mohammed Alattraqchi[2], Ahmed Abbas Shlaka[3], Shaymaa Abdul Lateef Alfadhul[4]

[1]Lecturer, Department of Neuro Medicine, Faculty of Medicine, University of Kufa, Iraq, [2]Doctor, Department of Community and Family Medicine, Ministry of Health, Iraq, [3]Doctor, Al Najaf Health Directorate, Ministry of Health, Iraq, [4]Assistant Professor, Department of Family and Community Medicine, Faculty of Medicine, University of Kufa, Iraq

Abstract

Objective: To determine the frequency, type, and associated determinants of neurological symptoms among covid19 patients.

Methods: A cross-sectional study was conducted among 161 doctors from different Iraqi cities using online questionnaires. They were provided information about their documented case. Data were collected from the 1st to 30th of October 2020. The questionnaire consists of 2 parts, first part concerns sociodemographic data of patients (age, gender, and severity of COVID-19 infection), while the second part deals with details of COVID-19 neurological symptoms. Data were stored and analyzed using SPSS version 24.

Results: A total of 161 COVID-19 cases were described in this study. Headache was found in 120 patients (74.5%); loss of smell in 108 patients (67.1%); and loss of taste in 86 patients (53.4%). It was found that ataxia more predominant in females (34.0%) than males (17.9%), statistically, there was a significant difference(P=0.024). Sever COVID-19 disease showed a significantly higher presentation of vertigo, hearing loss, loss of smell, disturbance of level of consciousness, sensory symptoms, motor symptoms, and stroke ($p<0.05$). Statistical analysis showed a significantly higher presentation of disturbance in level of consciousness, and stroke symptoms in patients older than 40 years($P<0.05$).

Conclusion: Different neurological presentations are reported fromCOVID-19 cases. Headache, loss of smell, and taste are the most frequent symptoms. Some neurological manifestations are found more predominant in females, older age, and severe cases.

***Keywords**: SARS-CoV2 · COVID-19, neurological symptoms.*

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious acute respiratory disease. the first patient was confirmed to have COVID-19 on 1st of March 2020 in Wuhan, China [(1)].

The pathogen, later on, was identified as severe acute respiratory syndrome coronavirus 2 (SARS-Cov2). Globally, until the 16th of August 2020, there have been 21,260,760 confirmed cases of COVID-19, including 761,018 deaths, reported to WHO [1]. Severe COVID-19 can cause progressive respiratory failure and death. Susceptibility is high among elderly

Corresponding Author:
Shaymaa Abdul Lateef Alfadhul:
Assistant Professor, Department of Family and Community Medicine, Faculty of Medicine, University of Kufa, Iraq

patients and those with comorbidities, recent surgery, and intrinsically or iatrogenically compromised immunity [2].

Neurological symptoms were reported in 0.04% of SARS and 0.2% of MERS, also, 28.2 million people of COVID-19 cases have neurological symptoms [3].

The most frequent question of neuroscientist is that if a virus direct infects CNS so need treatment with antiviral or virus is cleared from the body then treated with anti-inflammatory therapy, Michael said the is difficult to find the virus in the brain, compared with other organs. The polymerase chain reaction (PCR) often do not detect it there, despite their high sensitivity, and other studies have failed to find any virus particles in the cerebrospinal fluid, this is maybe due to that the ACE2 receptor, a protein on human cells that the viruses use to gain entry, is not much found in brain cells [3].

Coronaviruses may cause Central nervous system manifestations (Headache, dizziness, consciousness disorder, acute brain disease, seizures, and ataxia) [4], and peripheral nervous system symptoms (loss of smell, loss of taste, visual impairment, and nerve pain) [5].

Coronaviruses are thought to cause neurological manifestation either directly through neuroinvasive capacity (ACE2 receptors on neuronal tissues) or indirectly through the response of the immune system (an inflammatory mechanism), Also both SARS-CoV-2 and COVID-19 have neurological manifestation, so the diagnosis of SARS-CoV-2 infection should be kept in mind when patients presented with neurological symptoms during the pandemic [6].

The current study aimed to determine the types, and frequency of neurologic manifestations of COVID-19 infection, and to find its association with age, gender, and severity of COVID-19 infection.

Methods

An internet-based cross-sectional survey was conducted. The survey was distributed among doctors who deal with covid19 patients. The participants' doctors were provided with an internet link to the survey created with the Google Forms application. After opening the invitation link, the respondent needs to agree to participate in research, before answering the questions. The data were collected from the 1st to 30th of October 2020. The questionnaire consists of 2 parts, of which part 1 concerns sociodemographic data (age, gender, and severity of COVID-19 infection). Part 2 deals with COVID-19 neurological symptoms. Data were analyzed using SPSS version 24, Mean and standard deviations were used for numerical variables, while frequency and percentages were used for categorical variables. A Chi-square test was used to test the significance of the association between variables.

Results

A total of 161 COVID-19 cases were described in this study. More than half of cases (94,58.4%) are females. Their mean age (stander deviation) is 38(14.8) years. The higher number of cases (71, 44.1%) are in the age group 18-29 years, followed by (42,26.1%) in the age group 30-39 years. According to COVID-19 Severity, 116(72 %) patients had a mild infection, 37 (23%) had a moderate infection, the rest had a severe infection, table1.

Considering neurological symptoms, the headache was found in 120 patients (74.5%); loss of smell in 108 patients (67.1%); and loss of taste in 86 patients (53.4%). Other symptoms like generalized weakness, vertigo, unsteadiness, and drowsiness were reported from (54.2%), (28.6%), (27.3%), and (34.2%) of patients, respectively, table1.

Table 2 described the gender differences in neurological symptoms. It was found that ataxia more predominant in females (34.0%) than males (17.9%), statistically there is a significant difference(P=0.024).

Meanwhile, loss of taste sensation is more in females than males (74.5% vs 23.9%), statistical analysis shows a highly significant difference(P=0.001).

Considering association of severity with presence of neurological symptoms, current results showed significantly higher percentages of neurological manifestation including vertigo, hearing loss, loss of smell, disturbance of level of consciousness, sensory symptoms, motor symptoms, and stroke in severe COVID19 disease (P<0.05), table (3).

Table4 demonstrated variation of neurological symptoms according to age groups, disturbance of level of consciousness is significantly higher in older (≥40 years) than younger age group (<40 years) (P=0.009), also, four patients (12.9%) of older age recorded stroke symptoms in comparison to only two (1.5%) of younger age group. Statistical analysis shows a highly significant difference(P=0.003).

Table 1: distribution of COVID-19 patients according to age, gender, severity, and neurological symptoms.

Variable		Frequency	Percentage(%)
Age In Years	Mean (S.D)	38 (14.8)	
Gender	Male	67	41.6
	Female	94	58.4
Age Group	Less Than 18	5	3.1
	18-29	71	44.1
	30-39	42	26.1
	40-49	12	7.5
	50-59	16	9.9
	≥60	15	9.3
COVID-19 Infection Severity	Mild	116	72.0
	Moderate	37	23.0
	Sever	8	5.0
Ataxia Unsteadiness	No	117	72.7
	Yes	44	27.3
Headache	No	41	25.5
	Yes	120	74.5
Vertigo	No	115	71.4
	Yes	46	28.6
Hearing Loss	No	154	95.7
	Yes	7	4.3
Loss Of Smell	No	53	32.9
	Yes	108	67.1
Seizure	No	157	97.5
	Yes	4	2.5
Disturbance In Level Of Consciousness	Drowsiness	55	34.2
	Confusion	9	5.6
	Delirium	1	0.6
	Coma	3	1.9
	Stupor	1	0.6
	Lethargy	25	15.5
	No	24	14.9
	All	43	26.7

Cont... **Table 1: distribution of COVID-19 patients according to age, gender, severity, and neurological symptoms.**

Sensory Symptoms	Paresthesia	10	6.2
	Anasthesia	8	5.0
	Burning Sensation	16	9.9
	Allodynia	13	8.1
	Hyperalgesia	4	2.5
	No	110	68.3
Motor Symptoms	Weakness	87	54.0
	Cramp	12	7.5
	Dystonia	1	.6
	No	47	29.2
	Tremor	12	7.5
	Imbalance	2	1.2
Stroke Symptoms	No	156	96.9
	Yes	5	3.1
Loss of taste sensation	No	75	46.6
	Yes	86	53.4

Table 2: Distribution of neurological symptoms according to gender

Variable(s)		Gender		P-value
		Male	Female	
Ataxia(Unsteadiness)	No	55(82.1%)	62(66.0%)	0.024
	Yes	12(17.9%)	32(34.0%)	
Headache	No	17(25.4%)	24(25.5%)	0.982
	Yes	50(74.6%)	70(74.5%)	
Vertigo	No	51(76.1%)	64(68.1%)	0.266
	Yes	16(23.9%)	30(31.9%0	
Hearing Loss	No	65(97.0%)	89(94.7%)	0.474
	Yes	2(3.0%)	5(5.3%0	
Loss Of Smell	No	21(31.3%)	32(34.0%)	0.719
	Yes	46(68.7%)	62(66.0%)	
Seizure	No	65(97.0%)	88(93.6%)	0.719
	Yes	2(3.0%)	6(6.4%)	

Cont... **Table 2: Distribution of neurological symptoms according to gender**

Disturbance In Level Of Consciousness	Drowsiness	15(22.4%)	19(20.2%)	0.759
	Confusion	5(7.5%)	6(6.4%)	
	Delirium	1(1.5%)	1(1.1%)	
	Coma	2(3.0%)	2(2.1%)	
	Sleepy	4(6.0%)	3(3.2%)	
	Lethargy	10(14.9%)	15(16.0%)	
	No	13(19.4%)	11(11.7%)	
	Drowsiness| Stupor | Sleepy Lethargy	3(4.5%)	8(8.5%)	
	All of above	14(20.9%)	29(30.9%)	
Sensory Symptoms	Paresthesia	4(6.0%)	6(6.4%)	0.905
	Anasthesia	4(6.0%)	4(4.3%)	
Motor Symptoms	Weakness	32(47.8%)	55(58.5%)	0.178
	Cramp	9(13.4%)	3(3.2%)	
	Dystonia	0(0.0%)	1(1.1%)	
	No	21(31.3%)	26(27.7%)	
	Tremor	4(6.0%)	8(8.5%)	
	Imbalance	1(1.5%)	1(1.1%)	
Stroke Symptoms	No	66(98.5%)	89(94.7%)	0.206
	Yes	1(1.5%)	5(5.3%)	
Loss Of Taste Sensation	No	51(76.1%)	24(25.5%)	0.001
	Yes	16(23.9%)	70(74.5%)	

Table3: Distribution of neurological symptoms according to severity of COVID-19 infection.

Variable		Mild	Moderate	Sever	P_Value
Ataxia-Unsteadiness	No	88(75.9%)	24(64.9%)	5(62.5%)	0.342
	Yes	28(24.1%)	13(35.1%)	3(37.5%)	
Vertigo	No	90(77.6%)	21(56.8%)	4(50.0%)	0.020
	Yes	26(22.4%)	16(43.2%)	4(50.0%)	
Hearing Loss	No	112(96.6%)	36(97.3%)	6(75.0%)	0.013
	Yes	4(3.4%)	1(2.7%)	2(25.0%)	
Loss Of Smell	No	31(26.7%)	20(54.1%)	2(25.0%)	0.008
	Yes	85(73.3%)	17(45.9%)	6(75.0%)	

Cont... **Table3: Distribution of neurological symptoms according to severity of COVID-19 infection.**

Seizure	No	113(97.4%)	33(89.2%)	7(87.5%)	0.081
	Yes	3(2.6%)	4(10.8%)	1(12.5%)	
Disturbance in Level of Consciousness	Drowsiness	24(20.7%)	10(27.0%)	0(0.0%)	0.001
	Confusion	2(1.7%)	8(21.6%)	1(12.5%)	
	Delirium	1(0.9%)	1(2.7%)	0(0.0%)	
	Coma	0(0.0%)	1(2.7%)	3(37.5%)	
	Sleepy	6(5.2%)	0(0.0%)	1(12.5%)	
	Lethargy	21(18.1%)	3(8.1%)	1(12.5%)	
	No	20(17.2%)	3(8.1%)	1(12.5%)	
	Drowsiness| Stupor | Sleepy Lethargy	10(8.6%)	1(2.7%)	0(0.0%)	
	All of above	32(27.6%)	10(27.0%)	1(12.5%)	
Sensory Symptoms	Paresthesia	6(5.2%)	4(10.8%)	0(0.0%)	0.001
	Anesthesia	3(2.6%)	2(5.4%)	3(37.5%)	
	Burning Sensation	8(6.9%)	7(18.9%)	1(12.5%)	
	Allodynia	8(6.9%)	4(10.8%)	1(12.5%)	
	Hyperalgesia	2(1.7%)	2(5.4%)	0(0.0%)	
	No	89(76.7%)	18(48.6%)	3(37.5%)	
Motor Symptoms	Weakness	62(53.4%)	23(62.2%)	2(25.0%)	0.001
	Cramp	10(8.6%)	1(2.7%)	1(12.5%)	
	Dystonia	0(0.0%)	0(0.0%)	1(12.5%)	
	No	37(31.9%)	9(24.3%)	1(12.5%)	
	Tremor	7(6.0%)	4(10.8%)	1(12.5%)	
	Imbalance	0(0.0%)	0(0.0%)	2(25.0%)	
Stroke Symptoms	No	112(96.6%)	37(100.0%)	6(75.0%)	0.003
	Yes	4(3.4%)	0(0.0%)	2(25.0%)	
Loss Of Taste Sensation	No	52(44.8%)	17(45.9%)	6(75.0%)	0.253
	Yes	64(55.2%)	20(54.1%)	2(25.0%)	

Table 4: distribution of neurological symptoms according to age group

Variable		Age<40 years	Age ≥40 years	P Value
Ataxia-Unsteadiness	No	95(73.1%)	22(71.0%)	0.813
	Yes	35(26.9%)	9(29.0%)	
Headache	No	30(23.1%)	11(35.5%)	0.154
	Yes	100(76.9%)	20(64.5%)	
Vertigo	No	92(70.8%)	23(74.2%)	0.705
	Yes	38(29.2%)	8(25.8%)	
Hearing Loss	No	125(96.2%)	29(93.5%)	0.523
	Yes	5(3.8%)	2(6.5%)	
Loss Of Smell	No	40(30.8%)	13(41.9%)	0.235
	Yes	90(69.2%)	18(58.1%)	
Seizure	No	124(95.4%)	29(93.5%)	0.672
	Yes	6(4.6%)	2(6.5%)	
Disturbance In Level Of Consciousness	Drowsiness	33(25.4%)	1(3.2%)	0.009
	Confusion	6(4.6%)	5(16.1%)	
	Delirium	2(1.5%)	0(0.0%)	
	Coma	1(0.8%)	3(9.7%)	
	Sleepy	5(3.8%)	2(6.5%)	
	Lethargy	21(16.2%)	4(12.9%)	
	No	20(15.4%)	4(12.9%)	
	Drowsiness| Stupor | Sleepy Lethargy	9(6.9%)	2(6.5%)	
	All of above	33(25.4%)	10(32.3%)	
Sensory Symptoms	Paresthesia	8(60.434.2%)	2(6.5%)	
	Anesthesia	5(3.8%)	3(9.7%)	
	Burning Sensation	15(11.5%)	1(3.2%)	
	Allodynia	12(9.2%)	1(3.2%)	
	Hyperalgesia	3(2.3%)	1(3.2%)	
	No	87(66.9%)	23(74.2%)	
Motor Symptoms	Weakness	71(54.6%)	16(51.6%)	0.167
	Cramp	11(8.5%)	1(3.2%)	
	Dystonia	0(0.0%)	1(3.2%)	
	No Symptoms	36(27.7%)	11(35.5%)	
	Tremor	11(8.5%)	1(3.2%)	
	Imbalance	1(0.8%)	1(3.2%)	
Stroke Symptoms	No	128(98.5%)	27(87.1%)	0.003
	Yes	2(1.5%)	4(12.9%)	
Loss Of Taste Sensation	No	61(46.9%)	14(45.2%)	0.860
	Yes	69(53.1%)	17(54.8%)	

Discussion

Recent evidence suggests that COVID-19 patients commonly had neurological symptoms manifested as acute stroke (6%), consciousness impairment (15%), and skeletal muscle injury (19%) [5]. Therefore, the current study conducted to demonstrate the types, and frequencies of neurological manifestations in COVID-19 patients through online reports of physicians dealing with laboratory documented COVID-19 cases.

In this study, different neurological symptoms were reported by participants, the highest frequencies were headache (74.5%), loss of smell (67.1%); and loss of taste (53.4%). The cause of headache in COVID-19 could be explained by trigeminal vascular activation, in addition to systemic inflammation (increased cytokines) that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binding to ACE2 on trigeminal nerve endings within the nasal cavity. This is also most likely the cause of the loss of the sense of taste and smell [7].

Consistent with other findings [7,8] muscle symptoms like generalized weakness were highly reported in this study. These symptoms could be explained by muscle injury caused by SARS-CoV2 as recognized by high creatine kinase levels [7]. Other symptoms like vertigo, unsteadiness, and drowsiness were reported in more than a quarter of cases. These presentations could be due to viral vestibular neuritis or due to damage to nerve tissue from hypoxia or hypercoagulopathy. A review of 14 studies that investigated dizziness as a symptom in COVID-19 cases reported dizziness in 4 to 30 percent of patients which was similar to the present finding [9].

Regarding gender differences in the presence of neurological symptoms, this study found that females reported ataxia and loss of taste sensation significantly higher than males($P<0.05$). Females are more significantly affected by gustatory dysfunction [10]. The higher susceptibility of females to develop gustatory dysfunctions could be attributed to the gender-related differences in the inflammatory reaction process [11].

Similar to previous findings [5], severe cases of COVID-19 infection were more likely to develop neurologic manifestations including vertigo, hearing loss, loss of smell, disturbance of level of consciousness, sensory symptoms, motor symptoms, and stroke. Therefore, close attention should be taken to the neurologic manifestations of COVID-19 patients, especially for those with severe infections, which may have contributed to their death. Also, during the epidemic period of COVID-19, physicians should consider SARS-CoV-2 infection as a differential diagnosis when seeing patients with these neurologic manifestations, to avoid misdiagnosis or delayed diagnosis.

In this study, disturbance of level of consciousness and stroke symptoms are significantly higher in older (≥40 years) than younger age group (<40 years). Whereas other neurological symptoms are not significantly differed between the two age groups. A previous study conducted in Tunisia among patients with COVID19 reported no significant differences in neurological manifestation according to age groups [12]. Acute stroke is a commonly reported neurologic complication of COVID-19, particularly in the elderly population [13,14]. Researchers have reported increasing trends of double-positive ACE2+TMPRSS2+ cell proportions with increasing age which could be a factor for disease severity in the elderly. These receptors had been found in tissues beyond the respiratory system, including oligodendrocytes in the brain. Additionally, neurologic autoimmunity had been suggested as a cofactor through the invasion of ACE2+TMPRSS2+ cells in organs such as the lungs and gut [15].

A limitation of this study is that all data were obtained through an online survey of physicians depending on their recall for cases, hence additional associated risk factors cannot ascertain. Besides, laboratory data and imaging studies were not available for comparison with the current results. However, this

is one of the earlier studies that focus on neurological manifestations in COVID-19, and documented reports of the physicians were dependent.

Conclusion

Different neurological symptoms have been reported from patients with COVID-19 infection. The most frequent neurological symptoms are headache followed by loss of smell and loss of taste. Some neurological manifestations are found more frequent in females, older age, and severe cases.

Ethical Clearance: Taken from University of Kufa ethical committee.

Conflict of Interest : The authors declare no conflicts of interest.

Financial Statement : The authors did not receive any financial support from any source

References

1- Zumla A, Niederman MS. The explosive epidemic outbreak of novel coronavirus disease 2019 (COVID-19) and the persistent threat of respiratory tract infectious diseases to global health security. Current opinion in pulmonary medicine. 2020 Apr 9.

2- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet. 2020 Mar 28;395(10229):1054-62.

3- Marshall M. How COVID-19 can damage the brain. Nature. 2020 Sep 17;585(7825):342-3.

4- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama. 2020 Mar 17;323(11):1061-9.

5- Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA neurology. 2020 Jun 1;77(6):683-90.

6- Zhou Z, Kang H, Li S, Zhao X. Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. Journal of neurology. 2020 Aug;267:2179-84.

7- Dr. Osman Shabir, P., 2021. *COVID-19 and Headaches*. [online] News-Medical.net. Available at: <https://www.news-medical.net/health/COVID-19-and-Headache.aspx> [Accessed 14 April 2021].

8- Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020. doi:10.1056/NEJMoa2002032.

9. Saniasiaya J, Kulasegarah J. Dizziness and COVID-19. Ear, Nose & Throat Journal. 2020;100(1):29-30.

10. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020 doi: 10.1007/s00405-020-05965-1.

11. Lefèvre N, Corazza F, Valsamis J, Delbaere A, De Maertelaer V, Duchateau J, Casimir G (2019) The number of X chromosomes influences inflammatory cytokine production following toll-like receptor stimulation. Front Immunol 10:1052. https://doi.org/10.3389/fimmu.2019.01052.

12. Kacem I, Gharbi A, Harizi C, Souissi E, Safer M, Nasri A et al. Characteristics, onset, and evolution of neurological symptoms in patients with COVID-19. Neurological Sciences. 2020;42(1):39-46.

13. Berardelli, A., Silani, V., Barone, P., Calabresi, P., Girlanda, P., Lopiano, L., et al. (2020). Neurology and the COVID-19 emergency. *Neurol. Sci.* 41,

1343–1344. doi: 10.1007/s10072-020-04465-8

14. Josephson, S. A., and Kamel, H. (2020). Neurology and COVID19. *JAMA* 324, 1139–1140. doi: 10.1001/jama.2020.14254.

15. Muus, C., Luecken, M. D., Eraslan, G., Waghray, A., Heimberg, G., Sikkema, L., et al. (2020). Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells. *bioRxiv. [Preprint]*. doi: 10.1101/2020.04.19.049254