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RESEARCH

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Unveiling the link: hepatitis C virus and Parkinson's disease

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Abstract

Background Parkinson disease (PD) is one of the disabling neurological disorders. The etiology of Parkinson disease is still unknown. Hepatitis C virus is one of the neurotropic viruses which is incriminated in the pathogenesis of Parkinson disease. Hepatitis C virus might affect the dopaminergic neurons, affecting the advancement of PD.

Methods This study is observational, cross-sectional study done on 2 phases: one phase on PD patients without history of HCV and another phase on HCV patients with no history of PD. 104 PD patient were tested for HCV antibodies and 40 HCV patients with various grades of liver fibrosis were assessed for early pre-motor symptoms of parkinsonism.

Results Among patients with parkinsonism, HCV Abs testing was negative in all the studied patients. On the other hand, chronic HCV group included 40 patients, 27.5% were cirrhotic (11/40). Child C patients showed significantly higher percentages of non-motor parkinsonian symptoms, and regarding the HCV group, the majority (85%) of the patients show cognitive impairment, (27.5%) were at stage 1 of anxious mood, while half (50%) of the patients were at stage 1 of fatigue as evaluated by UPDRS Score. Cirrhosis was a significant factor for having non-motor (early) parkinsonism.

Conclusion Here we show that advanced cirrhosis is associated with a variety of neurological symptoms including parkinsonian, which needs awareness for better preventive and therapeutic measures for early treatment of hepatitis avoiding the occurrence of cirrhosis, which can lead to parkinsonism.

Keywords Parkinsonism, HCV, Neurological manifestations, Acquired hepato-cerebral degeneration, Parkinson's disease, The link, Non-motor parkinsonian symptoms

Background

Parkinson disease (PD) is a neurodegenerative illness characterized by loss of dopaminergic neurons in the substantia nigra. It is the second most common neurodegenerative problem, after Alzheimer disease [1]. The etiology of PD remains unknown till now. Genetic predisposition, neurodevelopmental insults, and environmental factors are considered to play an important role in the pathogenesis of PD [2]. Loss of neurons and gliosis of the pars compacta of the substantia nigra and the presence of Lewy bodies (LBs), eosinophilic to basophilic concentric structures with peripheral halos, in pigment nuclei such as the nucleus basilaris, are hallmarks of PD. LBs contain the abnormal aggregates of misfolded α-syn which was discovered as a non-amyloid component of the senile plaques in AD [3–12].

Some neurotropic viruses have been related to intense and persistent parkinsonism, including flu, coxsackie, herpes and human immunodeficiency virus [13–15]. As HCV has neurotropic capacities and can duplicate in the CNS, it might affect dopaminergic neurons and may

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assume part in the advancement of Parkinson's disease [16–19].

The symptoms of PD can be divided into motor symptoms and non-motor symptoms (NMSs). Motor-related symptoms include muscle rigidity, tremors and changes in speech. Sensory complaints, mental abnormalities, sleep disturbances, and autonomic dysfunction are common NMSs experienced by people with PD. Non-motor symptoms can occur in the earliest stages of the disease, even before motor impairment is clinically apparent [20–25].

An estimated 58 million people have chronic HCV infection globally, with about 1.5 million new infections occurring per year and estimated 3.2 million adolescents and children infection [26]. According to 2015 Demographic and Health Survey (DHS) in Egypt, Egypt had the highest prevalence of HCV infection worldwide. 10% of the Egyptian population between 15 and 59 years of age were seropositive for HCV antibodies and 7% had viremia [27].

Hepatitis C virus infection is a systemic disease, its clinical impact and prognosis do not depend only on liver-related complications, but also on HCV-related extra-hepatic manifestations including HCV-related autoimmune or lymphoproliferative disorders, cardiovascular, renal, metabolic, and central nervous system disease [28–33].

Studies on the association between Parkinsonism and chronic HCV have conflicting results. Some reported increased prevalence of Parkinson's disease (PD) in patients with chronic HCV [34–38]. Others reported no association between both diseases [39].

The aim of the current study was to evaluate the association between parkinsonism and HCV by assessing the prevalence of HCV in a cohort of known Parkinson's disease patients on follow-up and on the other hand assessing early parkinsonian symptoms in another cohort of HCV patients in different stages of the disease.

Methods

This study is an analytical, observational, cohort study. The study passed through two phases. In the first phase, we included 104 patients with Parkinson's disease who were on follow-up in neurology clinic and had no previous history of HCV disease and/or treatment and their age was ≥ 18 years old. The second phase has been done on patients known to have HCV but without history of parkinsonism or other neurological disorders.

The first cohort study was conducted at neurology clinic and the viral treatment center affiliated to the national committee for control of viral hepatitis (NCCVH) in the period from April 2020 to June 2021. The study was endorsed by the ethical committee On April 2020. Code: MS-330-2019 and all included patients signed an informed consent.

We excluded patients with history of HCV disease and/or treatment or patients diagnosed to have other chronic liver disease as chronic HBV, autoimmune liver disease, and primary biliary cirrhosis.

All included patients were subjected to: history taking as regards risk factors for HCV infection, symptoms suggestive of chronic liver disease and family history of HCV. Clinical examination for Parkinson's disease signs (rigidity, tremors, bradykinesia, postural instability and flexed posture) as well as signs suggest chronic liver disease (jaundice, lower limb edema, abdominal distension, and ecchymosis). Hepatitis C virus screening using rapid test (ABON kits from smart trade company for detecting HCV antibodies) by taking a convenient blood sample from the patients, samples were centrifuged, then few drops from the remaining plasma or serum were put on the kit, then waiting for 10 min to read the results, which if 2 lines appeared means that the patient is positive for HCV and if one line appeared this means negative result. Positive cases would perform a confirmatory PCR for detection of HCV-RNA quantitatively (Abbott real-time detection kit for HCV, Abbott Inc, Germany) using ABI 7500 real-time PCR instrument (Applied Biosystems, USA). The routine work-up for HCV treatment including CBC, ALT, AST, BIL, ALB, INR, creatinine, and abdominal US was completed for each positive HCV patients. FIB4 would be calculated for fibrosis assessment.

In the second phase, we made a reversion of screening method by screening patients with known HCV presenting to virology clinic at Kasr Alainy to receive anti HCV therapy for early parkinsonism using non-motor part symptoms questionnaire of UPDRS scoring method [40].

The study included 40 cases of HCV patients, patients were either naïve, or experienced for HCV therapy (relapses or non- responders). Relapse was defined as the reappearance of HCV-RNA in the serum of treated patients after achieving SVR (sustained virologic response), means after more than 12 or 24 weeks post-SVR [41]. Non-response was defined as patients who failed to achieve SVR. However, this is rare [42].

We also included non-cirrhotic, or cirrhotic patients with child A, B, C classification [43], with age of more than 18 years old. We excluded patients with other associated chronic liver diseases as chronic HBV, autoimmune liver disease, and primary biliary cirrhosis. All patients were screened for Parkinson's symptoms with a questionnaire of non-motor part of UPDRS which was translated into Arabic [44].

Data were analyzed using SPSS version 21. Qualitative data were presented by number and percentage. Quantitative data were presented by mean, standard deviation,

median and interquartile range. Statistical tests were done for parametric and non-parametric data accordingly, correlation and regression was done. Level of significance was considered if p equal to or below 0.05. All collected questionnaires were revised for completeness and logical consistency. Pre-coded data were entered on Microsoft Office Excel program for Windows 2010.

Data were transferred to the statistical package for social science version 15 (SPSS-V 15) for quantitative data analysis [45].

The following approaches for statistical data analysis and presentation were done:

Simple frequency distribution tables have been developed to provide description for study group.

Continuous, normally distributed quantitative data were presented using mean and standard deviation. For qualitative data, the cross-tabulation presenting the number and percentage for the study group was used with chi-square test used for statistical significance for comparison.

Difference was considered significant at p value ≤ 0.05.

Results

The current study was conducted at neurology clinic and the viral treatment center affiliated to the national committee for control of viral hepatitis (NCCVH) in the period from April 2020 to June 2021.

The first phase of the study included 104 patients with Parkinson's disease.

The mean age was 57.5 ± 8.7 years. (70.2%) were males. Duration of Parkinson's disease was less than 5 years in most of patients (82.7%). (71.2%) were smokers, (61.5%) were diabetic and about (73%) were hypertensive. The majority (92.3%) of the patients did not receive blood transfusion or undergo previous operations. Testing of HCV Ab by rapid test was negative in all the studied patients (Table 1).

Regarding to the clinical manifestation of Parkinson's disease, the highest percentage of patients was at stage 1 and having either right or left upper limb rest tremors (34.6% and 45.2%), left lower limb rest tremors (46.2%) or bradykinesia (55.8%) as staged by UPDRS score (Figs. 1, 2).

As all screened Parkinson's disease patients revealed negative results for HCV Ab testing, we proceeded to the second phase of the study and reversed the screening method, by screening a group of HCV-positive patients for early non-motor manifestations of Parkinson's disease.

Positive hepatitis C virus group included 40 patients. The mean age was 43 ± 12.1 years. (67.5%) were males, (27.5%) were cirrhotic (11/40). (54.6%) of cirrhotic patients were of Child score C.

Table 1 Multivariate analysis of factors associated with positive symptoms of Parkinson's disease in HCV patients

	Odds ratio	*p* value	95%CI	
			Lower	Upper
Cognitive impairment				
Age	1.308	0.12	0.93	1.84
Sex	0.0	0.99	0.0	–
Cirrhosis	0.0	0.99	0.0	–
Smoking	2.69	0.36	0.32	22.77
DM	0.25	0.21	0.03	2.22
Depressed mood				
Age	1.06	0.16	0.98	1.15
Sex	2.27	0.43	0.30	17.19
Cirrhosis	0.08	0.02	0.01	0.60
Smoking	2.63	0.3	0.42	16.53
DM	0.79	0.83	0.1	6.19
Anxious mood				
Age	1.11	0.04	1	1.24
Sex	0.28	0.34	0.02	3.79
Cirrhosis	0.06	0.01	0.01	0.54
Smoking	4.98	0.12	0.65	37.85
DM	0.09	0.053	0.008	1.03
Apathy				
Age	1.34	0.11	0.9	1.91
Sex	0.0	0.99	0.0	–
Cirrhosis	0.0	0.99	0.0	–
Smoking	0.77	0.85	0.05	11.77
DM	0.13	0.08	0.013	1.29
Sleep disorders				
Age	1.04	0.45	0.94	1.15
Sex	0.49	0.60	0.04	6.76
Cirrhosis	0.05	0.01	0.01	0.43
Smoking	8.92	0.03	1.23	64.62
DM	0.82	0.87	0.08	8.21
Daytime sleepiness				
Age	1	0.19	0.97	1.15
Sex	1.7	0.58	0.26	11.17
Cirrhosis	0.0	0.99	0.0	–
Smoking	7.43	0.09	0.73	75.32
DM	0.19	0.18	0.02	2.2
Pain and other sensations				
Age	7.1	0.99	0.0	4.9
Sex	–	0.99	0.0	–
Cirrhosis	666	1	0.0	–
Smoking	0.0	0.99	0.0	–
DM	0.0	0.99	0.0	–
Urinary problems				
Age	1.14	0.03	1.01	1.28
Sex	0.87	0.93	0.05	15.27
Cirrhosis	0.14	0.09	0.01	1.41
Smoking	1.35	0.79	0.14	12.3

Table 1 (continued)

	Odds ratio	*p* value	95%CI	
			Lower	Upper
DM	0.12	0.04	0.015	0.99
Light-headedness on standing				
Age	1.06	0.16	0.97	1.16
Sex	1.3	0.80	0.15	11.43
Cirrhotic	0.07	0.01	0.01	0.54
Smoking	0.36	2.42	0.36	16.2
DM	0.17	0.24	0.03	1.85

Predictors: Patients age (numerical continuous). Sex (categorical binary): 0 = Male 1 = Female

Disease condition (categorical binary): 0 = Non-cirrhotic 1 = Cirrhotic

HCV: hepatitis C virus

DM: diabetes mellitus

Regarding the laboratory investigations of HCV patients, more than two-third of the studied group (77.5%) represented with low Hb, (62.5%) represented with high AST level and about (87.5%) with high ALT level.

Regarding early non-motor neurological manifestations of Parkinson's disease among the studied HCV group, the majority (85%) of the patients show cognitive impairment, (27.5%) were at stage 1 of anxious mood, while half (50%) of the patients were at stage 1 of fatigue as evaluated by UPDRS score.

Regarding the relation between early neurological manifestations of Parkinson's disease and liver status, Child C patients showed significantly higher percentages of sleep disorders, daytime sleepiness and fatigue (83%, 83%, and 67%) compared to other Child scores (p value 0.04, 0.02, and 0.03).

Multivariate analysis of factors associated with positive symptoms of Parkinson's disease in HCV patients revealed that cirrhosis was a significant factor for presence of depressed mood, sleep disorders and light headedness on standing ($p < 0.05$), while age and cirrhosis were the significant factors for anxious mood and urinary problems ($p < 0.05$). DM was a significant factor regarding to the urinary symptoms ($p < 0.05$), while smoking was a significant factor regarding to the sleep disorder symptoms ($p < 0.05$).

Finally, a relation was found between HCV and early non- motor Parkinson's features especially cognitive impairment, fatigue and sleep-related disorder. Unfortunately no patient with full, advanced stage of Parkinson's disease has been found to be HCV negative.

Discussion

Parkinson's disease (PD) is the second most prevalent chronic progressive neurodegenerative disease characterized by motor symptoms, such as tremor, rigidity, and hypokinesia. The prevalence of PD is approximately 0.2% on average in the general population, but it is increasing with age up to 1.9%. The disease affects primarily the elderly, imposing a serious burden on the aging societies.

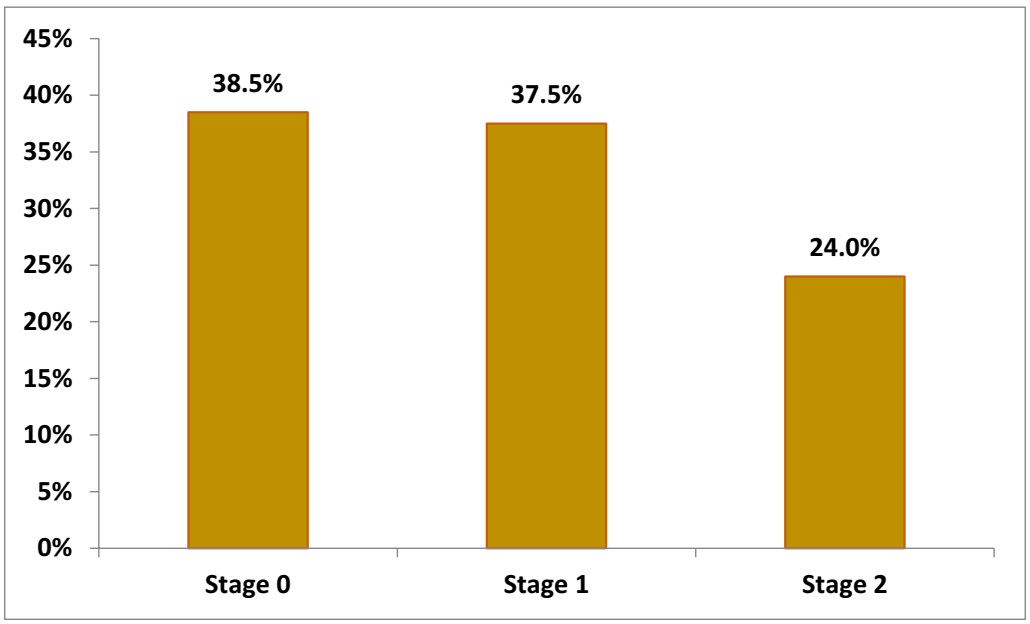

Fig. 1 Distribution of speech difficulties among the studied group

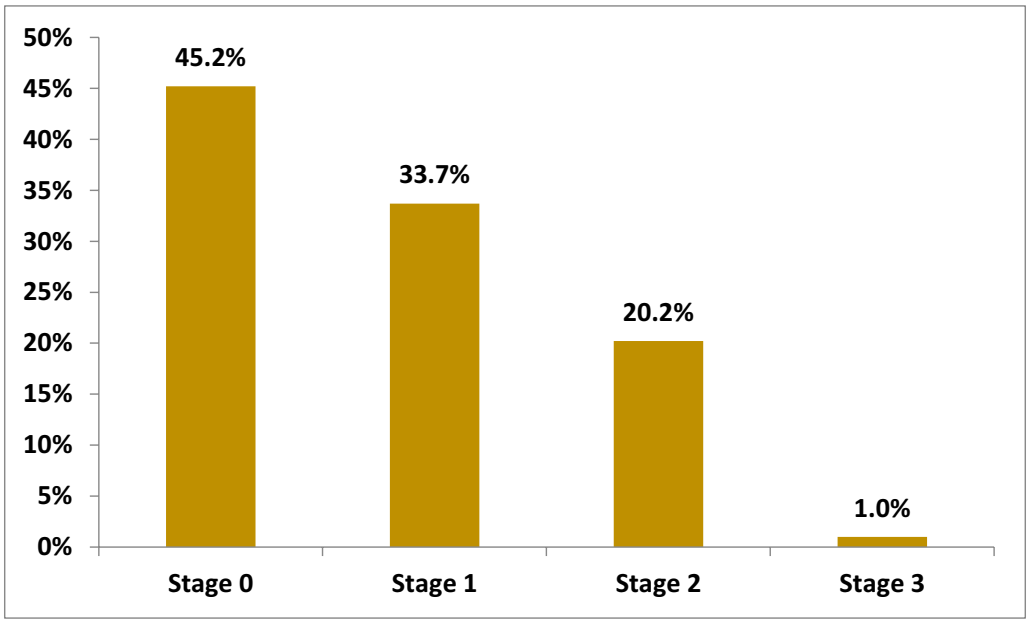

Fig. 2 Distribution of Facial rest tremors among the studied group

The non-motor symptoms may appear in early stages of the disease and even before the appearance of classical motor symptoms. The comorbidity is common in PD patients [46].

Studies about the association between Parkinsonism and chronic HCV have conflicting results. The aim of the current study was to evaluate the association between Parkinsonism and HCV by assessing the prevalence of HCV in a cohort of known Parkinson's disease (PD) patients on follow-up and on the other hand assessing early parkinsonian symptoms in another cohort of HCV patients in different stages of liver disease.

Our study was done on two phases: one phase on Parkinson's patients who have no history of hepatic troubles and the next phase were done on hepatic patients who have no history of neurological deficits. HCV antibodies are tested in the first group, and clinical examination using the UPDRS was done for the second group trying to find an association between HCV and PD.

All PD patients in the first group revealed negative results for HCV Ab testing. Regarding early non-motor neurological manifestations of Parkinson's disease among the studied HCV group, the majority (85%) of the patients show cognitive impairment, (27.5%) were at stage 1 of anxious mood, while half (50%) of the patients were at stage 1 of fatigue as evaluated by UPDRS score.

Our results revealed lack of association between parkinsonism and HCV where negative HCV antibody testing was noted among all the studied patients with Parkinson's disease. These results are matching with Golabi and colleagues in 2017, who found no relation between HCV and Parkinson's disease as the prevalence of Parkinson's disease was even significantly lower in the HCV group in their study compared to non-HCV group (0.7% in HCV with HBV, 0.5% in HCV only; 1.6% in HBV only, and 1.3% in No HCV and No HBV, $p < 0.00001$) [47].

The results of the current study also match with that of [39] who performed a nationwide retrospective study on 4,514,807 persons to assess the association between hepatitis C and B viruses and Parkinson's disease and found a minor increased risk for PD in patients with HCV. The OR calculated for PD in HCV-positive patients in their cohort was 1.18 (95% CI 1.04–1.35) [33].

On the other hand, Wu and colleagues, 2015 were found that patients with chronic HCV had 1.9 times higher risk for acquiring Parkinson's disease [28]. Similarly, Tsai and colleagues in their study on 49,967 Taiwanese people found that HCV had 2.5 times higher risk of getting Parkinson's disease [48]. In a systematic review and meta-analysis including 323,974 participants, higher risk of Parkinson's disease among HCV patients was noted with pooled OR of 1.35. The main limitation of this study was the limited accuracy of diagnosis of PD in the primary studies which were coding-based studies [49].

The discrepancy between our results and the previously mentioned studies may be due to smaller number of study population in the current study, the difference in genetic, ethnic, and environmental factors and to the recently achieved lower incidence of HCV transmission in Egypt after the very high success of HCV eradication

campaign launched in the late 2018 by the Egyptian ministry of health.

Owing to the negative HCV Ab testing results in the cohort of Parkinson's disease patients in our study, we reversed the screening method by screening a cohort of chronic HCV patients with different stages of liver disease for the pre-motor symptoms of Parkinson's disease (the earliest signs of PD) using a translated into Arabic UPDRS questionnaire. Among HCV-positive patients in our study, Child C patients showed significantly higher percentages of sleep disorders, daytime sleepiness, and fatigue (83%, 83%, and 67%) compared to other Child scores. On performing multivariate analysis for factors associated with positive parkinsonian symptoms, cirrhosis was a significant factor regarding the depressed mood, sleep disorders and light headedness on standing ($p < 0.05$). Cirrhosis and age were significant factors for having anxious mood and urinary problems ($p < 0.05$). These findings point to that cirrhosis itself may be the responsible factor for having such neurological manifestations rather than HCV infection. These findings are matching with the results of Lilach and colleagues, 2019 who found increased risk for PD in a group of patients with NASH with OR of 1.13, which raised the possibility that liver disease per se is a risk factor for PD rather than viral infection. They also concluded that the association of neurological symptoms with cirrhotic NASH patients may be the result of the occurrence of cirrhosis-induced parkinsonism-like symptoms that were misclassified as PD [33].

Cirrhosis-induced parkinsonism-like symptoms or known as acquired hepato-cerebral degeneration (AHD) is a syndrome seen in patients with advanced hepatic disease or cirrhosis who present with different neurological manifestations, among them parkinsonism symptoms are the most common. AHD is also different from hepatic encephalopathy being chronic and progressive in nature in contrast to hepatic encephalopathy, which is an acute and reversible condition, often preceding AHD [48]. Mechanism of AHD is believed to be due to accumulation of toxic substances, such as ammonia or manganese, in some areas of the brain, leading to inflammation in nervous system and subsequently to degeneration [50–53]. As basal ganglia appear to be susceptible to accumulation of these toxic materials, parkinsonism is the most common clinical syndrome seen [54–59].

The current study main point of strength comes from assessing the two aspects of the coin for possible relation between Parkinsonism and HCV. However, the main limitation is the small number of patients included, so we recommend performing further multi-center study to include larger number of patients with different spectrum of both diseases.

Conclusion

PD is really a disabling disease with its many drawbacks on the patient and his relatives and the whole society. The etiology of the disease is still unknown. Hence, many observational studies are needed. Based on the results of the current study, we can conclude that advanced cirrhosis but not chronic HCV infection is associated with a variety of neurological symptoms including parkinsonian symptoms that may be attributed to acquired hepato-cerebral degeneration (AHD) which should increase attention to perform more studies on larger number of patients to verify and apply preventive and therapeutic measures for better quality of life for this cohort of patients. Other neurotropic viruses should be assessed in patients with Parkinson's disease and not only HCV. Future studies should pay attention for including larger number of patients especially for early hepatic infection.

Abbreviations

HCV	Hepatitis C virus
HCV abs	Hepatitis C virus antibodies
CNS	Central nervous system
DHS	Demographic and health survey
NCCVH	The national committee for control of viral hepatitis.
NMS	Non-motor symptoms
PD	Parkinson disease
UPDRS	Unified Parkinson disease rating scale
HBV	Hepatitis B virus
AHD	Acquired hepato-cerebral degeneration
PCR	Polymerase Chain Reaction
US	Ultrasound

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Author contributions

R. E: supervision of the clinical work, writing the paper. E. Elh: performing the clinical part of the work and data collection. S. S.M: The neurology consultant who examined and followed the Parkinson cases, writing the paper and the corresponding author. I. H: Idea of the study, supervision of the whole work. A. H: supervising the clinical work, writing the paper.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was endorsed by the ethical committee in Kasr Al-Ainy in April 2020. Code: MS-330-2019 and all included patients signed an informed consent. All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all included subjects.

Consent for publication

Not applicable.

Competing interests

No competing interests.

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