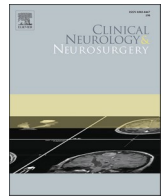




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Neurological symptoms of COVID-19 infection; a cross-sectional study on hospitalized COVID-19 patients in Iran

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19), a global issue now, can have a variety of clinical manifestations. Hundreds of articles have discussed different aspects of this infectious disease, such as physiopathology, epidemiology, clinical manifestations and treatment protocols. Recently, neurological manifestations of the disease have been found to be pretty common among COVID-19 patients. Here, neurological symptoms of COVID-19 infection with a focus on non-cerebrovascular complications are discussed in a large study population. **Methods:** Neurological symptoms of 891 hospitalized COVID-19 patients from March to June 2020 in a major Hospital, Tehran, Iran, were reviewed. Demographic characteristics and neurological manifestations were analyzed.

Results: Among 891 hospitalized COVID-19 patients, the following symptoms were observed: headache (63.9%), sleeping problems (51.3%), hyposmia/anosmia (46%), dizziness (45.4%), hypogeusia (42.1%), memory issues (31.5%), auditory disturbances (17.5%), paralysis (3.7%) and seizures (1.7%). In 29.7% of the patients, a neurological symptom was the initiating symptoms of the infection. Females were more likely to show headache and dizziness compared to males (p value<0.05). Headache intensity was also higher in females compared to males (p value<0.05). Headache prevalence was lower in older patients (p value<0.05), while memory loss and impaired consciousness were higher by increasing age (p values=0.002 and 0.001, respectively).

Conclusion: Neurological manifestations were common among COVID-19 patients under study. Headache, as the most common neurological symptom among COVID-19 patients, was the most prevalent and intense among the female population. Headache, dizziness, sleeping problems, hyposmia/anosmia and hypogeusia were common COVID-19 neurological manifestations, while memory issues, auditory disturbances, paralysis, and seizures were less common.

1. Introduction

Coronavirus disease 2019 (COVID-19) outbreak started from Wuhan, China, in late 2019 [1], presenting with unusual pneumonia of unknown etiology suspiciously related to a seafood market [2]. Today the issue is global with 226,675,069 confirmed cases and 4,663,104 deaths worldwide (until September 15, 2021) [3]. Since the initiation of the pandemic, a huge amount of articles has been published about COVID-19 and a global interest among researchers has been generated,

resulting in hundreds of articles discussing the disease's different aspects, such as epidemiology, clinical presentation, routes of transmission, and therapy protocols [4–6].

COVID-19 is believed to be transmittable via air droplets during incubation and symptomatic phases. The incubation period of the disease is about five days, on average. The main clinical symptoms of COVID-19 are fever, musculoskeletal pain, dyspnea, dry cough, diarrhea, nausea and vomiting [7–12]. Most COVID-19 cases (about 80%) experience non-severe disease; however, a few of them (about 20%) develop

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pneumonia after about five days. Approximately 5% of COVID-19 infected individuals develop severe infection with pulmonary, renal or cardiac failure and ARDS [13,14]. The disease mortality rate is around 2–3%, while it is believed to be about 4–11% among those who need hospital admission [15].

Although most of the clinical manifestations of COVID-19 are respiratory, cardiac, or gastrointestinal, many patients also experience neurological symptoms. These manifestations can be caused by the direct effect of the virus on the nervous system or para-infectious/post-infectious immune-mediated disorders [16]. The most common neurological symptoms seen during COVID-19 infection are headache, dizziness, olfactory disturbances and neuralgia. On the other hand, some neurological complications, such as cerebrovascular events, impaired consciousness, and encephalopathy are observed as well [17,18]. Here, 891 COVID-19 cases were studied and neurological manifestations and associations of the disease were discussed in the study population.

2. Material and methods

2.1. Study design and setting

We conducted a retrospective, observational study in a major hospital in capital of Iran, Tehran. We reviewed the medical records of 891 patients diagnosed with COVID-19 referred to the hospital from March 1st to June 30st, 2020. The data was collected by two neurologists using hospital's health informative system (HIS) via checklists. All patients had a confirmed laboratory diagnosis of COVID-19, either with a positive result for IgG/IgM antibodies against SARS-CoV-2 in a blood test or through detection of SARS-CoV-2 RNA with a real-time reverse transcription-polymerase chain reaction (RT-PCR) of throat swab samples. Demographic data such as age, sex, previous co morbidities (hypertension, diabetes, dyslipidemia, heart disease, immune suppression and neurological diseases) were recorded. We categorized neurological symptoms including headache, dizziness or vertigo, insomnia, impaired consciousness, seizures, paralysis, hearing loss, hyposmia/anosmia and hypogeusia.

All 891 patients included in the study were COVID-19 hospitalized patients of whom 35 ones were admitted to ICU (15 patients due to seizures and 20 patients due to stroke) and 856 patients were admitted to general COVID-19 ward. The severity of COVID-19 disease among patients of this study was ranged from moderate to critical which is defined as; moderate: clinical symptoms such as fever and respiratory manifestations with pneumonia on imaging; severe; at least one criterion of the following: (1) respiratory rate ≥ 30 times/minute with shortness of breath; (2) arterial partial pressure of oxygen/fraction of inspiration of oxygen ≤ 300 mmHg; (3) finger oxygen saturation $\leq 93\%$ in the resting state; and (4) lesion progression of more than 50% in 24–48 h on the chest imaging. Critical: at least one on the following conditions: (1) respiratory failure needing mechanical ventilation; (2) shock; and (3) failure of other organs, and the need for intensive care unit admission [19,20].

Headache severity was measured using numerical VAS (visual analogue scale) pain scale in which patients are asked to circle the number between 0 and 10 that fits best to their pain intensity [21]. Insomnia was defined as trouble starting or maintaining sleeper Early-morning awakening with inability to return to sleep according to Diagnostic and statistical manual of mental disorders five (DSM5) criteria [22]. Sleep disturbances due to coughing, sneezing and respiratory problems were not considered. Paralysis was defined as hemiplegia, paraplegia and facial paralysis. Memory loss was defined as unusual forgetfulness in which you may not be able to remember new events, recall one or more memories of the past, or both. Stroke was defined as either hemorrhagic or ischemic stroke.

This is a cross sectional and non-interventional study; we did not perform any experiments in human subjects. This study was registered in our center (identifier: 99000321) and it received approval from the

institutional ethical standards committee.

2.2. Statistical analysis

The statistical analysis was performed using the SPSS software, version 25 (SPSS, Chicago, IL). The ratios were compared using the Chi squared test and the Fisher's exact test when the sample size was too small. The comparison between quantitative variables was performed if indicated. Logistic regression analysis was used to evaluate the risk factors for developing neurological symptoms during COVID-19. Variables with $P < 0.05$ in the univariate analysis test were entered into a multivariate logistic regression analysis with the forward method.

3. Results

From a total of 891 COVID-19 patients whom we studied, 3.5% were 10–20 years old, 12% were 21–30, 29.1% were 31–40, 23.1% were 41–50, 20.5% were 51–60, 7.6% were 61–70% and 4.2% were 71 years old or higher. 57.2% of participants were male while 42.8% were female.

55.2% of study participants suffered from underlying disorders with hypertension as the most prevalent disorder (15.4%) and diabetes (11.6%), cardiovascular disease (CVD) (8.5%), respiratory disorders (8.3%) and auto-immune diseases (4.3%) coming next. About 12% of participants mentioned a history of a previously existing neurological disorder with headache and migraine as the most prevalent one (18.7%) and stroke (1.9%) and seizures (1.2%) coming next. (Table 1).

The findings in two subgroups of patients with and without neurological symptoms during COVID-19 infection revealed that the neurological symptoms have significantly occurred among patients with history of pre-existing neurological conditions [P-value: 0.004, OR: 10.906, CI: (1.498–79.377)] and Migraine and other primary headaches [P-value: 0.007, OR: 3.411, CI: (1.351–8.612)], whereas other co-morbidities did not have significant correlation with the distribution of subgroups (with and without neurological symptoms) (Table 2).

An adjusted logistic regression analysis was conducted to evaluate the factors associated with presence of neurological symptoms during COVID-19. Variables with P-value < 0.05 in the univariate analysis test including any pre-existing neurological condition and migraine and other primary headaches were entered into logistic regression analysis. Results revealed that these two variables significantly possess predictive values as risk factors for the developing neurological symptoms during COVID-19 [(Any pre-existing neurological condition: OR_{Adj}: 8.315, 95% CI: 1.129–61.235, P-value=0.038), (Migraine and other primary headaches: OR_{Adj}: 2.624, 95% CI: 1.030–6.688, P-value=0.043)] (Table 3).

Because the CI of any pre-existing neurological disorder was very wide another analysis was done to see whether the significance of any pre-existing neurological disorder was driven by headache or not (Table 4).

From a total 891 patients of our study, 63.9% mentioned headache, 51.3% mentioned sleeping problems, 46% mentioned hyposmia/anosmia, 45.4% mentioned dizziness, 42.1% mentioned

Table 1
Underlying neurological and non-neurological conditions.

Underlying non-neurological conditions	(Prevalence %)	Underlying neurological conditions (prevalence %)	(Prevalence %)
Hypertension	15.4	Migraine and other primary headaches	18.7
Diabetes	11.6	Stroke	1.9
CVD	8.5	Seizures	1.2
Respiratory disorders	8.3		
Auto-immune diseases	4.3		

Table 2
Prevalence of co-morbidities among patients with and without neurological symptoms.

Variables	Status	Neurological symptoms during COVID-19 disease		Missing patients	P-Value	OR	95% confidence interval	
		Shown [N, (%)]	Not-shown [N, (%)]				Lower	Upper
Diabetes	Yes	89,(11.6)	9,(12.9)	5	0.846	0.892	0.428	1.859
	No	676,(88.4)	61,(87.1)	51				
Hypertension	Yes	121,(15.8)	9,(12.9)	7	0.607	1.273	0.616	2.633
	No	644,(84.2)	61,(87.1)	49				
Heart disease ^a	Yes	69,(9.0)	6,(8.6)	1	1.000	1.057	0.442	2.531
	No	696,(91.0)	64,(91.4)	55				
Respiratory disease ^b	Yes	68,(8.9)	4,(5.7)	2	0.394	1.610	0.569	4.552
	No	697,(91.1)	66,(94.3)	54				
Autoimmune and rheumatologic disease ^c	Yes	35,(4.6)	3,(4.3)	0	1.000	1.071	0.321	3.574
	No	730,(95.4)	67,(95.7)	56				
Any pre-existing neurological condition ^d	Yes	104,(13.6)	1,(1.4)	3	0.004	10.906	1.498	79.377
	No	660,(86.4)	70,(98.6)	53				
Migraine and other primary headaches	Yes	159,(20.8)	5,(7.1)	3	0.007	3.411	1.351	8.612
	No	606,(79.2)	65,(92.2)	53				
Epilepsy	Yes	11,(1.4)	0,(0)	0	0.613	-	-	-
	No	754,(98.6)	70,(100)	56				
Stroke	Yes	17,(2.2)	0,(0)	0	0.387	-	-	-
	No	748,(97.8)	70,(100)	56				
Multiple sclerosis	Yes	6,(0.8)	0,(0)	1	0.674	-	-	-
	No	759,(99.2)	70,(100)	55				

^a Congestive heart failure (CHF), old myocardial infarction (MI), coronary artery disease (CAD), unstable angina (UA) and arrhythmia.

^b Asthma, chronic obstructive pulmonary disease(COPD), chronic lung diseases, sinusitis.

^c Systemic lupus erythematosus, rheumatoid arthritis(RA), behcet's disease, sjogren's syndrome.

^d Any primary chronic headache, stroke, epilepsy, multiple sclerosis (MS), Parkinson's disease, Alzheimer disease, meningitis, myasthenia gravis and any other confirmed neurological disorder.

Table 3
Multivariate logistic regression of variables associated with neurological symptoms during COVID-19.

variable	P-Value	OR _{adj} ^a	95% C.I. ^b	
			Lower	Upper
Any pre-existing neurological condition	0.038	8.315	1.129	61.235
Migraine and other primary headaches	0.043	2.624	1.030	6.688

^a Odds ratio adjusted.

^b 95% confidence interval.

hypogeusia,31.5% mentioned memory issues, 17.5% mentioned auditory disturbances,3.7% mentioned paralysis (hemiplegia, paraplegia and facial paralysis), 1.7% mentioned seizures, and 29.7% mentioned a neurological symptom as the first symptom of the disease during the timeline of COVID-19 infection. Headache was the most prevalent initiator symptom of the disease among those who's the first illness symptom was a neurological one (26.6%) (Table 5).

Headache and dizziness were significantly higher among female COVID-19 patients rather than male ones (p value<0.05). Other neurological symptoms did not show significant difference by sex. Age

Table 4
The significance of pre-existing neurological disorders vs. headache.

Variables	Status	Headache during COVID-19 disease		P-Value	OR	95% Confidence Interval	
		Yes [N,(%)]	No [N,(%)]			Lower	Upper
Any pre-existing neurological condition	Yes	82,(14.4)	25,(7.8)	0.005	1.977	1.235	3.166
	No	488,(85.6)	296,(92.2)				
Migraine and other primary headaches	Yes	139,(24.4)	28,(8.7)	0.000	3.394	2.203	5.229
	No	430,(75.6)	294,(91.3)				
Epilepsy	Yes	8,(1.4)	3,(0.9)	0.755	1.516	0.399	5.756
	No	561,(98.6)	319,(99.1)				
Stroke	Yes	12,(2.1)	5,(1.6)	0.621	1.366	0.477	3.912
	No	557,(97.9)	317,(98.4)				
Multiple sclerosis	Yes	6,(1.1)	1,(0.3)	0.277	3.421	0.410	28.541
	No	563,(98.9)	321,(99.7)				

was found to be effective on prevalence of headache, memory loss and impaired consciousness. We found that headache prevalence decreases in older patients (p value<0.05). Headache as a neurological presentation of COVID-19 was mostly seen among patients between 31 and 40 years of age. On the other hand, the prevalence of memory loss and impaired consciousness are increased in older participants (p values=0.002 and 0.001 respectively) (Table 6).

The most common neurological symptom among both female and male subgroups was headache. The pattern of headache and dizziness is discussed in Table 7. Headache was significantly more intense among females rather than males (p value<0.05) while the intensity of other

Table 5
Prevalence of neurological symptoms in COVID-19 patients.

Neurological symptom	Prevalence (%)	Neurological symptom	Prevalence (%)
Headache	63.9	Memory issues	31.5
Sleeping problems	51.3	Auditory disturbances	17.5
Hyposmia/anosmia	46	Paralysis	3.7
Dizziness	45.4	Seizures	1.7
Hypogeusia	42.1		

Table 6
Distribution of symptoms by age.

Age Symptom prevalence	10–20 N, (%)	21–30 N, (%)	31–40 N, (%)	41–50 N, (%)	51–60 N, (%)	61–70 N, (%)	>70 N, (%)	P value
Headache	21,(67.7)	73,(68.2)	182,(70.3)	141,(68.4)	103,(56.3)	31,(45.6)	18,(48.6)	0.000
Memory loss	8,(26.7)	16,(16.3)	81,(32.5)	64,(33)	53,(30.5)	25,(39.7)	19,(52.8)	0.002
Impaired consciousness	3,(10)	2,(2)	11,(4.4)	10,(5.2)	14,(8.2)	8,(13.1)	9,(25)	0.001
Dizziness	14,(48.3)	38,(38)	121,(48.2)	98,(51.3)	70,(41.4)	22,(35.5)	18,(48.6)	0.634
Hyposmia/anosmia	12,(38.7)	47,(49)	116,(46.8)	101,(52.3)	65,(38.7)	27,(42.9)	16,(44.4)	0.299
Dysgeusia	11,(39.3)	39,(40.2)	104,(41.8)	94,(49.2)	65,(38.7)	22,(37.3)	13,(37.1)	0.715
Auditory disturbances	2,(6.7)	14,(14.4)	44,(17.1)	37,(19.1)	31,(18.5)	10,(16.4)	8,(22.9)	0.191
Sleeping problems	13,(43.3)	45,(46.4)	124,(49.6)	111,(56.9)	81,(47.4)	32,(53.3)	24,(66.7)	0.146
Seizures	1,(3.3)	0,(0)	2,(0.8)	5,(2.6)	4,(2.3)	1,(1.6)	1,(2.9)	0.152
Paralysis	1,(3.2)	3,(2.8)	8,(3.1)	2,(1)	12,(6.6)	3,(4.4)	4,(10.8)	0.063

neurological symptoms did not show statistically significant difference between male and female subgroups.

Previously existing diseases were effective in prevalence of neurological symptoms among COVID-19 patients as we found that headache, dizziness, hyposmia/anosmia, hypogeusia, auditory disturbances, sleeping problems, memory loss and paresthesia in hands and feet were significantly higher among patients with underlying disorders in compare to others (p values=0.001, 0.007, 0.014, 0.011, 0.005, 0.035, 0.001 and 0.011 respectively).

Underlying neurological diseases were found to be effective in prevalence of neurological symptoms among COVID-19 cases. We determined that headache, hyposmia/anosmia, hypogeusia, sleeping problems, paresthesia in hands and feet, paralysis, impaired consciousness and memory loss are significantly higher among patients with Underlying neurological diseases comparing to others (p values=0.005, 0.048, 0.027, 0.001, 0.024, 0.020, 0.003 and 0.018 respectively). The most prevalent neurological underlying disorder among COVID-19 patients who experienced neurological symptoms was headache which was seen in almost 75% of participants with neurological symptoms as a neurological underlying disorder. On the other hand, the most prevalent preexisting non-neurological disorder among COVID-19 patients was hypertension which was seen in 12.5% of COVID-19 cases with neurological symptoms.

Stroke as an important neurological underlying condition was seen mostly among patients over 70 years old while seizures was an underlying condition seen mostly among patients between 10 and 20 years of age.

4. Discussion

In this retrospective observational study, neurological manifestations were shown to be pretty common among COVID-19 patients. In several cases (27%), the initiating symptoms of the illness were neurological. 63.9% of the study population presented at least one neurological symptom during the course of infection, which was pretty higher than the proportion suggested by previous data [23].

The mechanism of neurologic involvement during COVID-19 infection is believed to be either a direct effect of the virus on the nervous

Table 7
Headache pattern of COVID-19 patients.

Headache pattern	Prevalence (%)	Dizziness pattern	Prevalence (%)
Global	31.2	Feeling of imbalance	26
One-sided	18.2	Light headedness	16
Tensional	15.3	True vertigo	9.3
Pulsate	12.6		
Accompanied by nausea and vomiting	10.5		
Sharp stabbing	2.5		

system or an indirect neurological effect caused by Para-infectious/post-infectious immune-mediated disease that leads to a breakdown in the blood-brain barrier (BBB), leaving it permeable to cytokines and making the nervous system vulnerable to neuro-inflammatory reactions [12, 23–27]. Direct COVID-19 neurologic invasion has been rarely described in the previous data. Moriguchi et al. reported a 24 years old man in Japan presenting with generalized seizures and reduced consciousness, whose CSF analysis was positive for COVID-19, and then the patient was diagnosed with SARS-COV-2 encephalitis [25]. Sohal et al. reported a 72 years old man in the USA presented with light headedness, altered mental status and seizures; he had a positive RT-PCR sample (source not specified) and then diagnosed with COVID-19 encephalitis [28]. Wong et al. reported a 40 years old man in the UK who presented with diplopia, ataxia, oscillopsia, and bilateral facial weakness (rhombencephalitis), whose nasopharyngeal swab sample was positive for COVID-19; however, CSF analysis was not performed and finally, he was diagnosed with COVID-19 encephalitis [29]. Another interesting study was a case report by Paniz-Mondolfi et al. about a patient presented with confusion, who finally died; the post-mortem analysis of this case showed the presence of the COVID-19 virus in the patient’s frontal lobe neurons and brain endothelial cells [26]. Among 891 patients of the current study, we had two unique cases which were previously published as case reports; A 40 y/o male with diplopia, nystagmus, and gait disorders who was diagnosed with CNS vasculopathy(arteritis) and discharged with full recovery after treatment and an 18 y/o female with generalized tonic-clonic seizures and a three week history of mood changes and depression accompanied by lack of concentration who was diagnosed with simultaneous anti-NMDAR and COVID-19 encephalitis and discharged with full recovery after treatment [30,31].

Underlying disorders in the current study were very much similar to the previous research. Hypertension was found as the most common underlying disorder among the study population (15.4%), similar to many earlier studies [32–36]. The next underlying disorders by prevalence order were: diabetes (11.6%), cardiac conditions (8.5%), respiratory disease (8.3%) and autoimmune disorders (4.3%). Pre-existing neurological conditions were also analyzed in the present study; it was shown that about 12% of the study population had a history of neurological diseases with headache and migraine as the most prevalent (18.7%), followed by stroke (1.9%) and epilepsy (1.2%). Previous data from Spain shows lower portions of pre-existing neurological disorders (8.4%) compared to the present study [23]. The novelty of the current work was to analyze the possible correlation between underlying neurological and non-neurological disorders and the risk of developing neurological symptoms. It was found that pre-existing neurological condition and migraine and other primary headaches were risk factors to develop neurological symptoms during the course of COVID-19 infection.

Headache has been discussed as one of the most prevalent non-specific neurological symptoms of COVID-19 in prior studies [23,24, 37–41]. Another novelty of this experience was to analyze the pattern of headache as the most prevalent neurological symptom among the study

population. Further, the prevalence of COVID-19-related headaches was analyzed in different age periods, and it was found that the peak of headache prevalence occurred in patients between 31 and 40 years old; however, it declined above this age. Memory loss and impaired consciousness, on the other hand, were positively correlated with age.

The peripheral nervous system (PNS) can be invaded by COVID-19, just like the central nervous system (CNS). Cranial and peripheral nerves can be involved during COVID-19 infection with direct and indirect mechanisms, as discussed before. Viral entry points to the PNS remain unclear; however, recently, it has been discovered that goblet and ciliated cells can be potential entry points for the SARS-CoV-2 virus to PNS [29]. Both goblet and ciliated cells over express ACE2 receptors, which are COVID-19's main entry routes to the cells [36]. Cranial nerve involvement can lead to hyposmia/anosmia, dysgeusia, and auditory disturbances, all of which are observed in the current experience. Peripheral nerve involvement can result in peripheral paralysis, which is also discussed in the present study.

Hyposmia/anosmia and hypogeusia are common neurological manifestations in the present study with higher occurrences compared to the Spanish population [23]. The exact underlying mechanism of hyposmia/anosmia and hypogeusia in COVID-19 infection remains unclear; however, theoretically, it can be a result of damage to the nasal epithelium or direct damage to the olfactory nerve and olfactory bulb [42,43]. These two symptoms are believed to be indicators of early infection [17,42,44]. However, these symptoms are not analyzed in the present work by the exact time of their occurrence in the infection timeline. This study shows that a small proportion of patients (3.7%) experience paralysis in different forms: 1.1% experience hemiplegia mostly seen in cerebrovascular events, 1.6% experience paraplegia possibly due to cerebrovascular events or peripheral neuropathy and 1.6% experience one-sided facial paralysis observed in both CNS and PNS involvement.

Dizziness is also a frequently mentioned symptom in earlier research [23,24,37–41]; however, the exact pattern of dizziness was analyzed in the current research. In this experience, sex is found to be effective in the prevalence of neurological symptoms of COVID-19. Further, it is showed that female patients are more likely to develop headaches and dizziness compared to male ones, while other neurological symptoms are not influenced by sex.

This study was designed to evaluate neurological symptoms of COVID-19. Outcomes of the disease were not to be evaluated in this study. However, it is recommended to evaluate outcomes of patients with COVID-19 related neurological symptoms in the further studies.

5. Conclusion

In conclusion, neurological manifestations were pretty common among COVID-19 patients. These manifestations can be initiated before the COVID-19 symptoms or appear later in the course of infection. Headache was the most common neurological symptom among COVID-19 patients with higher prevalence and intensity among the females. Headache, dizziness, sleeping problems, hyposmia/anosmia and hypogeusia were very common neurological manifestations of COVID-19 infection, while memory issues, auditory disturbances, paralysis and seizures were other less common ones. Further investigation in larger scales is recommended to get more precise results about COVID-19 neurological manifestations.

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Data Availability Statement

Any data used to write this article is available and will be shared if necessary. All Statistical analysis files and data are available and will be

shared in necessary.

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