



# Early neurological manifestations of hospitalized COVID-19 patients

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## Abstract

**Introduction** Neurological manifestations can occur during coronavirus disease 19 (COVID-19). Several pathogenic mechanisms have been hypothesized, without conclusive results. In this study, we evaluated the most frequent neurological symptoms in a cohort of hospitalized COVID-19 patients, and also investigated the possible relationship between plasmatic inflammatory indices and olfactory disorders (ODs) and between muscle pain and creatine kinase (CK).

**Methods** We consecutively enrolled hospitalized COVID-19 patients. A structured questionnaire concerning typical and neurological symptoms, focusing on headache, dizziness, ODs, taste disorders (TDs), and muscle pain, was administrated by telephone interviews.

**Results** Common neurological symptoms were reported in the early phase of the disease, with a median onset ranging from 1 to 3 days. Headache showed tension-type features and was more frequently associated with a history of headache. Patients with ODs less frequently needed oxygen therapy. Inflammatory indices did not significantly differ between patients with and without ODs. Muscle pain did not show any association with CK level but was more frequently associated with arthralgia and headache.

**Conclusion** In our cohort, ODs were an early symptom of COVID-19, more frequently reported by patients with milder forms of disease. Headache in association with arthralgia and muscle pain seems to reflect the common symptoms of the flu-like syndrome, and not COVID-19 infection-specific.

**Keywords** COVID-19 · Neurological manifestations · Headache · Test and smell disorders · Muscle pain

## Introduction

In recent weeks, an increasing number of studies have claimed the occurrence of neurological manifestations during coronavirus disease 19 (COVID-19) [1, 2]. Among central nervous system (CNS) manifestations, headache and dizziness were the most frequently reported [1, 2], whereas olfactory (ODs) and taste disorders (TDs) [3], as well as muscle pain, were commonly observed among peripheral nervous system symptoms [1, 2].

Previously, ODs were associated with high level of interleukin 6 (IL-6) in plasma and nasal mucus of patients with hyposmia, suggesting an underlying role of local and systemic inflammatory processes [4].

Moreover, a recent study [1] found a correlation between muscle pain and creatine kinase (CK) in hospitalized COVID-19 patients, speculating that this could be due to a direct skeletal muscle injury.

In the present study, we aimed to evaluate the occurrence of neurological manifestations among hospitalized COVID-19 patients, focusing on headache, dizziness, ODs, TDs, and muscle pain.

We also investigate the relationship between laboratory inflammatory indices and ODs occurrence and between CK and muscular pain.

## Methods

Two trained neurologists administered a structured questionnaire by weekly telephone interviews from the hospital admission over a 30-day follow-up, investigating the occurrence of

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**Table 1** Reported frequencies of typical and investigated neurological symptoms

Typical symptoms	N/Total (%)	N (%) 1st day	Median onset (day)	Range onset (day)
Fever	99 (92)	82/99 (83)	1	1–5
Cough	68 (63)	38/68 (56)	1	1–16
Diarrhea	55 (51)	10/55 (18)	4	1–15
Anorexia	53 (49)	15/53 (28)	3	1–15
Dyspnea	45 (42)	5/45 (11)	5	1–11
Arthralgia	39 (36)	22/39 (56)	1	1–20
Sore throat	15 (14)	8/15 (53)	1	1–3
Rhinorrhea	12 (11)	7/12 (58)	1	1–3
Investigated neurological symptoms				
Headache	46 (43)	19/46 (41)	2	1–9
Dizziness	11 (10)	6/11 (55)	1	1–13
Smell disorders	40 (37)	14/40 (35)	2	1–25
Taste disorders	66 (61)	14/66 (21)	3	1–17
Muscle pain	37 (34)	18/37 (49)	2	1–10

typical and neurological symptoms during COVID-19, focusing on headache, dizziness, ODs, TDs, and muscle pain (Supplementary material). Laboratory testing (blood count, C-reactive protein [CRP], IL-6, CK, lactate dehydrogenase [LDH]) performed at the time of hospital admission was collected in order to explore some clinical-laboratory correlations. The study was approved by the local ethic committee AVEC (CE285-2020). Patients gave their informed consent at the time of hospital admission.

## Statistical analyses

Median and range were used for data not normally distributed. Categorical variables were expressed as counts and percentages. For continuous variables, the Mann-Whitney *U* test was used to test differences between two groups. The chi-square

test was adopted for categorical variables, and odds ratio (OR) and 95% confidence interval (CI) were reported. For statistical tests,  $p < 0.05$  was considered significant.

## Results

Of 192 hospitalized patients, 133 gave their informed consent to participation. Due to clinical deterioration, 25 patients dropped out the study. A total of 108 patients completed the study (median age of 59 years, range 18–83 years; 57% males). Median time between the onset of symptoms and hospital admission was 7 days (range 2–28).

We found that investigated neurological symptoms were reported during the early phase of the disease, showing a median onset ranging from 1 to 3 days (Table 1).

As regards headache, 86% of patients reported a tension-type pain, usually responsive to paracetamol, while 14% of patients reported migraine. Headache was more frequently complained by patients with headache history (81% vs 36%, OR 5.4 [CI 95%: 1.798–16.332],  $p < 0.001$ ).

ODs were significantly more common in patients with TDs as compared to patients without TDs (57% vs 4%, OR 27 [CI 95%: 6.046–121.851],  $p = 0.0001$ ). When TDs were associated with ODs, the onset was earlier (median: 2 vs 5 days,  $p = 0.014$ ) and the duration longer (median: 15 vs 10,  $p = 0.014$ ). ODs and TDs, despite showing progressive improvement, persisted over the 30 days follow-up in 28% and 21% of patients respectively.

ODs were not associated with rhinorrhea, as well as with IL-6 and CRP levels (Table 2).

**Table 2** Biochemical data of COVID-19 patients expressed as median (range)

	Pts with ODs	Pts without ODs	<i>P</i> value
IL-6 (pg/ml)	20.9 (2–130)	26.9 (5.8–601)	0.22
CRP (mg/dl)	4.18 (0.11–21.37)	7.79 (0.2–37.4)	0.402
	Pts with myalgias	Pts without myalgias	
CK (U/L)	88.5 (28–444)	105 (26–431)	0.357
LDH (U/L)	253 (148–537)	273 (165–707)	0.166
CRP (mg/dl)	3.92 (0.11–17.18)	5.96 (0.2–37.4)	0.236

CK creatine kinase, CRP C-reactive protein, IL-6 interleukin 6, LDH lactate dehydrogenase, mg/dl milligrams/deciliters, pg/ml picograms/milliliters, Pts patients, U/L units/liter

Moreover, patients with ODs less frequently needed oxygen therapy (32% vs 61%, OR 0.3 [CI 95%: 0.89–1.013]  $p = 0.044$ ).

Muscle pain was not related to increased levels of CK and LDH as compared to patients without as well as CRP (Table 2), but it was significantly more frequent in patients with headache (54% vs 19%, OR 5 [CI 95%: 2.106–11.681],  $p < 0.0001$ ) and arthralgia (72% vs 13%, OR 16.970 [CI 95%: 6.315–45.604],  $p < 0.0001$ ).

## Discussion

In this study, we evaluated the occurrence of common neurological symptoms related to COVID-19, showing that they were reported in the very early phase of the disease.

Headache has been reported as a minor symptom related to COVID-19 [1, 2], but the pathophysiological mechanism and detailed features have not been discussed before. In our cohort, headache showed tension-type features and was more frequently associated with muscle pain and a history of headache, falling along a “flu-like” syndrome affecting more frequently patients with “pain sensitivity” [5].

We also confirmed the high prevalence of ODs in COVID-19 patients, which was not related to rhinorrhea [3], and did not correlate with plasmatic IL-6 levels, as previously reported [4]. These data suggested that ODs in COVID-19 could be directly related to a direct virus invasion as previously suggested [6], although an association with other inflammatory mechanisms could not be excluded.

Interestingly, patients with ODs seemed to need less frequently oxygen therapy, confirming previous studies showing that smell disorders were very frequent in ambulatory patients [7, 8]. Therefore, these data support that smell disorders were more frequent in milder forms of disease, even in a hospital setting.

Despite the high association between ODs and TDs occurring in the early stage of disease, there are some patients who developed only TDs with a later onset and shorter duration, probably related to non-specific causes (i.e., medical treatments).

Muscle pain was not associated with CK and LDH high levels, supporting the notion that this symptom was not directly accounted for by muscle injury. Indeed, ACE2 receptors have not been found in skeletal muscle by post-mortem examination [9], making a direct viral mechanism unlikely, although it cannot be completely ruled out.

Muscle pain was more frequent in patients also presenting headache, and arthralgia, within a symptomatic set of flu-like syndrome.

Our results should be interpreted with caution due to study limitations: symptoms were self-reported through a questionnaire, the sample was relatively small and geographically limited, not hospitalized patients were not included, and data regarding the subsequent course of the disease were not available.

We conclude that ODs, an early common symptom in COVID-19, may be associated with milder forms of the disease in hospitalized patients. Muscle pain in association with headache and arthralgia seems to be part of common symptoms usually reported within flu-like syndrome.

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**Data availability** All anonymized data from this study will be shared by request from any qualified investigator.

## Compliance with ethical standards

The study was approved by the local ethic committee AVEC (CE285-2020).

**Competing interests** The authors declare that they have no conflicts of interest.

**Patient consent for publication** Patients gave their consent for publication.

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