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# Cluster Headache and COVID-19, a Retrospective Study on Disease Evolution during the Pandemic

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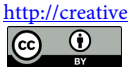



## Abstract

Background: Cluster headache (CH) is a recurrent disease, characterized by severe intensity periorbital headache associated with ipsilateral autonomic signs and symptoms; attacks may occur several times per day, for periods of weeks (so-called cluster), with a relapsing periodic pattern during the year. COVID-19 pandemic has induced many lifestyle changes on the general population, especially related to the so-called lockdown. Aim of this study was to assess the clinical evolution of cluster headache patients during the lockdown period. Methods: Patients included in this observational retrospective study had a definite diagnosis of cluster headache, with a minimum 5-year disease duration. Main collected data included diagnosis, age, disease duration, number of clusters per year, cluster duration, number of attacks per day and attack duration (both pre and post pandemic onset). Statistical analysis was performed to assess differences in cluster headache clinical manifestations before and after pandemic onset. Results: The study included 44 patients, with mean age of 48.8 ± 12.6 years and male prevalence (35 male patients (79%)). Mean disease duration was 16.9 ± 8.5 years. Episodic CH was prevalent, with 40 patients with diagnosis of episodic CH (91%) and only 4 patients with diagnosis of chronic CH (9%). Comparing pre-pandemic period and lockdown period, mean cluster number per year was 1.6 ± 0.9 vs 0.7 ± 1.2 ($p = 0.001$), mean cluster duration was 70.6 ± 98.4 days vs 24.4 ± 61.4 days ($p = 0.001$), mean headache attacks per day were 2.8 ± 1.2 vs 0.8 ± 1.0 ($p < 0.001$), mean headache attack duration was 47.1 ± 31.0 minutes vs 15.3 ± 20.9 minutes ($p < 0.001$). Pain intensity measured using the Numerical Rating Scale was 10 for all patients vs 4.3 ± 5.0 ($p < 0.001$). Conclusion: The results of this study showed a

significant reduction in disease severity for cluster headache patients comparing the pre-pandemic and the lockdown period; this finding may be partly due to the lifestyle changes occurring as a consequence of the lockdown restrictive measures (with subsequent changes in circadian rhythm, sleep-wake cycle and hypothalamic function), even though the observed results were normalized considering the single-patient specific lifestyle and job activity performed during the lockdown, further underlining the peculiarity of this phenomenon.

## Subject Areas

Neurology

## Keywords

Cluster Headache, COVID-19, Pandemic, Lockdown

## 1. Introduction

Cluster headache (CH) is a chronic disease, characterized by recurrent episodes of very severe pain, unilateral, localized to the orbital, supraorbital or temporal area, with a duration between 15 and 180 minutes, manifesting with a frequency between 1 episode every 2 days to 8 episodes per day, with a periodic pattern over several months.

Cluster headache is classified according to the International Classification of Headache Disorders Third Edition (ICHD-III) [1] among the Trigeminal Autonomic Cephalalgias (TACs), along with Paroxysmal Hemicrania, Hemicrania Continua and Short-lasting Unilateral Neuralgiform Headache Attacks. Diagnostic criteria for Cluster Headache are the following: A: at least 5 attacks fulfilling criteria B-D; B: severe or very severe unilateral orbital, supraorbital or temporal pain lasting 15 - 180 minutes; C: either or both of the following: 1: at least one of the following symptoms ipsilateral to the headache: conjunctival injection or lacrimation, nasal congestion or rhinorrhea, eyelid edema, forehead and facial sweating, miosis or ptosis; 2: a sense of restlessness or agitation; D: occurring with a frequency between one every other day and 8 per day; E: not better accounted for by another ICHD-III diagnosis.

The temporal manifestation of CH is typically characterized by periods with attacks (called clusters), alternating with periods free from headache episodes. Cluster periods may have variable duration, usually between 2 weeks and 3 months. The temporal relation between periods with and without attacks distinguishes episodic from chronic CH. If pain-free remission periods lasting 3 or more months occur between cluster periods, episodic CH is diagnosed; if a pain-free period of at least 3 months is not observed between clusters, then chronic CH is diagnosed. Episodic CH is observed in 85% - 90% of CH patients, while chronic CH is rarer, observed in 10% - 15% of patients [1].

During the cluster period, headache attacks occur regularly and may be

exacerbated by trigger factors such as alcohol intake, smoking, alterations in sleep-wake cycle, climatic changes, histamine or nitroglycerin [2]; pain is initially localized to the orbital area but may spread to other cephalic areas. Severe attacks urge the patients to walk back and forth, with impossibility to lie down and rest.

Epidemiologically, CH is a rare disease, occurring in 0.1% of the general population [3]. Age at disease onset ranges between 10 and 68 years, with higher incidence between 20 and 29 years of age. CH is 3-times more prevalent in males than females [4]. Cluster periods are more frequent during spring and autumn, but geographical differences in months with higher attack incidence may be observed [5].

CH pathophysiology remains not completely understood so far. Trigeminovascular system seems likely to be involved, along with cranial parasympathetic system [6], which could have a role in the typical CH orbital pain observed during attacks and in the accompanying autonomic symptoms. The hypothalamus is reasonably thought to play a major role in CH periodic manifestations, possibly related to its role in regulation of circadian rhythm and homeostasis [7].

A possible role for genetic factors in CH pathophysiology has been hypothesized; 5% of CH cases may have an autosomal dominant genetic transmission pattern [2]; moreover, persons with a first or second-degree relative suffering from CH have a higher risk of developing the same disease, compared to the general population [8]. Some studies have suggested an autosomal recessive genetic transmission for CH, while others hypothesize a multifactorial transmission pattern [9].

CH treatment usually comprises a symptomatic treatment and a preventive treatment. Symptomatic treatment is based on injective triptans (such as subcutaneous Sumatriptan 6 mg) and high-flow oxygen. These therapies are warranted as soon as the headache attack begins, to possibly achieve rapid and complete pain freedom. Preventive treatment is focused on reducing the length of the cluster period and achieving the longest possible cluster-free period. Main medications used in this case are Verapamil and Lithium. Corticosteroids are used as a bridge-therapy, to achieve faster headache attacks-freedom until the beneficial effect of preventive treatments starts.

The 2020 COVID-19 pandemic has induced significant changes on the life of millions of citizens, especially as a consequence of the disease-containment and management measures adopted by the political institutions, in particular the so-called "lockdown". This consisted of limitations in the freedom to move outside of one's own house, except for job, health or other proven necessity reasons. The lockdown was adopted in Italy from early March 2020 to the beginning of summer 2020 and again (not completely but with significant reduction of social life) from the end of 2020 to spring 2021, when COVID-19 cases incidence showed a significant reduction. During the lockdown, schools were closed, along with every commercial or leisure activity deemed not necessary; when possible, smart working from home was adopted.

Several studies have inquired the effects of the lockdown on migraine patients, with documented modifications on disease manifestations during this period, usually with a worsening of the clinical conditions of these patients [10]-[14]; no studies, instead, are available in the current scientific literature which have assessed the effects of the lockdown on CH patients.

Aim of this study was therefore to evaluate the effect of the restrictive measures adopted during the lockdown and subsequent lifestyle changes on cluster headache patients currently in treatment at the Headache Centers participating in the study.

## 2. Materials and Methods

This study included patients with a definite diagnosis of cluster headache according to ICHD-III diagnostic criteria [1], currently in treatment at several Headache Centers of northern Italy.

Included patients had to have at least 5 years of disease duration before year 2020, and they were contacted telephonically by the medical staff to obtain the clinical data needed for analysis.

Patients were contacted in a time period from August to December 2023. Collected clinical data regarded pre-COVID period (up to December 2019) and pandemic period (from January 2020 to March 2022).

Data collected and analyzed comprised:

- Diagnosis (episodic or chronic CH).
- Age.
- Gender.
- Disease duration.
- Number of clusters per year (pre-pandemic and during pandemic).
- Cluster duration (pre-pandemic and during pandemic).
- Number of headache attacks per day (pre-pandemic and during pandemic).
- Headache attack duration (pre-pandemic and during pandemic).
- Pain intensity (described using the Numerical Rating Scale).
- COVID-19 infection and/or vaccination.

Inclusion criteria were the following:

- Age > 18 years.
- Definite diagnosis of CH according to ICHD-III criteria [1] for at least 5 years prior to 2020.
- Ability to understand the aim and modality of the study and to give informed consent to be included in the study.

Exclusion criteria were:

- Inability to understand the study and to give informed consent.
- Diagnosis of another headache subtype different from CH.

Informed consent was obtained verbally from the included patients; the study was carried out according to the Declaration of Helsinki principles and current regulations regarding clinical studies on human subjects.

Statistical analysis was performed to assess for differences in CH clinical manifestations before and after pandemic onset, in order to document a possible effect of the pandemic and its consequences, in particular the personal limitations and lifestyle modifications enforced by the lockdown.

Continuous variables were described as mean and standard deviation; the presence of significant differences between continuous variables at different time points was assessed using repeated measures ANOVA. Further analysis for patients' subgroups was performed using Students' T Test to assess differences of continuous variables. Categorical variables were described as frequency and percentage; Chi-squared Test was adopted to assess different distributions of categorical variables in patients' subgroups. Statistical analyses were performed using IBM SPSS version 25, with statistical significance set at $p < 0.05$.

## 3. Results

This study included 44 patients, with mean age of 48.8 ± 12.6 years (range 22 - 83 years). Male prevalence was observed, with 35 male patients (79%) and 9 female patients (21%).

Mean disease duration at the time of inclusion in the study was 16.9 ± 8.5 years (range 4 - 39 years). Regarding cluster headache diagnosis, episodic CH was prevalent in the studied sample, with 40 patients with diagnosis of episodic CH (91%) and only 4 patients with diagnosis of chronic CH (9%).

COVID vaccination was reported by 43 patients (98%), with only 1 patient (2%) not vaccinated. Previous documented COVID infection was reported by 36 patients (81%).

Considering pre-lockdown period, mean cluster number per year was 1.6 ± 0.9 (range 1 - 6 per year). Mean cluster duration was 70.6 ± 98.4 days (range 5 - 365 days). Mean headache attacks per day were 2.8 ± 1.2 (range 1 - 6 per day). Mean headache attack duration was 47.1 ± 31.0 minutes (range 15 - 120 minutes). Pain intensity measured using the Numerical Rating Scale was 10 for all patients.

After COVID-19 outbreak and subsequent lockdown period, mean cluster number per year was 0.7 ± 1.2 (range 0 - 6 per year). Mean cluster duration was 24.4 ± 61.4 days (range 0 - 365 days). Mean headache attacks per day were 0.8 ± 1.0 (range 0 - 4 per day). Mean headache attack duration was 15.3 ± 20.9 minutes (range 0 - 60 minutes). Mean pain intensity measured with the Numerical Rating Scale was 4.3 ± 5.0 (range 0 - 10).

Repeated measures ANOVA showed statistically significant reduction in both mean cluster number per year ($p = 0.001$), mean cluster duration ($p = 0.001$), mean headache attacks per day ($p < 0.001$), mean headache attack duration ($p < 0.001$) and mean NRS pain intensity ($p < 0.001$), comparing the pre-COVID period with the pandemic and lockdown period (**Figures 1-4**).

Moreover, 25 patients (57%) of the studied sample achieved complete disease remission after COVID-19 outbreak and subsequent lockdown, with 0 clusters from 2020 to the present day.

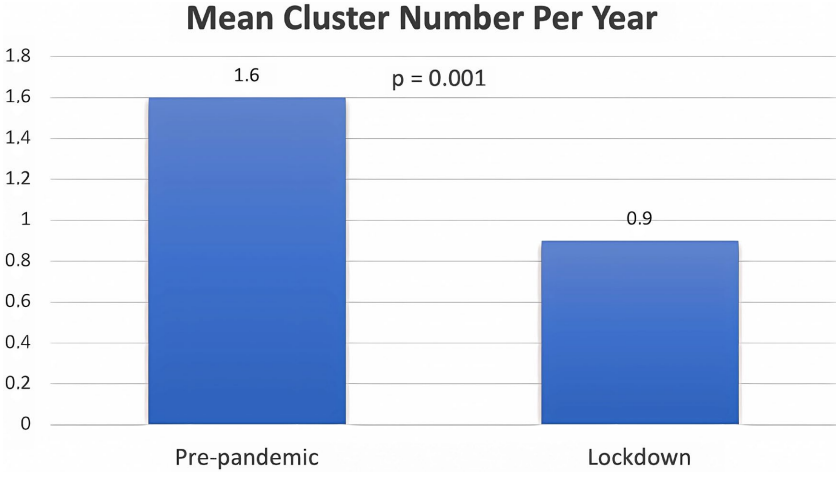


**Figure 1.** Mean cluster number per year before and after pandemic onset.

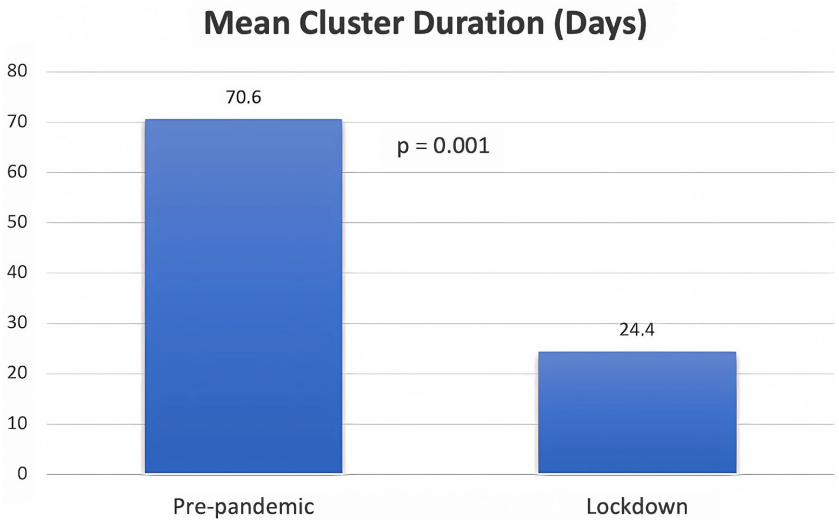


**Figure 2.** Mean cluster duration (days) before and after pandemic onset.

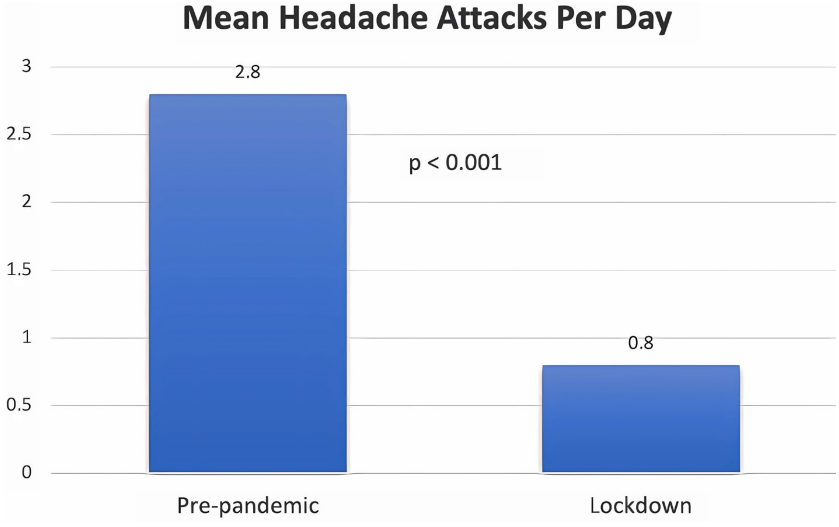


**Figure 3.** Mean headache attacks per day before and after pandemic onset.

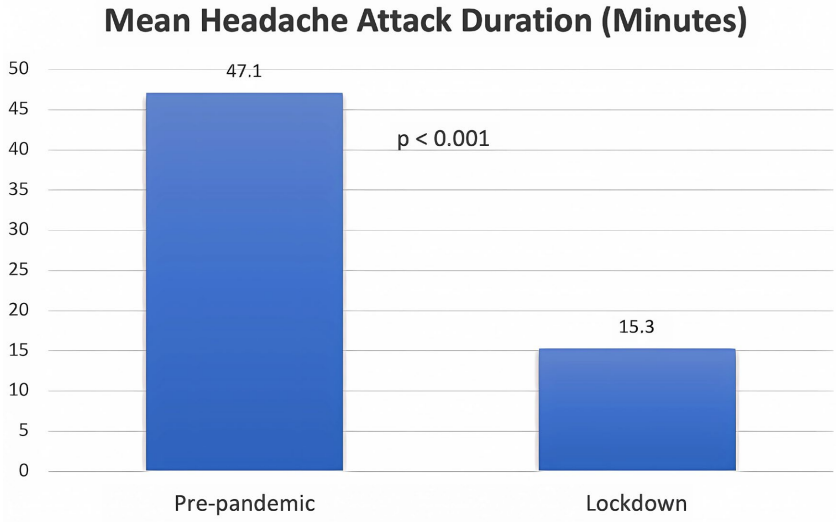


**Figure 4.** Mean headache attack duration (minutes) before and after pandemic onset.

## 4. Discussion

This study included a significant number of CH patients from several Headache Centers of northern Italy, currently in treatment for the disease. Demographic variables showed a sample of patients with male prevalence and mean age of 48.8 years. Most patients had a diagnosis of episodic cluster headache, with only 4 patients out of 44 with a diagnosis of chronic cluster headache. Disease duration was also significant, with a mean of 16.9 years of disease duration.

Considering the clinical course of the disease before and after pandemic onset, the results of this study showed an improvement in every collected variable; in fact, both variables regarding cluster manifestations during the year (cluster number per year and cluster duration) and variables assessing the single cluster manifestations (number of headache attacks per day and headache attack duration) were significantly reduced comparing the pre-pandemic disease course and the disease features after pandemic onset. Data regarding pain intensity during the headache attacks were also significantly reduced after pandemic onset.

As a whole, these interesting results demonstrate a statistically significant improvement in disease manifestations for the observed patients after the 2020 COVID pandemic outbreak. The reasons behind this observation may be related to the lifestyle changes which were forcedly adopted as a consequence of the so-called lockdown. Italy, in fact, as other countries around the world, adopted restrictive measures with significant limitations to the possibility for people to move outside of one's own house, except for motivated reasons; schools were closed and smart work from home was adopted whenever possible. The subsequent significant changes in one's work, school, leisure or personal routine may have had a role on the disease, with an improvement in cluster headache manifestations.

Several studies have assessed the effects of COVID pandemic on migraine patients, showing a worsening of the disease during the lockdown period [10]-[14]. These clinical changes were predominantly related to the changes in routine

activity and to the emotional and psychological burden related to the pandemic and its consequences on everyday life.

These interesting opposite findings in two primary headache disorders are definitely intriguing, possibly reflecting a different role of emotional and psychological factors, along with anxiety and depressive disorders, which are more strongly associated with migraine than with CH. On the contrary, CH may be significantly influenced by routine activity and everyday stressors with an effect on circadian rhythm, sleep-wake cycle and hypothalamic function (which have a significant role on CH pathophysiology [7]).

Limitations of this study may be the number of patients included, partially limited by the compliance of patients to participate in the study, and the observational retrospective design of the study.

Main strength of the study is the aim of the study itself, which inquired an issue not previously assessed in the current scientific literature.

Possible future developments on this subject should focus on better understanding the biological mechanisms underlying the clinical manifestations of cluster headache, in order to make it possible to adopt a more personalized treatment strategy, better fitting the single-patient scenario.

## 5. Conclusions

Cluster headache is a recurrent headache disorder with significant debilitating headache attacks and related disability for the patients.

Its periodic pattern of clinical recurrence showed a significant improvement comparing the pre-pandemic period with the COVID pandemic and lockdown period, with many patients showing complete remission and no subsequent attacks.

This finding is opposite to the course of migraine disease observed during the same lockdown period, reported in current literature.

This may suggest a different role and importance of comorbid manifestations such as anxiety and depressive disorders, more strongly associated with migraine, and routine activity, circadian rhythm and everyday stressors, with a major role in cluster headache.

## Compliance with Ethical Standards

- The authors declare no potential or actual conflicts of interest.
- The authors received no financial support for the research, authorship or publication of this article.
- The study involved human participants who were informed of the research target and provided their consent to participate.
- The patients gave permission to send the paper for publication.

## Authors' Contributions

Conceptualization, Marco Bolchini and Giorgio Dalla Volta; Data curation,

Marco Bolchini, Matteo Cortinovis, Paola Zavarise, Michele Gennuso, Paola Merlo and Natascia Beretta; Formal analysis, Marco Bolchini and Giorgio Dalla Volta; Investigation, Marco Bolchini, Matteo Cortinovis, Paola Zavarise, Michele Gennuso, Paola Merlo and Natascia Beretta; Methodology, Marco Bolchini and Giorgio Dalla Volta; Project administration, Michele Gennuso, Paola Merlo and Giorgio Dalla Volta; Software, Marco Bolchini and Giorgio Dalla Volta; Supervision, Michele Gennuso, Paola Merlo and Giorgio Dalla Volta; Writing – original draft, Marco Bolchini and Giorgio Dalla Volta; Writing – review & editing, Marco Bolchini and Giorgio Dalla Volta.

## Conflicts of Interest

The authors declare no conflicts of interest.

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