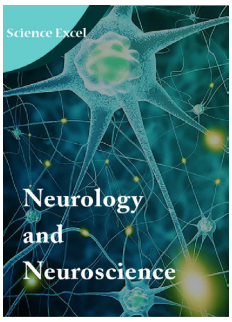
Neurology & Neuroscience

Original



Right-to-left shunt and obstructive sleep apnea in cluster headache

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- Received Date: 06 Feb 2020;
- Accepted Date: 23 Feb 2020;
- Publication Date: 07 Mar 2020.

Keywords:

cluster headache, oxygen, sleep, seasonality, patent foramen ovale

Abbreviations:

CH: cluster headache; R-to-LS: right-to-left shunt; OSA: obstructive sleep apnea; ICHD: International Classification of Headache Disorders; AHI: Apnea-Hypopnea Index

Abstract

Introduction: Cluster headache (CH) is a trigeminal autonomic cephalalgia characterized by extremely painful, strictly unilateral, headache attacks accompanied by ipsilateral autonomic symptoms. Only few studies investigated a possible role of right-to-left shunt (R-to-LS) and sleep apnea (OSA) in cluster pathogenesis or expression and no prior studies were located that combined the two conditions in CH patients. Objective: To define the potential combined effect of right-to-left shunt and obstructive sleep apnea in patients with cluster headache and their possible influence on the frequency of attacks and on response to oxygen therapy of headache attacks. Methods: 33 patients with cluster headache were recruited and subsequently invited to undergo polysomnography and a transcranial doppler bubble study. Polysomnography is used for the diagnosis of obstructive sleep apnea whereas transcranial doppler bubble study can help diagnose a cardiac right-to-left shunt. Results: Transcranial doppler results demonstrated that 10 out of 31 patients in our cohort had a right-to-left shunt (RLS). Polysomnography revealed that 10 out of 32 patients had obstructive sleep apnea (OSAS). Nineteen out of 33 subjects had one of the two conditions but only one of our 33 patients had both conditions simultaneously. In this sample patients with clear seasonality to their cluster attacks had a higher frequency of obstructive sleep apnea than patients without seasonality. Also a good response to oxygen treatment of the attacks was higher in OSAS patients. Conclusion: the presence of RLS or OSAS, by their possible influence on blood oxygenation, seems to be independently able to predispose to cluster headache or to make it clinically manifest, while the hypothesizable synergistic role between them in favoring cluster headache was not put in evidence. Additionally, our study suggested that the seasonality of cluster headache, may be influenced by the seasonal nature of obstructive sleep apnea. Finally, the presence of sleep breathing alterations seems to be also able to modulate the efficacy of oxygen inhalation on cluster headache attacks.

Introduction

Cluster headache (CH) is a primary headache. It is included in the chapter of trigeminal autonomic cephalalgias. It is characterized by extremely painful, strictly unilateral, headache attacks accompanied by ipsilateral autonomic symptoms. Even if it is a primary headache, several conditions seems to be able to induce clusters or to influence attacks frequency. Among these factors alcool intake, smoke and sleep disturbances are the widely investigated. The increased prevalence of Cluster Headache among smokers and the use of oxygen inhalation to treat CH attacks induce to suppose a possible role of blood oxygenation on this type of headache. Both right-to-left shunt (R-to-LS) and obstructive sleep apnea (OSA) may negatively influence blood oxygen levels even if in a different way: RLS by the direct passage of a small fraction of blood from the right to the left atrium without the passage through the pulmonary circulation and OSA by reducing alveolar oxygenation. The limited studies that are available about the link between CH and right-to-left shunt (R-to-LS) and the link between CH and obstructive sleep apnea (OSA) respectively indicate increased prevalence of R-to-LS and OSA in cluster headache subjects.[1–7] No prior studies were located that combined the two conditions. Both conditions, as said, can interfere with the oxygenation of blood.[8,9] The response to acute oxygen therapy in a certain proportion of patients with CH suggests, as previously underlined, that hypoxemia, possibly resulting from the combination of the above conditions [10–14] may play some role in cluster pathogenesis or expression. Furthermore, the effect of obstructive sleep apnea on oxygen saturation is predominantly nocturnal as are typical cluster attacks. Also, OSA has a higher prevalence in men, with a male-to-female ratio similar to a cluster headache distribution [15,16].

Aims of the study

The first aim of this study was to evaluate the co-presence of these two conditions in patients with cluster headache, in search of a possible synergistic effect in determining the pathogenesis of cluster headache or in triggering the attacks.

Citation: Damavandi PT, Rizzoli P, Pecis M, et al. Right-to-left shunt and obstructive sleep apnea in cluster headache. Neurol Neurosci. 2020;1(1):1-4.

Secondary objectives of this study were to evaluate the possible relationship between the presence of OSA and/or R-to-LS on clinical characteristics, O_2 response and the seasonality of the clusters.

Material and methods

In this pilot study, subject selection included patients who had visited the headache center of the L. Sacco hospital in Milan or of the Policlinico "G. Martino" in Messina, in the last 6 years and respected the diagnostic criteria of cluster headache according to the ICHD-III. Fifty-six patients, who met the inclusion criteria, were selected and given a questionnaire for surveying their medical history. This questionnaire was created with Google Form and allowed us to collect data on general information of the patient: age and sex, type and characteristics of headache, lifestyle habits, intolerances, allergies, co-diseases and other therapies. This data and the subsequent analysis were automatically collected on an online Excel document, accessible to all the authors. The sample size was based on the available data. Thirty-three out of the 56 patient selected to fill the questionnaire and to join the study were subsequently contacted to perform a transcranial doppler bubble study and polysomnography.

In order to investigate the prevalence of R-to-LS and OSA in our sample we used two diagnostic tools: polysomnography and transcranial doppler. The first one measures a series of parameters during sleep, including airflow, O_2 saturation, respiratory efforts and it is traditionally used for the diagnosis of obstructive sleep apnea. Transcranial doppler bubble study, with intravenous injection of a physiological solution mixed with tiny bubbles, can show the presence of a shunt. Micro-bubble transcranial doppler ultrasound is innocuous, quick and requires no fasting or sedation.[17]

We recorded the following parameters for 32 of the 33 recruited subjects: Apnea-Hypopnea Index (AHI), average O2 saturation, T90 and the possible presence of obstructive sleep apnea. One patient stopped polysomnography during the night and his recording was excluded from the analysis. Thirty one of 33 patients were evaluated with TCD, with a standard protocol for right-to-left shunt diagnosis, by monitoring the right middle cerebral artery before and after a Valsalva maneuver. TCD data from two patients could not be obtained in consequence of technical problems and were not available for the analysis. We analyzed data using the Chi-squared and the Student's T test. Chi-squared test ($\chi 2$) was applied, in order to verify that the frequencies of the observed figures would adapt to the theoretical frequencies of a probability distribution. As the cutoff for significance we set p-value less than 0.05. This was then used for:

- Comparative analysis of the distribution of the two diagnostic conditions studied in patients with cluster headache
- Comparative analysis of the distribution of obstructive sleep apnea in patients with seasonal clusters and patients without the seasonality
- Comparative analysis of the distribution of the different clinical manifestations of the bouts between the different diagnostic groups

Finally, paired T-test, a tool widely used in statistics to evaluate if the deviation between the average value of a distribution and the reference value is significant, was used to compare the average age of the beginning of the cluster headache with the average age of the emergence of the two conditions studied.

This study was conducted in accordance with the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Participants gave written informed consent before taking part to this study.

Results

Our final sample included 33 patients, 19 males and 14 females, all diagnosed with episodic cluster headache, all of them out of a cluster. The sample was distributed over different age groups, from age 19 to 71 years, with an average group age of approximately 48 years old. TCD results demonstrated that 10 out of 31 patients (32%), 5 females and 5 males, had a right-to-left shunt. Polysomnography revealed that 10 (7 males, 3 females) out of 32 patients (31%) had OSA: 7 were mild (5 <AHI <15), 3 severe (AHI> 30). Only one of the 33 patients had both conditions. 19 patients (61%) had at least one of the two conditions and 12 patients (39%) had neither. Patients with clear seasonality of the clusters had a higher frequency of OSA (40%) than patients without seasonality (23%).

All 10 patients with obstructive sleep apnea (100%) were smokers, while only 13 of the 22 patients without OSA were smokers (59%). Of these 13, 3 were ex-smokers (they quit smoking more than 5 years ago).

By comparing patients who were responsive to oxygen (9) with those who are unresponsive or have never used oxygen (24), there was a significant difference based on the presence of OSA: 5 of the 9 patients who were responsive to oxygen had OSA and 5 of those 24 who were unresponsive (4) or never tried oxygen therapy (20) had OSA.

In our sample snorers had an average AHI score significantly higher than non-snorers (t = 0,04), as one would expect. Snoring data can be used to aim polysomnography measurements.

Discussion

As previously described, also our sample of CH patients was characterized by an increased proportion of subjects with at least one among RLS and OSA, both able, in a different way, to reduce blood oxygenation. In fact, 32% of our cluster patients had a shunt, which is a slightly higher percentage than the 25% found in the general population [18] and 31% resulted affected by OSA. Also the prevalence of OSA is increased if compared to the general population.[19–25] Therefore, regarding the role of the factors favoring hypoxemia, we found that 61% of our patients had at least one of the two conditions and only 39% had neither, which was more than expected, based on the prevalence of the two conditions in the general population.

Only one patient had both conditions simultaneously and therefore the hypothesized synergistic role of OSA and RLS in inducing or triggering CH was not found.

On the contrary, the high prevalence of OSA and R-to-LS in our sample might indicate that the manifestation of one of the two conditions is sufficient and perhaps necessary to facilitate the development of the cephalalgic motif in predisposed subjects.

With regards to the possible relationship between OSA and the seasonality of attacks, our results suggest that, in patients with a clear CH seasonality there is a greater frequency of OSA (40% vs 23%), as if the seasonality of the headache was affected by the seasonality of the nocturnal respiratory disorder.

As to the impact of smoking, a well-known trigger of cluster attacks, several studies show that patients with CH are usually smokers but that they rarely improve after quitting smoking.[26,27]We noted that all of our patients with OSA were smokers, while only 59% of those without OSA were smokers or former smokers. This evidence suggests a possible indirect effect: smoking could favor nocturnal apnea and through this, the development or expression of cluster itself.

Finally, by subdividing patients into those who responded to oxygen therapy and those who did not (or never tried it), there was a significantly greater response in subjects with OSA (p = 0,05). This could suggest that the effectiveness of this treatment was potentially mediated by the presence of an underlying respiratory problem.

Further, we also showed that no significant correlation could be proven between the age of cluster headache onset and the two conditions studied, as well as no significant correlation between the accompanying symptoms of headache and the two conditions examined.

Conclusion

In conclusion, our data suggests a possible role for factors favoring hypoxemia in predisposing to cluster headache or in making it clinically manifest. The hypotesized synergistic role between obstructive sleep apnea and right-to-left shunt in favoring cluster headache was not confirmed. As for the seasonality of cluster headache, we can say that it may be influenced by the seasonal nature of OSA. Oxygen, notoriously effective in a certain proportion of patients during a cluster headache bout, seems more effective in those who also have OSA: as consequence of this observation, a polysomnographic study seems to be recommended in all CH subjects, especially in those with a good response to oxygen in order to treat the possible associated OSA and, viceversa, to suggest oxygen inhalation as therapy of choice in all OSA patients with CH.

Also, in this study the importance of smoking in the pathogenesis of CH is reiterated, but in an indirect way: by predisposing patients to developing sleep apnea syndrome, it could also favor cluster headache.

Our small sample size limits the statistical significance of our results and suggests the need for further investigation with a larger group of patients

Author contributions

All authors contributed to the study conception and design, material preparation, data collection and analysis. The first draft of the manuscript was written by Payam Tabaee Damavandi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Milano Statale. All the participants gave written informed consent before taking part to this study.

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