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Article

Improving the Cognitive Impact of Migraine: A Real-World Study on the Ability to Concentrate

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Abstract: Patients with chronic (CM) and high frequency episodic migraine (HFEM) report cognitive complaints that contribute to migraine burden. Although, there is little evidence about the effects of migraine treatments on these symptoms. Objective: To evaluate the effect of preventive treatment on the impact of cognitive symptoms, specifically the ability to concentrate, in individuals with CM and HFEM. Methods: Prospective cohort study in patients with CM and HFEM initiating treatment with botulinum toxin (BT) or anti-CGRP/R monoclonal antibodies (mAbs). Patients were evaluated at baseline and after 3 months of treatment, using a headache diary and a question about the impact of migraine attacks on concentration (never, rarely, sometimes, often, and always). Results: 108 patients (105 females, 44.3 years of age on average), 75% with CM and 27% with HFEM were included, 55 received a first session of BT and 53 received 3 injections of a monthly mAb. In both groups, there was a significant decline on the impact of migraine in concentration (related samples Wilcoxon signed rank test <0.001) compared to baseline. Reduction in monthly headache days was the main predictor of any concentration improvement, while treatment group, age, ongoing medication with topiramate or baseline medication overuse were not significant. Conclusion: Preventive treatment of HFEM or CM with drugs not acting on central nervous system is associated with a decrease of the impact of migraine attacks on concentration, predicted by the decline in headache days. These results indicate that migraine preventive treatment also improves non-pain symptoms, which is relevant given the contribution of cognitive complaints to the impact of headache attacks

Keywords: cognitive impact; chronic migraine; migraine burden

1. Introduction

Migraine is a very disabling condition, with impact in familial, social and professional life [1] and is associated with depression, anxiety, sleep disorders and other comorbidities [2,3]. Its impact is particularly severe in patients with frequent migraine attacks, either chronic migraine, defined according to the ICHD-2018 [4] by the presence of headache in 15 or more days per month, for more than three months, eight days fulfilling the diagnosis of migraine, or high frequency episodic migraine (between 8 and 14 days of migraine per month).

It has been increasingly recognized that migraine involves much more than pain and is associated with a wide spectrum on non-headache features, including cognitive complaints [5,6]. These complaints affect about 73% of chronic migraine patients [7] and consist in poor attention and concentration, difficulty performing simultaneous tasks, slower processing speed, poor word retrieval and memory difficulties. These symptoms are reported in the different phases of a migraine attack but also interictally [8]. They affect daily activities in work, school, household or social life contributing to migraine interictal burden [9]. The cognitive assessment of patients with chronic migraine has confirmed that they achieve lower scores in executive and memory tasks compared to either healthy individuals or those with episodic migraine. This dysfunction cannot be attributed to

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pain since evaluations were performed during the headache free days [10]. Furthermore, this impairment has been consistently found in chronic migraine [7,11–15].

The mechanism behind cognitive difficulties in chronic migraine remains unclear. While these difficulties may arise from the recurrence nature of migraine attacks, all studies have shown that chronic migraine is, per se, an independent predictor of low cognitive performance [7,11–15]. However, few studies have established a direct association between cognitive performance and the frequency of the attacks. Additionally, factors such as sleep disorders, depression, and certain preventive medication, like topiramate, may also contribute to the cognitive impairment.

Despite the recommendation to include non-headache features of migraine as possible outcomes of migraine in clinical trials, there is limited evidence regarding the benefit of current migraine treatments on patients´ cognitive complaints or performance [16–18]. Yet the improvement in cognitive symptoms is relevant because they have been shown to contribute to the disability of migraine attacks [19]. In this study we aimed to investigate a) the effect of migraine preventive treatment on the impact of migraine attacks on the ability to concentrate, b) whether improvement is related to a particular migraine treatment; and c) to identify the main predictors of cognitive improvement following treatment.

2. Materials and Methods

The study was designed as a real-world, observational cohort study and was carried out in the Headache Unit of a University Hospital. Patients with migraine attending the headache outpatient clinic or the ambulatory treatment unit were invited by the attending neurologists to participate during their regular scheduled appointment.

Inclusion criteria were: a) the clinical diagnosis of migraine with or without aura, confirmed by a neurologist, fulfilling the ICHD-3 criteria)(4), b) age >18 years; c) diagnosis of migraine for at least one year and starting before the age of 50 years; d) current diagnosis of high frequency episodic (i.e. more than 8 headache days per month, according to patients headache diary) or chronic migraine, e) failure/intolerance or contraindication for oral preventive treatment with the need to start a treatment either with botulinun toxin (BT) or monoclonal antibody against CGRP/receptor (mAbs). The latter are the local requirements for patients to receive these treatments that are free of costs in a public hospital. Patients were excluded if they had a diagnosis of severe psychiatric or of uncontrolled medical disorder, illiteracy, or inability to provide informed consent.

After informed consent, demographic (age, gender) and clinical data were gathered. The latter included current headache frequency and severity (categorized as monthly days with severe, moderate or mild headache), calculation of a composite index score of headache severity extracted from patients headache calendar (calculated by the sum of 3X severe days, 2x moderate days and 1x mild headache days per month, ranging from a maximum of 84 and a minimum of zero in a 28 days period,), the diagnosis of medication overuse; ongoing preventive treatment; need for new preventive treatment (due to insufficient improvement, intolerance or contraindications of ongoing oral preventive treatment). Patients were also asked to fill the Headache Impact Test (HIT-6) questionnaire (to evaluate the impact of migraine attacks) [20]. The sixth item of that scale ("In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?") was used to evaluate the impact of headache on the ability to concentrate. This item is scored as 13, 11, 10, 8 or 6 according to patients' response as always, very often, sometimes, rarely, or never, respectively.

Patients taking oral preventives with some, albeit insufficient benefit were allowed to maintain that medication while starting the new treatment. Patients receiving BT were treated according to the PREEMPT protocol [21] ranging between 155 to 195 units per session with 31 fixed points and additional points in a follow-the-pain strategy. Patients receiving monoclonal antibodies were prescribed one of the hospital available anti-CGRP/R mAbs, either erenumab (70mg), fremanezumab (225 mg) or galcanezumab (120mg), monthly subcutaneous injections. In the case of galcanezumab the first administration consisted in a loading dose of 240 mg.

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Patients underwent a follow-up evaluation three months later during a scheduled appointment. Mean monthly headache days and mean monthly days with moderate or severe pain, and the composite index score were extracted from the headache diary. Patients were revaluated with the HIT-6 scale global score and Item 6 score. Patients were classified as treatment responders if they had a reduction of mean monthly headache days ≥ 30% in relation to baseline. The study protocol and informed consent were reviewed and approved by the Institution Ethics Committee.

Continuous variables (age, migraine composite index, mean monthly headache, monthly moderate/severe headache days and scores on HIT-6) were presented in mean, standard deviation and median and interquartile range, according to normality. Categorical variables are expressed as number and percentage. Impact of migraine on the ability to concentrate was scored in five ranks (6, 8, 10, 11, 13). A nonparametric related-samples Wilcoxon Signed Rank Test was performed to assess differences between baseline and 3 months on the 6-item of HIT-6 score. Additionally, a repeated measures general linear model was employed to evaluate improvement in migraine metrics (mean days of headache and mean of severe/moderate days per month and migraine index score). To evaluate the impact of migraine improvement on the ability to concentrate, a Spearman correlation was computed between the change in monthly headache days and the change on impact of migraine in concentration. Any improvement in concentration (yes/no) was defined as any decrease between baseline and follow up in the 6th item of HIT-6. A logistic regression analysis was undertaken to identify predictors of improvement in concentration. This included variables that exhibited a statistically significant difference in the univariate analysis and variables that could influence the outcome (age, ongoing topiramate intake, treatment group (BT or mAbs) and medication overuse at baseline).

3. Results

A total of 108 patients were included, 75% (n=81) with chronic migraine and 25% (n=27) with high frequency episodic migraine. Fifty-five patients (50.9%) received the first treatment with BT and 53 (49.1%) received the first 3 monthly injections of a mAb. Patients' demographics and clinical characteristics of the study population by treatment group are summarized in Table 1. There were no statistical differences at baseline between the two treatment groups, except on the average monthly headache days and ongoing treatment with topiramate. The former was higher in patients treated with BT, since that group includes more patients with chronic migraine which is in the line with migraine treatment guidelines. Among patients receiving monoclonal antibodies, 10% (n=5) received erenumab, 34% (n=19) fremanezumab and 56% (n=29) galcanezumab.

Table 1. Population: baseline data.

Baseline data	Total sample (n=108)	Treatment group		
		Botulinum toxin (n=55)	CGRP monoclonal antibodies (n= 53)	Treatment group comparison
Gender (F/M)	105/3	53/2	52/1	n.s.
Age (mean ± SD, range)	44.3 ±10.8 (18-71)	43.1 ± 10.7 (18-71)	45.5 ±11.3 (20-65)	n.s.
HFEM, N (%)	27 (25%)	11 (20%)	16 (30.2%)	n.s.
CM, N (%)	81 (75%)	44 (80%)	37 (69.8%)	
Monthly headache days (of any severity) (mean ± SD)	19.5 ± 7.0	21.9 ± 6.2	18.9 ± 7.5	Mann-Whitney p= .016
Mean monthly Moderate/severe headache days (mean ± SD)	16.9 ± 7.2	18.2 ± 7.2	15.8 ± 7.2	Mann-Whitney n.s.
Composite Index (mean ± SD)	46.6 ± 18.4	50.9 ± 17.9	43.3 ± 18.1	Mann-Whitney p= .05, n.s.

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Headache impact test score (HIT-6) (median, IQR)	68 [65-70]	67 [65-70]	68 [64-69]	n.s.
Migraine impact on Concentration (median)	11	11	11	
Always (N)	21	12	9	n.s.
Very often (N)	73	36	37	
Sometimes (N)	11	6	5	
Rarely (N)	3	1	2	
Never (N)	0	0	0	
Ongoing treatment with topiramate				Chi square=8.6
Yes, N (%)	32 (34%)	21 (50%)	31 (59.6%)	p=.03
No, N (%)	62 (66%)	21 (50%)	21 (40.4%)	
Medication overuse				
Yes, N (%)	60 (61.2%)	29 (63%)	31(56.6%)	n.s.
No, N (%)	38(38.6%)	17(37%)	21 (40.4%)	

CM = chronic migraine; F/M=female/male; HFEM= high frequency episodic migraine; n.s= non-significant; SD= standard deviation.

After 3 months of treatment there was an improvement of migraine reflected in a reduction in mean monthly headache days, mean monthly moderate to severe headache days, composite index and HIT-6 total score. No significant differences were observed between the two treatment groups (Table 2).

Table 2. Follow up data: changes in patient reported measures from baseline to the end of the 3 month period.

	Treatment group			
	Total (n=108)	Botulinum toxin (n=55)	CGRP monoclonal antibodies (n= 53)	Treatment group comparison
Change in the impact of migraine in the ability to concentrate score (mean, SD)	2.0 ± 6.4	1.16	2.73	n.s.
Change in monthly headache days (MHD); (mean, SD)	4.9 ± 7.1	3.6 ± 6.3	5.9 ± 7.5	n.s.
Change in monthly severe/moderate headache days (mean, SD)	5.3 ± 6.9	4.7 ± 6.3	5.9 ± 7.5	n.s.
Composite index change (mean, SD)	13.5 ± 18.2	11.8 ± 16.9	14.8 ± 19.1	n.s.
Change in HIT-6 score (mean, SD)	4.6 ± 6.9	5.1 ± 5.3	5.7 ± 7.8	n.s
Percentual decrease of MHD compared to baseline				
≥ 30% (responders), N (%)	43 (43.4%)	15 (32.6 %)	28 (52.8%)	Chi square
< 30% (non-responders), N (%)	56 (56.6%)	31 (67.4%)	25 (47.2%)	4.1 , p= .04

MHD=monthly headache days; n.s= non-significant; SD= standard deviation.

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There was a decrease in the score measuring the impact of migraine on the ability to concentrate compared to baseline, and this score change correlated with the change in monthly headache days from baseline (Spearmen´s Rho=.452, p<.001), the change in monthly moderate/severe headache days from baseline (Spearmen´s Rho=.34, p<.001), and the change in composite index score (Spearmen´s Rho=.412, p<.001), suggesting a direct relation with migraine improvement.

Within the entire sample, the majority of patients (N= 65, 60.2%) reported any improvement of the impact of migraine attacks on the ability to concentrate compared to baseline (i.e. any decline in 6th item of HIT-6 scale score). This improvement was more frequent in patients receiving monoclonal antibody (66%) than in those treated with botulinum toxin (54.5%), although the difference was not statistically significant.

To identify factors that predicted a reduction of the impact of migraine attacks on the ability to concentrate a logistic regression was conducted. In this analysis, the independent variable was any decrease in HIT-6 6th item score, while the dependent variables were the difference in monthly headache days, age, treatment group (monoclonal antibodies or botulinum toxin), ongoing treatment with topiramate (yes, no) and baseline medication overuse (yes, no) (Table 3). The only predictor identified was the difference in monthly headache days.

Table 3. Logistic regression on the impact of migraine attacks on concentration, controlling for age medication overuse, ongoing topiramate treatment and treatment group.

	OR	95% CI	P - value
Change in monthly headache days	1.209	1.085 -1.347	<.001
Age	1.001	.948 – 1.057	.966
Medication overuse	.635	.218-1.850	.405
Topiramate treatment	1.155	.364-3.665	.807
Treatment group	1.449	.485-4.324	.507

4. Discussion

In this cohort of patients with high frequency episodic or chronic migraine, that were unresponsive to oral preventives, we observed a decrease of the impact of migraine on the ability to concentrate after treatment with either mAbs or BT. The effect occurred in both treatment groups and there were no differences between the groups. The only predictor for this effect was the improvement of migraine, quantified by the change from baseline in mean monthly migraine days. It could not be predicted by patients age, or by baseline medication overuse or ongoing topiramate treatment. The degree of improvement was correlated with the change in headache days, the change in severe/moderate headache days and a composite measure that quantifies the days of headache based on its severity.

Given that both treatments, anti CGRP monoclonal antibodies and botulinum toxin, do not exert their effects on the central nervous system and are unlikely to have any direct central modifying effect, these results suggest that the decrease of the impact of the attacks on the ability to concentrate is mediated by an improvement of the attacks themselves, i.e. is a result of migraine improvement. These results corroborate previous findings that showed an improvement in cognitive performance in chronic migraine in patients treated with botulinum toxin or oral preventives [16,17]. The latter was conduted on headache free days, with the goal of assessing the interictal cognitive performance in chronic migraine. In these studies patients underwent cognitive tests twice [17] or three times [16], within a follow up time of 3 months. However, the studies did not control for the learning effects associated with test repeated test administration. Another study analyzed a large series of patients with HFEM and CM, who participated in phase 2 clinical trials with fremanezumab [18]. Patients were evaluated on headache free days and also reported an improvement of the subjective perception of cognitive functioning on 3 questions related to processing speed, concentration and mental fatigue. However, the authors could not find a direct relation of these questions with the increase in number

of headache free days [18]. The present sample differs from those three previous reports because it evaluated the impact of migraine attacks on the ability to concentrate. This is relevant because it has been shown that the cognitive symptoms of migraine attacks contribute to attack related disability [19]. Therefore, to support patients' cognitive improvement, it is crucial to observed patients in the interictal but also in the ictal period.

The mechanisms of cognitive disability associated to migraine are not very clear. It has been well documented that migraine attacks are associated with a transient cognitive decline that is observed in the preictal, ictal and postictal phase of the attacks [6,8]. In patients with very frequent attacks, with HFEM and CM, it is possible that headache free days do not correspond to interictal days, since on headache-free days patients might be in the preictal phase of the subsequent attack or in the postdromal phase of the previous attacks. The continuous state of migraine, with no interictal days, may explain the persistence of cognitive symptoms and impairment even on the headache-free days. Additionally, it is also known that patients with chronic migraine have both structural and functional brain changes [22,23], including increased white matter hyperintensities [24], grey matter changes [25] and changes in neural network organization [26,27]. These changes encompass networks involved in cognition such as the dorsal attention network and the executive network. More recently changes in the glymphatic system have been shown to occur in chronic migraine [28]. There is some evidence that functional changes may improve with treatment [29]. However, it remains unclear if these changes underlie the cognitive impairment observed in migraine.

We acknowledge some limitations to the present study. We did not control for other factors that may contribute to cognitive impairment such as mood and sleep disorders. The sample size is relatively small, although identical to other studies focusing on cognition in chronic migraine. The degree of migraine improvement was less pronounced than what has been observed in other real-world studies, particularly in patients receiving botulinum toxin. Although it is important to note that the sample comprises HFEM and chronic migraine patients who had already failed several oral treatments. The treatment period is relatively short, particularly in what concerns botulinum toxin, that may potentially be more effective with repeated sessions. A similar pattern can be observed in some patients receiving monoclonal antibodies, as they may show a response later than 3 months.

5. Conclusions

We conclude that chronic and high frequency episodic migraine patients may improve their cognitive function after treatment with drugs not acting on the CNS. We also highlight that this change and the relation between cognitive improvement and migraine improvement suggest that cognitive decline can be reverted with migraine treatment and should be looked upon on future clinical trials.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Buse, D.C.; Fanning, K.M.; Reed, M.L.; Murray, S.; Dumas, P.K.; Adams, A.M.; Lipton, R.B. Life With Migraine: Effects on Relationships, Career, and Finances From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. *Headache* **2019**, *59*, 1286–1299, doi:10.1111/head.13613.
2. Buse, D.C.; Manack, A.; Serrano, D.; Turkel, C.; Lipton, R.B. Sociodemographic and Comorbidity Profiles of Chronic Migraine and Episodic Migraine Sufferers. *Journal of Neurology, Neurosurgery & Psychiatry* **2010**, *81*, 428–432, doi:10.1136/jnnp.2009.192492.
3. Minen, M.T.; Begasse De Dhaem, O.; Kroon Van Diest, A.; Powers, S.; Schwedt, T.J.; Lipton, R.; Silbersweig, D. Migraine and Its Psychiatric Comorbidities. *J Neurol Neurosurg Psychiatry* **2016**, *87*, 741–749, doi:10.1136/jnnp-2015-312233.

4. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd Edition. *Cephalalgia* **2018**, *38*, 1–211, doi:10.1177/0333102417738202.
5. Karsan, N.; Goadsby, P.J. Migraine Is More Than Just Headache: Is the Link to Chronic Fatigue and Mood Disorders Simply Due to Shared Biological Systems? *Frontiers in Human Neuroscience* **2021**, *15*.
6. Gil-Gouveia, R.; Martins, I.P. Cognition and Cognitive Impairment in Migraine. *Curr Pain Headache Rep* **2019**, *23*, 84, doi:10.1007/s11916-019-0824-7.
7. Ferreira, K.S.; Teixeira, C.T.; Cáfaro, C.; Oliver, G.Z.; Carvalho, G.L.P.; Carvalho, L.A.S.D.; Silva, B.G.; Haes, F.B.B.; Ciciarelli, M.C. Chronic Migraine Patients Show Cognitive Impairment in an Extended Neuropsychological Assessment. *Arq. Neuro-Psiquiatr.* **2018**, *76*, 582–587, doi:10.1590/0004-282x20180085.
8. Gerstein, M.T.; Wirth, R.J.; Uzumcu, A.A.; Houts, C.R.; McGinley, J.S.; Buse, D.C.; McCarrier, K.P.; Cooke, A.; Touba, N.M.; Nishida, T.K.; et al. Patient-reported Experiences with Migraine-related Cognitive Symptoms: Results of the MICOAS Qualitative Study. *Headache* **2023**, *63*, 441–454, doi:10.1111/head.14484.
9. Vincent, M.; Viktrup, L.; Nicholson, R.A.; Ossipov, M.H.; Vargas, B.B. The Not so Hidden Impact of Interictal Burden in Migraine: A Narrative Review. *Front. Neurol.* **2022**, *13*, 1032103, doi:10.3389/fneur.2022.1032103.
10. Braganza, D.L.; Fitzpatrick, L.E.; Nguyen, M.L.; Crowe, S.F. Interictal Cognitive Deficits in Migraine Sufferers: A Meta-Analysis. *Neuropsychol Rev* **2022**, *32*, 736–757, doi:10.1007/s11065-021-09516-1.
11. Santos-Lasaosa, S.; Viloria-Alebesque, A.; Morandeira-Rivas, C.; Lopez Del Val, L.J.; Bellosta-Diago, E.; Velazquez-Benito, A. [Mnemonic complaints and chronic migraine]. *Rev Neurol* **2013**, *57*, 145–149.
12. Cai, X.; Xu, X.; Zhang, A.; Lin, J.; Wang, X.; He, W.; Fang, Y. Cognitive Decline in Chronic Migraine with Nonsteroid Anti-Inflammation Drug Overuse: A Cross-Sectional Study. *Pain Res Manag* **2019**, *2019*, 7307198, doi:10.1155/2019/7307198.
13. Latysheva, N.; Filatova, E.; Osipova, D.; Danilov, A.B. Cognitive Impairment in Chronic Migraine: A Cross-Sectional Study in a Clinic-Based Sample. *Arq. Neuro-Psiquiatr.* **2020**, *78*, 133–138, doi:10.1590/0004-282x20190159.
14. Bottiroli, S.; Rosi, A.; Sances, G.; Allena, M.; De Icco, R.; Lecce, S.; Vecchi, T.; Tassorelli, C.; Cavallini, E. Social Cognition in Chronic Migraine with Medication Overuse: A Cross-Sectional Study on Different Aspects of Mentalization and Social Relationships. *J Headache Pain* **2023**, *24*, 47, doi:10.1186/s10194-023-01578-1.
15. Gómez-Beldarrain, M.; Carrasco, M.; Bilbao, A.; García-Moncó, J.C. Orbitofrontal Dysfunction Predicts Poor Prognosis in Chronic Migraine with Medication Overuse. *J Headache Pain* **2011**, *12*, 459–466, doi:10.1007/s10194-011-0340-6.
16. Ho, S.; Darby, D.; Bear, N. Cognitive Effects of onabotulinumtoxinA in Chronic Migraine. *BMJ Neurol Open* **2020**, *2*, e000014, doi:10.1136/bmjno-2019-000014.
17. González-Mingot, C.; Gil-Sánchez, A.; Canudes-Solans, M.; Peralta-Moncusi, S.; Solana-Moga, M.J.; Brieva-Ruiz, L. Preventive Treatment Can Reverse Cognitive Impairment in Chronic Migraine. *J Headache Pain* **2022**, *23*, 121, doi:10.1186/s10194-022-01486-w.
18. VanderPluym, J.; Dodick, D.W.; Lipton, R.B.; Ma, Y.; Loupe, P.S.; Bigal, M.E. Fremanezumab for Preventive Treatment of Migraine: Functional Status on Headache-Free Days. *Neurology* **2018**, *91*, doi:10.1212/01.wnl.0000544321.19316.40.
19. Gil-Gouveia, R.; Oliveira, A.G.; Martins, I.P. The Impact of Cognitive Symptoms on Migraine Attack-Related Disability. *Cephalalgia* **2016**, *36*, 422–430, doi:10.1177/0333102415604471.
20. Kosinski, M.; Bayliss, M.S.; Bjorner, J.B.; Ware Jr., J.E.; Garber, W.H.; Batenhorst, A.; Cady, R.; Dahlöf, C.G.H.; Dowson, A.; Tepper, S. [No Title Found]. *Quality of Life Research* **2003**, *12*, 963–974, doi:10.1023/A:1026119331193.
21. Diener, H.; Dodick, D.; Aurora, S.; Turkel, C.; DeGryse, R.; Lipton, R.; Silberstein, S.; Brin, M. OnabotulinumtoxinA for Treatment of Chronic Migraine: Results from the Double-Blind, Randomized, Placebo-Controlled Phase of the PREEMPT 2 Trial. *Cephalalgia* **2010**, *30*, 804–814, doi:10.1177/0333102410364677.
22. Aurora, S.K.; Barrodale, P.M.; Tipton, R.L.; Khodavirdi, A. Brainstem Dysfunction in Chronic Migraine as Evidenced by Neurophysiological and Positron Emission Tomography Studies*. *Headache* **2007**, *47*, 996–1003, doi:10.1111/j.1526-4610.2007.00853.x.

23. Domínguez, C.; López, A.; Ramos-Cabrer, P.; Vieites-Prado, A.; Pérez-Mato, M.; Villalba, C.; Sobrino, T.; Rodriguez-Osorio, X.; Campos, F.; Castillo, J.; et al. Iron Deposition in Periaqueductal Gray Matter as a Potential Biomarker for Chronic Migraine. *Neurology* **2019**, *92*, doi:10.1212/WNL.0000000000007047.
24. Al-Hashel, J.Y.; Alroughani, R.; Gad, K.; Al-Sarraf, L.; Ahmed, S.F. Risk Factors of White Matter Hyperintensities in Migraine Patients. *BMC Neurol* **2022**, *22*, 159, doi:10.1186/s12883-022-02680-8.
25. Messina, R.; Rocca, M.A.; Colombo, B.; Pagani, E.; Falini, A.; Goadsby, P.J.; Filippi, M. Gray Matter Volume Modifications in Migraine: A Cross-Sectional and Longitudinal Study. *Neurology* **2018**, *91*, doi:10.1212/WNL.0000000000005819.
26. Coppola, G.; Di Renzo, A.; Petolicchio, B.; Tinelli, E.; Di Lorenzo, C.; Parisi, V.; Serrao, M.; Calistri, V.; Tardioli, S.; Cartocci, G.; et al. Aberrant Interactions of Cortical Networks in Chronic Migraine: A Resting-State fMRI Study. *Neurology* **2019**, *92*, doi:10.1212/WNL.0000000000007577.
27. Michels, L.; Koirala, N.; Groppa, S.; Luechinger, R.; Gantenbein, A.R.; Sandor, P.S.; Kollias, S.; Riederer, F.; Muthuraman, M. Structural Brain Network Characteristics in Patients with Episodic and Chronic Migraine. *J Headache Pain* **2021**, *22*, 8, doi:10.1186/s10194-021-01216-8.
28. Wu, C.; Chang, F.; Wang, Y.; Lirng, J.; Wu, H.; Pan, L.H.; Wang, S.; Chen, S. Impaired Glymphatic and Meningeal Lymphatic Functions in Patients with Chronic Migraine. *Annals of Neurology* **2023**, ana.26842, doi:10.1002/ana.26842.
29. La Rocca, M.; Laporta, A.; Clemente, L.; Ammendola, E.; Delussi, M.D.; Ricci, K.; Tancredi, G.; Stramaglia, S.; De Tommaso, M. Galcanezumab Treatment Changes Visual Related EEG Connectivity Patterns in Migraine Patients. *Cephalalgia* **2023**, *43*, 03331024231189751, doi:10.1177/03331024231189751.