ABSTRACTS

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ORAL COMMUNICATIONS

Do neuropsychiatric comorbidities influence the outcome of Greater Occipital Nerve Injections for headache prevention in paediatric patients? Preliminary results from a UK experience

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Background: Primary headaches are the most common cause of pain in childhood and adolescence. Migraine prevalence in childhood is around 10%, with comorbidities such as major depressive disorders and anxiety ranging from 10 to 20%. Greater occipital nerve injections (GONI) are an effective, safe and well tolerated treatment, which can be used for primary headache prevention both in adults and in children. We aim to evaluate if the presence of neuropsychiatric comorbidities influences GONI response.

Methods: We retrospectively analysed the clinical history and therapeutic response of all paediatric patients with a primary headache diagnosis who underwent GONI from June to December 2022 at the Headache Centre of Great Ormond Street Hospital in London, UK. GONI were performed unilaterally using a mixture of 40 mg methylprednisolone and 30 mg 1% lidocaine. We analysed demographic characteristics including gender, age at first injection, headache diagnosis, psychiatric diagnosis, considering separately mood disorders (anxiety/depression) and neurodevelopment comorbidities (autism, ADHD, learning disabilities). Our primary outcome was response to treatment, considered as a >50% reduction in monthly headache days following twelve weeks from the GONI.

Results: 85 patients were included, of whom 80% were female. Mean age at first injection was 14 years ± 1.6. The most frequent headache diagnosis was migraine without aura (n=44), followed by migraine with aura (n=25), NDPH (n=8), TTH (n=1) and cluster headache (n=1). 40 patients had previously received a neuropsychiatric diagnosis, n=25 had mood disorders and n=15 neurodevelopment comorbidities, of which the most frequent were learning disabilities (47%), ADHD (40%), autism (20%) and eating disorders (20%). For our primary outcome, n=57 (67%) patients showed >50% reduction in monthly headache days.
There was no significant difference in GONI response in patients with mood comorbidity respect to those without ($\chi 2$=1.007). We also found no difference in response in patients with neurodevelopment comorbidity ($\chi 2$=0.884).

Conclusion: In our sample the presence of psychiatric comorbidities did not influence the effect of GONI for primary headache prevention. GONIs are helpful in adolescents with and without neuropsychiatric comorbidities.

Coping strategies to stressful events in adolescents with migraine

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Background: We aimed to explore: 1) coping responses to stressful events and their possible association with migraine severity (frequency of attacks and pain intensity) and the use of prophylactic treatments in adolescents with migraine; 2) the association between coping strategies, anxiety and depression levels.

Methods: We included 81 adolescents (m.a. 13.8±1.6 years; 18 M and 63 F). They were divided into: (1) high frequency (weekly to daily episodes) and low frequency (≤4 episodes per month); (2) mild and severe pain; (3) need for prophylactic treatment or not. To evaluate patients' anxiety, depression and coping strategies we used respectively SAFA-A, SAFA-D and CRI-Y questionnaires.

Results: In our sample, high frequency of attacks was associated with "Logical Analysis" (p=0.012) and "Positive Reappraisal" (p=0.002) strategies of coping. Patients with severe intensity of pain showed levels above the normal range in "Problem Solving" (p=0.050) and "Cognitive Avoidance" (p=0.034) subscales. No significant association was found between the use of a prophylactic treatment and coping responses. We found higher symptoms of "Total anxiety" (p=0.025), "School anxiety" (p=0.024) and "Feeling of hopeless" (p=0.029) in patients with the tendency to use a "Positive Reappraisal" strategy of coping; on the other hand, higher symptoms of depression were associated with "Cognitive Avoidance" (p=0.033) style.

Conclusion: Adolescents with migraine tend to use a coping style characterized by an approach to the problem. In particular, cognitive coping strategies may be more prevalent in high frequency patients, while behavioral coping strategies could be more commonly used in severe intensity patients.

Schoolchildren's headache: difference between children and mothers' perceptions and awareness

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Background: In preschool and early school years, the history of headache in both epidemiological and clinical settings can be difficult because of the age of children and the need to gather information from parents who sometimes tend to prevail either denying or aggravating the symptomatology. The purpose of this study is to assess the presence of headache in a sample of children not selected for such reasons and the correspondence of their responses with those of the mother using ID migraine questions.

Methods: A sample of the fifth grade of elementary school, together with their mothers, were given the ID Migraine questionnaire with questions related to children's headache, separately.

Results: The sample consisted of 68 children (35F / 33M) in an age range of 10-12 years. They were positive for a history of headache episodes in the past 3 months 24/68 (45.7%). Reported by both or at least one of the two component respondents, headache was reported by 16/35 F amounting to 45.7% and 8/33 M amounting to 24.2%. Among all of them: only 2/68 (2.95%) had 2 out of 3 criteria to be defined as possible migraineurs, 11/68 (16,1 %) met at least 1 item and 11 did not satisfy none of the three items however they claimed the occurrence of headache episodes in the past 3 months. Child and mother disagreed in their answers in 23/68 of cases (33.8%), of these: 14 (about 61%) did not agree on the question about presence of headache in the past three months, while 9 (about 49%) were the cases in which they did not match the response to the Migraine ID items between mother and child.

Conclusion: Our data support the difficulties in collecting data on the headache of children under 12 years. There is a difference between the child's and mother's responses despite asking simple questions, and in 60% one of the two components denies the presence of headache in the past three months claimed by the other. In addition, the prevalence of migraine appears to be lower than literature data, casting doubts on the usefulness of the Migraine ID as an effective and rapid screening for suspected migraine to help pediatricians or to perform epidemiological studies.

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Increase of cerebral vasoreactivity in migraine patients after anti-CGRP monoclonal antibodies therapy

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Background: CGRP is a potent vasodilator and plays a crucial role in migraine pathogenesis and anti-CGRP monoclonal antibodies (mAbs) represent a new promising and effective treatment for migraine patients. Literature evidence suggests that migraine patients have a reduced vascular tone and a maintained vasodilation due to the excessive stimulus exerted by CGRP. Therefore, its receptor or ligand blockade would counteract this effect on intracranial vascular tone, thus inducing an increase of Vasoreactivity Index (VRI). The few studies on the effect of anti-CGRP mAbs on cerebral hemodynamics reported increased mean velocity values in large intracranial arteries in responder patients. The present study was aimed to assess any variation in cerebral blood flow and vasoreactivity in migraine patients before and during anti-CGRP mAbs therapy.

Methods: In the January 2022-January 2023 period, 44 chronic or high-frequency episodic migraine patients (37 females, 7 males), eligible for anti-CGRP mAbs treatment, were recruited. They underwent transcranial doppler (TD) examination before starting (T0), and at one month (T1), three months (T2), six months (T3) and twelve months (T4) of treatment. At each visit scores of migraine related disability and headache impact scales (MIDAS, HIT-6) were assessed.

Results: The basal mean attack frequency/month was 17.8±7 days. The mean MIDAS and HIT-6 scores were 124.6±42 and 66.9±6.75, respectively. All patients completed the T2 treatment period, 7 ended after one year of treatment. A significative reduction in headache frequency and MIDAS scores was detected in 95.4% of patients after three months of treatment. An increase in vasoreactivity index (VRI) of the middle cerebral artery (MCA) was found compared to baseline, with significant differences already at T2 ($p=0.046$).

Conclusion: Anti-CGRP-mAbs therapy may induce modifications in cerebral vasoreactivity consistently with the clinical benefit for the patients. TD is a rapid and non-invasive tool to verify these modifications before and during anti-CGRP-mAbs treatment.

"Dim Light Melatonin Onset" and chronotype profiling in patients with episodic and chronic migraine

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Background: Chronic migraine with medication overuse headache (CM-MOH) represents one of the most disabling phenotypes across the migraine spectrum. Patients with CM-MOH suffer several comorbidities, including sleep disorders. The aim of this study was to better define the chronotype of migraine patients by means of subjective clinical scales and salivatory melatonin measurements.

Methods: We enrolled 40 patients with CM-MOH, 18 patients with episodic migraine (EM) and 32 healthy controls (HCs). All subjects completed the Morningness–Eveningness Questionnaire (MEQ), the Pittsburgh Sleep Quality Index (PSQI) and a prospective sleep diary, and underwent 5 saliva melatonin samplings (at hourly intervals with the first sample collected 3 h before the subject's regular bedtime). We calculated the "Dim Light Melatonin Onset" (DLMO), a well-known biological marker of circadian phase in humans. Furthermore, we considered the clinical and demographic features and the psychological profile of subjects enrolled.

Results: EM patients were younger when compared to CM-MOH patients and HCs. According to the PSQI, symptoms of depression and anxiety and sleep disturbances were more frequent in CM-MOH when compared to EM, as expected. MEQ score was higher in CM-MOH (59.6±7.7) when compared to EM (53.3±11.9, p=0.045) and HCs (51.0±10.1, p=0.001). According to MED, a subjective morningness profile was more prevalent in CM-MOH (56.8%) when compared to EM (33.3%) and HCs (17.2%) (p=0.001). DLMO occurred earlier in CM-MOH (20:31±52 minutes) and in EM (20:28±0:49 minutes) when compared to HCs (21:17±63 minutes; p=0.05 and p=0.014, respectively). This was confirmed in a multinominal regression after correction for age and sex. DLMO did not differ between CM-MOH and EM groups (p=1.000). According to DLMO, a biological morningness profile was more prevalent in CM-MOH (32.4%) and in EM (33.3%) when compared to HCs (7.4%) (p=0.019).

Conclusion: Migraine patients showed a morning-oriented chronotype when compared to HCs. Chronotype evaluated according to DLMO did not differ between CM-MOH and EM, suggesting an endogenous phenotype of migraine biology without association with disease severity. By contrast, CM-MOH patients described themselves as more morning oriented, showing a role of behavioral aspects related to the more severe phenotype of disease.

Central sensitization mechanisms in chronic migraine with medication overuse headache: a study of thalamocortical activation and lateral cortical inhibition

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Background: It is unclear whether cortical hyperexcitability in chronic migraine with medication overuse headache (CM-MOH) is due to increased thalamocortical drive or to aberrant cortical inhibitory mechanisms.

Methods: Somatosensory evoked potentials (SSEP) were performed by electrical stimulation of the median nerve (M), ulnar nerve (U), and simultaneous stimulation of both nerves (MU) in 27 patients with CM-MOH and for comparison in 23 healthy volunteers (HVs) of a comparable age distribution. We calculated the degree of cortical lateral inhibition using the formula [100–(MU/(M+U) *100)], and the level of thalamocortical activation by analyzing the high frequency oscillations (HFOs) embedded in parietal N20 median SSEP.

Results: Compared to HV, CM-MOH patients showed higher lateral inhibition (CM-MOH 52.2% ± 15.4 vs HV 40.4% ± 13.3; p=0.005), which positively correlated with monthly headache days, and greater amplitude of pre-synaptic HFOs (p=0.010) but normal post-synaptic HFOs (p=0.122).

Conclusion: Our findings suggest that central neuronal circuits are highly sensitized in CM-MOH patients, at both thalamocortical and cortical levels. The observed changes could be due to the combination of dysfunctional central pain control mechanisms, hypersensitivity and hyperresponsiveness directly linked to the chronic intake of acute migraine drugs.

Phenotyping ictal and perictal migraine patients according to clinical and psychophysical characteristics

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Background: This study aims to 1) identify different migraine phenotypes according to clinical and psychophysical characteristics, and 2) assess the clinical validity of the different migraine phenotypes.

Methods: This observational study included Episodic Migraine (EM) patients assessed in the ictal, preictal, and postictal phases and Chronic Migraine (CM) assessed in the ictal phase and was divided into two parts. In part 1, headache frequency, disability, cervical active range of motion (AROM), pressure-pain threshold (PPT) over temporalis, two cervical areas (C1/C4 vertebral segments), and two distal pain-free areas (hand/leg) were assessed and used to subgroup migraine patients into different Clusters. In part 2 clinical characteristics (multiple questionnaires), somatosensory function [comprehensive quantitative sensory testing (QST)], and cervical musculoskeletal impairments (cervical musculoskeletal assessment) were assessed and compared across headache clusters and a group of 56 healthy controls matched for sex and age.

Results: Part 1: 100 patients were included, and two clusters were identified. Cluster-1.1 No Psychophysical Impairments (NPI, 19%) and Cluster-1.2 Increased Pain Sensitivity and Cervical Musculoskeletal Impairment (IPS-CMD, 81%). Cluster 1.1 had a higher percentage of men and lower disability compared to Cluster 1.2 (all, $p<0.037$). Cluster 1.2 had reduced AROM in flexion, extension, and left/right lateral flexion, and lower PPT value in all areas compared to Cluster 1.1 (all, ($p<0.037$).
Part 2: Cluster-1.2(IPS-CMD) had higher headache intensity, worse headache-related and neck-related disability, worse quality of life, higher symptoms related to sensitization and psychological burden (all, $p<0.048$) vs. Cluster-1.1 (NPI). Cluster-1.2 (IPS-CMD) had 1) reduced cervical active and passive range of motion reduced functionality of deep cervical flexors, and reduced values in all QST (higher sensitization) vs. controls (all, $p<0.023$); and 2) reduced active mobility in flexion, left/right lateral flexion, and reduced values in QST vs. Cluster-1.1(NPI) (all, $p<0.045$). Cluster 1.1 (NPI) had reduced functionality of deep cervical flexors and higher QST values (lower sensitization) vs. Controls (all, $p<0.049$).

Conclusion: In the ictal/perictal phase, two clinically relevant clusters were identified according to clinical and psychophysical characteristics, with one group showing no psychophysical impairment, and one with increased pain sensitivity and cervical musculoskeletal dysfunctions.

Brain Perfusion Magnetic Resonance during aura in the first case of persistent sensorimotor Familial Hemiplegic Migraine due to PRRT2 gene deletion

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Background: Migraine aura (MA) might mimic stroke, particularly in Familial Hemiplegic Migraine (FHM), a rare genetic disease in which MA stroke-like symptoms can last up to weeks. Notoriously, advanced perfusion-weighted brain imaging techniques can represent a valid tool to discriminate a MA from a stroke. Aim of this study is to analyse a brain perfusion Magnetic Resonance Imaging (pMRI) performed during and at the end of aura in the first patient with persistent FHM sensorimotor aura due to PRRT2 gene deletion.

Methods: A 27-year-old with FHM-related right limbs weakness and hypoesthesia lasting for several weeks performed two different qualitative and quantitative brain pMRI. The first one was performed during persistent MA symptoms (T0), the second one 6 months after the resolution of symptoms and during treatment with valproic acid (T1). An expert neuroradiologist dealt with imaging acquisition and examination. Mean Transit Times (MTT), Time To Peak (TTP), Cerebral Blood Volume (CBV) and Cerebral Blood Flow (CBF) maps were bilaterally acquired in two different Regions of Interest (ROI) in basal ganglia at T0 and T1.

Results: The standard sequences and the qualitative analysis of both MRI at T0 and T1 did not allow to recognise significant asymmetries of brain perfusion. On the contrary, the elaborated quantitative analysis detected at T0 a relative hypoperfusion in the ROI of the left basal ganglia compared to the contralateral site, which was congruent with MA symptoms. At T1 the relative hypoperfusion resolved.

Conclusion: pMRI evidenced a left relative unilateral basal ganglia hypoperfusion in the first patient described with right persistent sensorimotor aura secondary to Familial Hemiplegic Migraine due to PRRT2 gene deletion. Hypoperfusion resolved with the resolution of symptoms

Prevalence of musculoskeletal dysfunctions in migraine patients with occipital migraine pain

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Background: In clinical practice it is common that migraine patients could refer occipital pain as usual pain site during a migraine attack. The convergence of the sensory input from the first division of the trigeminal nerve and upper cervical roots on the brainstem trigeminocervical complex could represent the anatomical basis of that observation. Clinical studies reported a higher prevalence of sub-occipital and cervical musculoskeletal dysfunctions in migraine compared to non-migraine subjects.
We hypothesized that the observed higher prevalence in musculoskeletal dysfunctions in migraine could be more prevalent in subjects with preeminent or exclusive dominance of migraine pain at occipital level when compared to migraine with the most prevalent orbito-fronto-temporal pain dominance.

Methods: Observational study in out-patient setting. Participants were stratified according to the migraine pain dominance as anterior (orbital, frontal and temporal sites) - (MIG-ANT) and posterior (occipital and suboccipital) - (MIG-POST) migraine pain suffers. Clinical data including monthly frequency and acute medication, headache severity and duration, migraine disability (MIDAS), neck disability (NDI), depression (PHQ-9) and kinesiophobia (TSK-I) were collected.
In all participants we evaluated the presence of musculoskeletal dysfunctions by using a standardized set of clinical examination including flexion-rotation-test (FRT), passive accessory intervertebral movements (PAIVMs), passive physiological intervertebral movements (PPIVMs), trigger points (TrPs) reproduction and resolution of usual head pain and temporo-mandibular joint movement, pain and restriction.

Results: We recruited 141 migraine subjects, 67 MIG-ANT and 76 MIG-POST of which 60 with Low Frequency EM, 53 with High Frequency EM and 23 with Chronic Migraine.
As main results, we observed a significant statistical higher prevalence (χ^2) of positive response at FRT ($p<0.001$), CROM ($p<0.001$), PROM($p=0.001$), TROM ($p=0.034$), PPIVMs C0-C1 ($p=0.001$), PAIVMs C1-C2 ($p=0.013$), PAIVMs T1 ($p=0.032$), T2 ($p=0.002$) and T3 ($p=0.013$) in MIG-POST when compared to MIG-ANT.

Conclusion: The dominance of the migraine pain at occipital site, emerged as linked to a higher prevalence of musculoskeletal dysfunctions at sub-occipital, cervical and thoracic level. The observed prevalence could be supported by the trigeminocervical convergence at brainstem level. On these bases, a multimodal physical therapy approach could be a valid complementary treatment in these subjects.


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POSTERS

Gut microbiota profiling of pediatric patients with migraine

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Background: We wanted to verify if gut microbiota (GM) in children with migraine showed differences in the profiling respect to healthy controls (HCs) and if different migraine phenotype (aura or not; presence of nausea/vomiting or photo/phonophobia during the attacks; duration of disease and frequency of monthly days with headache) are associated with differences in GM.

Methods: Patients aged between 6 and 18 years were recruited.
The GM profiling was obtained by the 16S rRNA region sequencing from faecal samples of migraine patients (n = 98) and of healthy subjects (n = 100, HCs).
Alpha and beta diversity analyses and multivariate (unsupervised Principal Component Analysis [PCA] and the supervised Partial Least Square Discriminant Analysis [PLS-DA]) and univariate (Linear Discriminant analysis [LDA] effect size [LEfSe]) tests were applied to compare the gut microbiota profiles between migraine and HC groups by R v4.0.2.

Results: α-diversity was not significantly different between MS and HC ($p > 0.05$). The analysis of β-diversity revealed a dissimilarity statistically significant among two groups ($p<0.01$), suggesting a different GM profile of MS compared with HCs.
Multivariate analysis evidenced the presence of GM fingerprints specific of MS and HC and two differential profiles of GM for MS and HC cohorts (fig2B). Compared to HCs, Bacteroides, Faecalibacterium, Butyricicoccuus, Lactobacillus and Enterobacteriaceae were assigned as biomarker of the patient's microbiota, while Bifidobacterium, Akkermansia, Collinsella, Eggerthella, Clostridium, Erysipelotrichaceae, Mogibacteriaceae and Coriobacteriaceae to GM of HCs. We found no significant differences in the subgroup analyses of MS.

Conclusions: Our study shows that pediatric migraine patients have a very different GM composition compared to HCs. These differences do not appear to be related to disease characteristics such as duration, presence of aura, or neurovegetative or sensory symptoms.

Disordered eating attitudes, psychological symptoms and migraine severity: which relationship?

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Background: Data on disordered eating attitudes in pediatric migraine are, so far, sparse. We aimed to investigate: 1) the prevalence of disordered eating behaviors and their association with the severity of migraine and body weight; 2) the possible mediating role of anxiety and/or depression in the association between disordered eating attitude and frequency of migraine attacks in children.

Methods: We included 103 adolescent girls with migraine (mean age 14.2±1.6 years). The frequency of migraine was divided into: 1) high frequency (from weekly to daily episodes) and 2) low frequency (≤4 episodes per month). According to their Body Mass Index, patients were divided into the following groups: "underweight" (<5th percentile), "normal weight" (from ≥5 to <85 percentile), "overweight" (from ≥85 to <95) and "obese" (≥95). Given the low number of obese patients, overweight and obese groups were considered together in the "Overweight" group. Due to their low frequencies, "underweight" patients were not included in our analysis. The Italian SAFA battery was used to investigate eating disorder risk (SAFA-P), anxiety (SAFA-A) and depression (SAFA-D).

Results: In our sample, 20.4% of patients had scores above the normal range in SAFA-P Total scale. We found bulimic and anorexic attitudes respectively in 17.5% and 22.3% of patients. Perfectionism was high in 46.6% of patients. We found significant higher bulimic symptoms in patients with high frequency of attacks (p=0.040). Overweight patients showed higher levels of disordered eating attitudes as compared with normal weight patients (SAFA-P Tot: p=0.011). We found a mediating role between bulimic and anorexic attitudes and high frequency for school anxiety (respectively, p=0.040 and p=0.045).

Conclusion: Our data suggest an association between bulimic attitudes and the frequency of migraine. We suppose that, in our sample, school anxiety may lead to disordered eating attitudes which may influence the frequency of migraine.

Ketogenic diet in migraine: an experience of a pediatric headache center

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Background: To evaluate the efficacy and tolerability of the ketogenic diet in pediatric patients with chronic migraine.
The ketogenic diet (KD) is a safe and well tolerated therapeutic tool for various metabolic and neurological disorders, used successfully for more than a century for epilepsy but its potential therapeutic efficacy on migraine has been less explored, especially in pediatric age. Different experimental models show that KD is able to reduce the propagation of cortical diffusion depression and to decrease cerebral excitability favoring GABAergic transmission. Furthermore, KD and ketone bodies can inhibit neuroinflammation, oxidative stress and free radical formation, which are processes involved in the pathophysiology of migraine.

Methods: We conducted a retrospective observational study on 5 chronic migraine patients who received a KD; mean age 15 years and all are female, mean baseline BMI is 25.8; baseline frequency of headache is 24.4 episodes/months.
Were evaluated at the baseline and then after 1, 3 and 6 months both from a neurological and a nutritional point of view, including BMI.

Results: Only 2 patients completed the 6-month follow-up; 2 patients discontinued the ketogenic diet respectively after 3 weeks and after one month due to metabolic acidosis and side effects. One patient discontinued after 3 months due to poor efficacy.
In the two patients who completed follow-up (FU), there was a reduction in headache frequency greater than 50% in one patient and less than 50% in the other, respectively. Only in one of the two patients there was also a reduction in BMI (from 24 to 20.1). In both patients there was a significant difficulty in adhering to the dietary pattern and they stopped DK at the end of FU.

Conclusions: KD as a preventive treatment for migraine seems to be effective, also in pediatric age; however, in children there is greater difficulty in adherence and tolerability to the dietary regimen, which is difficult to apply as a first-line prophylaxis.

The importance of family functioning in children and adolescents with migraine and tension-type headache

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Background: Decades of research have established the complexity of headache etiopathogenesis, which is a disorder in which biological factors are intertwined with psychological and environmental factors in the genesis, and maintenance of the symptom. Indeed, it has been described how individuals suffering from headache often present psychological or psychopathological disturbances; moreover, the psychological profile of their family members (for example a parent) also affects headache in children and adolescents. Nevertheless, although factors related to family functioning are known to be relevant in other somatoform pathologies, their influence on the genesis and maintenance of headache has been less investigated so far. Hence, in our study, we explored the level of functioning of families of children and adolescents with different types of headaches, namely migraine and tension-type headache (TTH).

Methods: We enrolled 45 patients with migraine (10 male, age range = 8.8-18.0 years old; mean=14.6 years old; SD=2.5) and 45 patients with TTH (16 male, age range=8.9–17.9 years old; mean=14.0; SD=2.5), together with a caregiver for each patient. Family functioning was assessed by asking patients and their caregivers to fill in the self-reported questionnaire FACES-IV (Family Adaptability and Cohesion Evaluation Scale–IV).

Results: We found that family functioning was not balanced in either migraine or TTH patients, with patients perceiving a more dysfunctional family functioning compared to their caregivers. Moreover, we observed that TTH patients (and their caregivers) reported more dysfunctional family functioning compared to migraine patients (and their caregivers). Accordingly, the level of family functioning was predictive of patients' type of headache, with the more dysfunctional family functioning predicting the presence of TTH.

Conclusion: Taken together, our results support the importance of evaluating and treating children and adolescents with different types of headache by applying a more global and multidisciplinary approach that considers the family context together with patients' and/or caregivers' psychological characteristics.

Migraine and sleep disturbances: ketogenic diet as a solution in a pediatric patients group

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Background: Migraine and sleep disorders are often related and they both have a high prevalence in the general population. Ketogenic diet therapy (KDT) is a hyperlipidic diet that induces a state of ketosis in the body, i.e. a metabolic condition in which the main energy source is represented by ketone bodies, which activate numerous endogenous metabolic pathways and induce epigenetic changes that stabilize or improve cellular metabolism. Treatment with KDT in migraine patients is gaining importance due to the relatively low responder rate of traditional preventive therapies and it could be considered a valid therapeutic alternative also because of the potential improvement of other aspects related to the disease (sleep disturbances, memory and attention fragility).

Methods: Subjects of both sexes (14-20 years) with diagnosis of primary headache were recruited. Patients remained on stable nutraceutical or pharmacological treatment for two months before KD initiation and during follow-up. Exclusion criteria were intellectual disability, medical and biochemical changes incompatible with KDT, brain injury documented on MRI, and poor compliance. The patients were evaluated through medical history, headache diary, vital parameters, ECG, blood exams, neurological and general examination, self-administered questionnaires and ambulatory polysomnography.

Results: After 3 months of follow-up, changes in the clinical presentation of migraine and sleep pattern have been evaluated. Improvement of headache in terms of mean duration of the attacks, frequency, and intensity was reported in four out of five patients enrolled. Polysomnography study showed a mean increase in total sleep time, REM and REM latency, with a consistent reduction of nocturnal awakenings.

Conclusion: In the absence of sufficient literature data, the current study aims to describe the clinical response with respect to migraine symptoms and associated symptoms in patients treated with KD. Some benefits from the introduction of the diet are evident both in headache symptoms and sleep. However, ketogenic diet is very difficult to apply. For this reason it is important to continue with research in this field in order to hypothesize the best candidate who can benefit from the therapy and have a better compliance to the treatment.

Childhood primary stabbing headache: a double center study

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Background: Primary stabbing headache (PSH) is an idiopathic headache disorder characterized by head pain occurring as a transient and localized single stab or a series of stabs. The aim of this study was to examine the characteristics of PSH in childhood.

Methods: In this retrospective study we included 60 patients seen at two headache clinics (Rome and Bari) between 2016 and 2022. A headache-focused history was obtained. All patients had normal neurological examination. PSH was defined according to ICHD-3 and we decided to use the term PSH also for probable PSH.

Results: Twenty-three patients were male (38%) and the median age at disease onset was 8 years (range 3-17). Stabs recurred with irregular frequency and the duration varied from a few seconds to 30 minutes. Stabs were located in a variety of regions of the cranium. Twenty-five patients (42%) underwent neuroimaging and all were normal. Only five children reported a limitation of activities of daily living and none had a chronic pattern. Forty-seven patients (78%) had a family history of primary headache, especially migraine, and forty-three had episodic syndromes (i.e. infantile colic, benign paroxysmal vertigo, motion sickness, recurrent abdominal pain, cyclic vomiting). Twenty patients had an associated primary headache: 16 migraine and 4 tension-type headache. According to ICHD-3, thirty-one patients had a diagnosis of probable PSH due to a stabbing duration longer than a few seconds (> 3 seconds) and the other two patients due to associated cranial autonomic symptoms.

Conclusion: Presentation of childhood PSH varies widely. As seen in previous studies, a lot of patients reported a stab duration longer than a few seconds and this might suggest that the current ICHD-3 criteria may be in need of adjustment to be applicable for children. The high frequency of associated migraine and episodic syndromes could suggest a common pathophysiological mechanism between PSH and migraine. In pediatric age, the far higher prevalence in very young children may also suggest that PSH represents a precursor of migraine. Large studies with long-term follow-up are needed to improve understanding of this condition.

Ketogenic diet as a therapeutic intervention in the primary headache of the developmental age

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Background: Headache is a neurological disease that significantly interferes with the quality of life of the subject and his/her family. The ketogenic diet aims to modify the patient's lifestyle (always desirable in subjects with this pathology) and to play the role of a real therapy. This diet induces a chronic state of ketosis, a metabolic condition in which ketones are used as the main energy source. The induced epigenetic regulation promotes neuroplasticity and a reduction of cellular oxidative stress, as well as an improved cellular energy availability that stabilizes neuronal membranes by normalizing thalamic-cortical excitability. Finally, the increase in ketones intervenes on neurogenic inflammation, with an anti-inflammatory action.

Methods: Subjects of both sexes (14-20 years) with diagnosis of primary headache were recruited. Pharmacological therapy, if present, had been stable for at least two months at the time of inclusion. Subjects with intellectual disability, cerebral malformations and/or lesions documented, and metabolic pathologies were excluded. Poorly compliant families were also excluded.

Results: Clinical anamnestic data relating to headache symptoms at baseline (T0) and at the first check-up (T1) were collected. Currently two patients have yet to start the diet; another one is scheduled for T1 in the coming months. Two patients self-suspended therapy before T1. Among those who continued follow-up, benefits were reported. They described reduction in the number of episodes, frequency and duration of attacks. Only one patient reported no benefits after three months of treatment. Of the 11 patients who reached T1, only four continued the therapy.

Conclusion: There are not many studies relating to this type of treatment in children and adolescents, nor in relation to this type of pathology. Some benefits from the introduction of the diet are evident. However, ketogenic therapy is very restrictive and requires close monitoring, often difficult for families. For this reason, it is important to continue with this study, also in order to outline the population of patients who find the greatest benefit in adopting this diet.

A virus that makes your head spin

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Background: The different neurological manifestations associated with SARS-CoV-2 infection are now widely known. Among these, in the pediatric setting, headache has been described as one of the most associated symptoms, with heterogeneous clinical presentations.

Case report: We describe a case of a 10-year-old boy with a new onset headache as main symptom during SarS-CoV2 infection. One month after this infection he presented at the Emergency department with persistent pulsating headache and onset of diplopia with left VI° cranial nerve deficiency; his brain magnetic resonance angiography and lumbar puncture were negative. We diagnosed a post-infectious VI° cranial nerve palsy and we started treatment with orally prednisone. During hospitalization the patient showed a gradual clinical improvement and he was discharged after a week completely asymptomatic. In the following 6 months he referred persistent post-COVID-19 sporadic headache with migraine characteristics.

Discussion: Headache-associated with COVID-19 (HCoV) has been described as a heterogeneous condition, that can occur either as a prodromal symptom, as part of the acute symptomatology of the infection or can become a long-lasting condition. The most common described features of HCoV are bilaterality, moderate to severe intensity, pulsating or constrictive quality with a tension-type or migraine-type phenotype. The pathogenesis of this manifestation remains uncertain, but the invasion of the central nervous system through the olfactory bulbs could represent one of the main pathogenetic mechanisms together with a direct viral damage and an involvement of the vascular endothelium. The association between persistent new onset headache and SarS-Cov2 infection has been described as "long COVID", highlighting a picture of migraine headache lasting from 90 days after the onset of infection up to over 180 days. Ophthalmoplegia represents one of the neurological manifestations associated with SARS-CoV2 infection, due to III° or VI° cranial nerve damage by direct viral action or as consequence of autoimmune mechanism.

Conclusion: This case report characterized by headache and a cranial nerve palsy allows us to better understand how the neurological aspects correlated with the Sars-CoV2 infection can be heterogeneous in their presentation framework and underlines the role of acquiring awareness on the possible long-term neurological sequelae in the pediatric population.

When migraine becomes chronic: headache and psychotherapy in a clinic case-study

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Background: Chronic migraine is a neurological condition characterized by migraine attacks for more than 15 days a month for at least 3 months, which can considerably affect the patient's quality of life. This case illustrates the clinical work with E., a 16-year-old adolescent who consulted her paediatrician due to the onset of intense daily headache shifted to chronic course. Therefore she was referred to the Psychology Service of the Headache Centre of the Regina Margherita Children's Hospital of Turin, Italy. E. reported numerous symptoms, including: daily migraine, fear of being abandoned, binge eating with purging behaviours, strong feelings of emptiness, low self-esteem. She described her parents as emotionally unattainable and extremely practical and controlling (e.g. on clothing). On one side there she reported an intrusive mother, who tended to confuse her own experience with that of her daughter; on the other, a cold and distancing father, who tended to exclude the physical and emotional contact. Due to the severity of the symptoms, the dysfunctional family environment and the resultant inconstancy of sessions, a parallel take over at the hospital's Child Neuropsychiatry was also required.

Methods: The proposed treatment was mainly based on relational-oriented psychotherapy consisting of weekly sessions lasting 45-50 minutes and psychodiagnostic test (TAT).

Results: The clinical work done so far has been aimed at welcoming her profound suffering and confusion and at trying to recognize the different emotions and feelings she experiences. Ample space was given to the re-signification of the headache symptom used, in her case, as a desperate attempt to shut everything down when the demands of the world get too loud and heavy. Thanks to the interpretative tools, through the therapeutic relationship, it was possible to start to symbolically unwind the ancient tape of E.'s story, which presents a development block in the separation-individuation phase.

Conclusion: This case highlights how some psychological and family factors can negatively affect both the chronicity of migraine symptoms and the continuity of the psychotherapy itself. Although some progress has been made in the months of therapy with E., the complexity of the situation and the seriousness of her symptoms require a long multidisciplinary take over.

Comparison of three headache cases: administration of the Rorschach Performance Assessment System

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Background: Primary headache in children and adolescents is a condition with high comorbidity, both on the somatic level (fibromyalgia, menstrual disorders, etc.) and on the psychological level (anxiety, depression, alexithymia). Therefore, patients accessing our specialist outpatient clinic are given special attention to identify possible comorbidities. In particular, we wanted to assess, in a more complex psychodiagnostic work, the existence or non-existence of peculiar personality patterns through the analysis of the RSH protocol, using the R-PAS method in three patients whose common denominator was headache.

Methods: All patients are female, aged 12-17 years, with intellectual level, assessed with WISC-IV in the normal range, with good knowledge of the Italian language, suffering from migraine, headache and fibromyalgia, headache and depression, respectively.

Results: Common elements emerge in the protocols examined. They concern the approach to the task, which is good in all cases, with a tendency to see and describe the globality of the stimulus. A better use of ideational resources has been observed compared to emotional ones, coping is based on rationality. The patients showed good ability to mentalize the other and good ability to differentiate the self from the other. Reality is read in a projective key, with particular reactivity to stressful elements; reality-testing is overall preserved and the self-image devalued.

Conclusion: The different intensity and quality of the elements in common, in the different protocols, characterizes the three different clinical cases.

Headache with cerebrospinal fluid problems: a case report of HaNDL Syndrome

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Background: The transient Headache and Neurological Deficit with cerebrospinal fluid Lymphocytosis (HaNDL) Syndrome is a rare form of primary headache. About 30 paediatric cases have been described in literature.

Methods: We report the case of a 15-year-old patient diagnosed with HaNDL at our Department of Pediatric Emergency.

Results: The patient was admitted because of paresthesias to the right side of the face and upper limb, asthenia and dysarthria, lasting about two hours, followed by left periorbital pulsating headache. In her medical history, she reported a gastrointestinal infection in the previous weeks. Head computed tomography (CT) and CT angiography, blood tests, electroencephalogram (EEG), head magnetic resonance imaging (MRI) and MR angiography, fundus oculi, thrombophilic screening and autoantibodies for disimmune encephalitis on cerebrospinal fluid (CSF) were all negative. At lumbar puncture, CSF was found with lymphocytosis (leukocytes 127/mmc, 100% lymphocytes), slight increase in proteinorrachia (62.2 mg/dL) and albumin (403 mg/L), absence of glycorrachia, negative Polymerase Chain Reaction for viruses and bacteria. In the following days, she presented a new episode of headache, without neurological symptoms. The diagnosis of HaNDL was then assumed. At follow-up, the girl reported a further episode of frontal, pulsating headache associated with photophobia, nausea and vomiting, followed by hypoesthesia of the left lower limb and spontaneous recovery after 30 minutes.

Conclusion: HaNDL is defined in details by the International Classification of Headaches, ICHD-3 (code 7.3.5). Only 15% of cases described in literature involve children. The aetiology is currently unknown, but autoimmune mechanisms have been proposed. The diagnostic work out includes lumbar puncture (with detection of lymphocytosis and possibly proteinorrachia and increased CSF pressure), neuroimaging (proving negative in the intercritical period, with the possibility of detecting delayed cerebral perfusion and narrowing of cerebral arteries during an episode) and EEG (possibly showing focal findings in the symptomatic period). The differential diagnosis should consider: stroke, structural lesions, seizures and neuro-infective pathologies. The treatment is symptomatic and the course is self-limiting, usually with resolution in about 3 months: during this period it is important to follow up the patient, reassuring him/her and urgently intercepting any episodes following the first one.

Migraine in childhood: Gender differences

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Background: Migraine involves up to 20% of children and adolescents. Although gender differences in migraine epidemiology and clinical characteristics have been largely investigated in adulthood, this issue is less known in children. We aim at providing an overview of gender differences in pediatric migraine.

Methods: The most recent literature was reviewed taking into account epidemiological, pathophysiological, and clinical differences between boys and girls with migraine.

Results: All the reviewed literature suggests that gender differences in migraine are not only characteristic of adulthood or post-pubertal adolescents, but they involve younger children. Epidemiological differences between genders depend typically on age, with an inversion of the male/female ratio during and after puberty. Indeed, while before puberty migraine prevalence is slightly higher in boys than in girls, the disease becomes more frequent in post-pubertal females. Also, clinical characteristics of the migraine attack can be different between males and females. Hormonal differences can account for many gender differences, especially after puberty, but other factors may be important to explain the different development trajectories of migraine in girls and boys. Promising results are those issued from genetic studies, which are trying to interpret some gender differences in terms of different genotypes. Also, neuroimaging investigation is discovering gender differences in the brain cortex structure.

Conclusion: Different aspects of childhood migraine may vary depending on gender and age, especially with regard to pubertal development. Future research should investigate: 1) genetic-clinical correlations in males and females; 2) correlation between migraine features and hormonal levels (estrogens and testosterone); 3) possible gender differences in the response to treatments; 4) possible gender differences in the migraine equivalents, which represent the early symptoms of the childhood migraine.

Trends in the use of neuroimaging in non-acute pediatric headache: does the experience of the doctors really matter?

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Objective: To identify trends in rates of use of diagnostic neuroimaging in non-acute pediatric headache and correlate them with the experience of neurologists at the headache center.

Methods: Retrospective analysis of neuroimaging rates was conducted on 135 children and adolescents aged 2 to 18 years with headache on their first visit to the pediatric headache center. Among the parameters of current practice were evaluated: age < 6 years, presence of neurological signs, nocturnal awakenings, occipital pain, pattern charge, sudden or abrupt onset, presence of typical or atypical aura, positional headache or precipitated by sneezing, coughing, or exercise; vertigo, failure to respond to analgesics.
Also, we analyzed the rate of neuroimaging prescription in relation to the experience of neurologists.

Results: The neuroimaging rate is inversely proportional to the years of experience at the headache center. The most criteria for neuroimaging are in accordance with the red flags (data in progress).

Conclusion: In the evaluation of pediatric patients with non-acute headache, neuroimaging rates are related, not only to the presence of red flags, but also to the experience of the physicians.

Nummular headache: a case report of remission following ketogenic diet and botulinum toxin type A injections

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Background: Nummular headache is an unusual facial pain disorder with no evidence-based therapy recommendations. The ketogenic diet is an alternative therapy that demonstrated to be effective in migraineurs, but it was never used in the setting of nummular headache.

Case: We describe a 58-year-old female patient with nummular headache successfully treated with a 6-months ketogenic diet and botulinum toxin type A injections.

Conclusion: Ketogenic diet could be an effective alternative/complementary therapy in nummular headache patients although more studies are needed to confirm our results.

A case of a woman with chronic migraine without aura and relapsing remitting multiple sclerosis (RRMS) treated with an anti-calcitonin gene related peptide (CGRP), galcanezumab

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Background: MS and migraine coexist in many young patients [1]. It's unclear if the diseases are causally linked. Several studies confirmed an association between migraine and MS, and others didn't find this relationship [2,3,4]. A recent review found that the prevalence of primary headaches among MS patients is 56%, with 27% being migraines and 10% being tension-type headaches [5]. Migraine in MS patients is more common in women (ratio 2:1) and more often started before MS diagnosis (78.8%) [11]. Migraine is the most common headache in RRMS and tension-type headaches among progressive forms of MS [6]. Migraine is three times more common in MS patients than in the general population [10,11]. Since the start of disease-modifying therapies (DMTs) headaches have been observed as side effects, especially with interferons and migraine [7,8,9]. Other drugs didn't induce headaches more frequently than the placebo group in randomised trials, although in other studies it was found that fingolimod and natalizumab can increase the frequency of migraine attacks in MS patients [9].

Methods: We describe the case of a 44-year-old woman with chronic migraine without aura (daily, intensity up to 10NRS and overuse of triptans and FANS) and RRMS (diagnosed in 2023). She had performed migraine prophylaxis with flunarizine (not tolerated), amitriptyline (not effective) and botulinum toxin (effective only first year). In September 2021 she started prophylaxis with anti-CGRP, galcanezumab, with progressive reduction of the frequency of migraine attacks (6-10/month) and intensity (4-6NRS), MIDAS from 72 to 30. In February 2023 she started a DMTs for MS, the cladribine, well tolerated.

Discussion and Conclusion: Female sex is a main risk factor for migraine and MS. Migraine is a comorbidity with acceleration in RRMS. Clinical studies have shown that migraine patients may have dysregulation in their immune system with B and T cell involvement [12,13]. In rodents, an abundance of B and T cells was reported in the meninges, with the expression of CGRP in B cells upon stimulation by nerve-growth-factor and the presence of CGRP-receptors on the B and T cells. CGRP levels were much lower in inactivated cells [14]. Activated lymphocytes, particularly B cells, could potentially play some role in increasing CGRP, which is able to promote inflammation. This inflammation can already contribute to migraine during relapses MS.

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Late-onset migraine mimicking secondary headaches: two cases successfully treated with OnabotulinumtoxinA

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Background: Migraine is one of the most common neurological disorders and its typical onset is in young adult age. Among the elderly, its prevalence varies from 3% to 8%. Headache onset in older adults requires an accurate diagnosis to exclude secondary forms and a careful management considering age and comorbidities often present in this subgroup of population. Goal of this report is to describe two patients with late onset migraine mimicking secondary headaches and to evaluate the effect of OnabotulinumtoxinA (BT-A) on their condition.

Methods: We describe two female patients with chronic migraine (CM) with onset after the age of 50 years. Because of atypical features and late onset, further investigations were performed to exclude secondary forms. Patient 1 had almost exclusively nocturnal attacks; patient 2 often experienced an associated vertiginous syndrome. Many attacks lacked typical migraine features such as nausea/vomiting and phonophobia/photophobia. They both underwent repeated injections with BT-A after first-line prophylaxis failure. Patients were treated with BT-A following the PREEMPT protocol[3] with additional specific "follow-the-pain" sites every three months for at least one year. We prospectively collected sociodemographic and clinical data at baseline and at every scheduled treatment. Outcomes measures included days of migraine and number of acute medications before the treatment (t0) and after three (t1), six (t2), twelve months (t3) and HIT-6 and MIDAS scores at t0 and t3.

Results: Days of headache/month decreased in both patients (patient 1: t0=20; t1=6; t2=3; t3=2; patient 2: t0=25; t1=18; t2=8; t3=5), just as acute medications intake (patient 1: t0=10; t1=5; t2=3; t3=2; patient 2: t0=25; t1=18; t2=7; t3=2). MIDAS score lowered after one year of treatment (patient 1: t0=55; t3=15; patient 2: t0=53; t3=11), as well as HIT-6 score (patient 1: t0=63; t3=52; patient 2: t0=62; t3=50).

Conclusion: The excellent response to BT-A in these patients suggests that, despite atypical features, a migraine physiopathological mechanism probably underlies their headache. BT-A might be a valid prophylaxis option for elderly patients suffering from late onset CM mimicking secondary headaches, not only for its effectiveness but also for its high tolerability profile and lack of interactions with other drugs frequently used in this subgroup of population.

Effectiveness and tolerability of rimegepant as acute treatment in a patient with refractory migraine and non-responder of two anti-CGRP monoclonal antibodies and oral triptans: a case report

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Background: Gepants and monoclonal antibodies (mAbs) against calcitonin gene related peptide (CGRP), have recently become available for migraine prophylaxis with proven efficacy. If the failure to an anti-CGRP/R mAbs precludes the effectiveness of gepants or viceversa is still unknown. Herein, we report the case of a patient with refractory migraine responsive to the acute use of rimegepant that previously failed two different anti-CGRP/R mAbs and with no response to other triptans.

Methods: The patient was instructed to collect effectiveness and tolerability of rimegepant 75 mg for every attack of moderate to severe intensity, after 2 hours from administration in an e-diary. The variables collected included: rating of headache severity, absence or presence of migraine-associated symptoms, use of rescue medications, the rating of functional disability and recurrence of headache pain at different time points. After 24h the patient collected the eventual re-occurrence of migraine, the use of rescue medication and migraine-related symptoms and disability. The effectiveness was defined as 2h pain freedom. Sustained pain freedom after 24h was also considered.

Results: A 56-year-old female patient with a long history of migraine without aura and chronic migraine. She reported having daily headaches that were severe in intensity. She reported no effect from the use of oral triptans or other oral symptomatic drugs. The patient reported failure for ineffectiveness or not tolerability of all classes of preventive pharmacological treatments (fulfilling refractory criteria) included galcanezumab and erenumab (70 mg then 140 mg). The patient completed the e-dairy for 5 attacks with intake of rimegepant 75 mg with an achievement of 2h pain free on 3/5 attacks with sustained response after 24 h and no rescue medication used. In the remaining 2 attacks the patients reported no changes and the need of rescue medications. The drug was taken at the onset of the headache attack (range 10-30 minutes) for all attacks. No adverse events were reported.

Conclusion: Rimegepant used as acute treatment seems to be effective and well tolerated in a patient with prior failures to two anti-CGRP/R mAbs and no response to oral triptans.

Sensorimotor Persistent Familial Hemiplegic Migraine aura due to PRRT2 gene deletion: the first case report

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Background: Familial Hemiplegic Migraine (FHM) is an uncommon genetic illness in which stroke-like symptoms occur in patients and at least one first- or second-degree relative. Three genes mutations, i.e. CACNA1A, ATP1A2 and SCN1A, are responsible for the largest part of FHM cases. Recently, another major cause of FHM has been identified: a loss of function of the neurotransmission-involved PRRT2 gene. Motor symptoms, that accompany and follow migraine pain, can last up to weeks. Nevertheless, a similar persistence of sensory symptoms has never been described. To describe a unique case of sensorimotor persistent aura related to PRRT2 gene deletion is the purpose of this study.

Methods: The clinical history and neurological symptoms of a 27-year-old male, migraineur since he was 4 years old, were evaluated.

Results: After being hospitalised for stroke-like symptoms, the patient's sister was given a hemiplegic migraine clinical diagnosis at our Headache Centre. The patient's headache initially seemed a typical migraine without aura. Since he was 15, a right hemibody strength deficiency that lasted for up to 12 hours accompanying the pain has been added. He also presented with a co-occurring right hemibody hypoesthesia since he turned 21. Then, weakness and sensitivity deficiencies lasting up to 12 hours on average have always been associated. Rarely, speech and visual deficits were added. Attacks duration was up to three days each month. At the age of 27, the patient was neurologically evaluated in our Headache Centre due to weakness and hypoesthesia in the right limbs exceptionally dating from three months before. Standard brain MRI, brain CT and EEG were negative. After the prescription of lamotrigine 50 mg/day, the patient began to improve, but the treatment was stopped after two months due to suicide thoughts. After two months of switching to valproic acid 300 mg/day, aura symptoms disappeared. Months later, genetic MLPA analysis detected a heterozygous deletion of the whole PRRT2 both in the patient and in his sibling.

Conclusion: For the first time, we discussed a unique case of FHM-related sensorimotor persistent aura due to PRRT2 gene deletion, responsive to antiepileptic drugs.

Prospective evaluation of aura during anti-CGRP monoclonal antibodies after 52 weeks of treatment: a case series

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Background: Clinical studies have demonstrated the efficacy, safety, and tolerability of anti-calcitonin gene related peptide monoclonal antibodies (CGRP mAbs) in both patients with migraine without (MwoA) and with aura (MwA). Post-hoc and small subgroup analyses have suggested that mAbs may also be effective in reducing the frequency and intensity of aura, but with still few data on specific aura features. Herein, we assessed the changes of aura during a long anti-CGRP mAbs treatment.

Methods: We evaluated all outpatients treated with anti-CGRP mAbs in a tertiary Headache Center. We included all patients who experienced at least one episode of aura per month, as reported in their medical history and during the baseline period. The study covered a one-year treatment, during which a detailed prospective evaluation of the aura phenomenon was conducted at baseline and in the last three months of treatment.

Results: We analyzed data from 13 patients with complete information on aura. Among them, 9 were females (69.2%), 12 had chronic migraine (92.3%), and 12 had MO (92.3%) at baseline. Among these patients, the diagnosis was both MwA and MwoA for 12 patients, and one patient only MwA. The mean duration from the onset of aura was 17.8±7.9 years, with an average duration of 34.2±15.7 minutes for aura episodes. Nine patients (69.2%) reported visual aura, while four patients (30.8%) experienced both visual and sensory aura. At baseline, the average number of MHDs was 22.3±7.5, with 9.08±9.1 preceded by aura. After 12 months of treatment, the number of days with aura were reduced to 2.6±2, which represented a stable reduction observed during the last three months of treatment. All patients, except one, reported a consistent reduction in aura occurrence throughout therapy. Additionally, three patients reported episodes of aura without subsequent headache, a phenomenon that was not present prior to anti-CGRP treatment. Among them, one reported only aura episodes without accompanying headaches.

Conclusion: Anti-CGRP mAbs reduced the frequency, intensity, and duration of aura consistently with the reduction of MHDs. Only one patient reported just episodes of aura without subsequent headache.

Atypical presentation of herpes zoster with cranial neuralgia and nodular skin lesions, a case report

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Background: Reactivation of varicella-zoster virus (VZV) leads to the manifestation of herpes zoster, typically presenting as vesicular lesions limited to one dermatome (usually thoracic), with associated acute pain and subsequent long-lasting neuropathic pain. Atypical presentations however exist, and here we present a case of nodular herpes zoster with cranial involvement.

Case presentation: We describe the case of a 39-year-old male complaining of a new-onset stabbing pain localized to the left parietal region of the head; the pain was defined as sharp, lasting 1-2 seconds and repeating every 5 seconds, all day long, more than 1000 times a day; no nausea, vomit, photo-phonophobia were reported. Diagnosed as "nummular headache" in another ER, the patient presented to our Clinic for persistence of pain. A brain and cervical contrast-enhanced MRI and MRA was performed, showing skin oedema and subcutaneous inflammation in left parieto-occipital region; no brain or cervical spinal cord alterations were observed. Haematological exams were performed, with results within normal values. As patient referred skin alterations in the same region, a dermatological evaluation was performed, which confirmed the presence of herpes zoster, with an atypical rare nodular variant, involving the skin territory innervated by left C2 spinal nerve. Serological confirmation was obtained by anti-VZV IgG and IgM testing. Antiviral treatment was started (Valaciclovir tablets 1000 mg x3/die), associated with topical Gentamicin to prevent bacterial superinfection. Pain treatment included anti-epileptic (Carbamazepine tablets 400 mg x2/die), anti-depressive (Amitriptyline 15 drops/die), anxiolytic (Bromazepam 20 drops x3/die) and nutraceutical (Normast tablets 600 mg x2/die). This therapy, associated with a paravertebral C2 nerve block with Lidocaine, achieved significant pain reduction. The patient was discharged with ongoing therapy; at follow-up visit one month later, the infection had resolved and complete pain-freedom was observed; treatment was, therefore, gradually reduced until complete discontinuation.

Conclusions: This case interestingly shows an atypical presentation of herpes zoster, for several reasons: the dermatological presence of nodular instead of vesicular lesions; the associated pain described as stabbing neuralgic pain instead of more frequent neuropathic pain; the involvement of C2 nerve territory, which is not considered as a skin region usually affected by herpes zoster.

First real-life experience with Rimegepant as symptomatic drug in difficult to treat patients: a Case Series

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Background: Triptans are a specific therapy for migraine attacks but they cannot be used by patients with vascular risk factors. Furthermore, not all patients respond to triptans, especially when attacks are related to the menstrual cycle. Calcitonin Gene-Related Peptide (CGRP) plays a pivotal role in migraine pathophysiology. Rimegepant is a new CGRP receptor antagonist which in phase 2 and phase 3 trials demonstrated a similar efficacy and fewer side effects than triptans and that was recently approved both for acute and preventive migraine therapy.

Methods: We describe seven adult female migraineurs. Six patients were suffering from chronic migraine and medication overuse headache and one from high frequency migraine. Six patients were triptan resistant (previous failure of at least three triptans). Paracetamol was ineffective in all patients. Four patients were resistant to NSAIDs too. They all received Rimegepant 75 mg for migraine attacks. Efficacy and tolerability were evaluated by a structured questionnaire. Patient's drug satisfaction was evaluated by using a 0-10 Likert scale (0 = not at all satisfactory – 10 =completely satisfactory).

Results: Three of the treated patients reported pain freedom at 2 hours. Two patients reported pain relief at 2 hours: in one case pain was reduced by at least 50% and in one case, it was reduced by at least 30% than baseline. One patient reported pain relief at 6 hours by at least 50%. One patient used the drug during the menstrual cycle with pain reduction of at least 50%. Rimegepant was also effective in reducing the most bothersome symptom (nausea). Three patients rated the drug satisfaction as 10, one patient rated it as 9, and three rated it as 7. Only one was not satisfied (0). Regarding tolerability, only one patient reported fatigue for approximately 30 minutes.

Conclusion: In this case series Rimegepant proved to be very effective (2-hour pain freedom was achieved by 71% of patients) and well tolerated by 86% of patients confirming that this new drug recently added to the migraine specific treatment options may be particularly useful in patients difficult to treat due to contraindications or resistance to other symptomatic drugs.

Role of the Default Mode Network in Episodic Cluster Headache: Cerebral Connectivity Analysis with HD-EEG

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Background: The pathophysiological mechanisms underlying episodic cluster headache (eCH), and shift between active and remission phases, are still not fully understood.

Methods: Twenty-four patients with eCH and 19 healthy controls (HCs) were enrolled. Patients with eCH were evaluated during both the active (T0) and the remission (T1) phases of disease. The DMN areas considered for the analysis were: the right and left angular gyrus (RANG and LANG), the medial pre-frontal cortex (MPC) and the posterior cingulate cortex (PCC).

Results: The study of internodal brain connectivity in patients showed lower connectivity at T1 (remission) when compared to T0 between PCC and MPC (T0=0.078±0.009 vs. T1=0.049±0.006, p=0.022) and between PCC and RANG (T0=0.076 ± 0.008 vs. T1=0.052±0.005, p=0.024). Furthermore, connectivity at T1 was lower when compared to HCs, specifically between PCC and MPC areas (CHe-T1=0.049±0.005 vs. HS=0.067±0.005, p=0.028).

Conclusion: eCH patients evaluated during a remission phase of disease showed lower brain connectivity between specific areas of the DMN when compared with either eCH patients tested during an active phase and HCs. This finding may represent a biological marker of disease, while the fluctuation in PCC connectivity may reflect pathophysiological mechanisms involved in the shift from one phase of disease to the other.

Impact of monoclonal antibodies against calcitonin gene-related peptide on pain system: a laser evoked potentials study

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Background: Anti-calcitonin gene-related peptide (anti-CGRP) monoclonal antibodies have opened a new scenario in the preventive treatment of migraine.
The aim of the study was to assess, using laser evoked potentials (LEPs), the impact on pain-processing pathways of a preventive treatment with Anti-CGRP monoclonal antibodies in migraine.

Methods: We studied 11 patients (10 women, mean age: 35.6 ± 12.4 years) affected by migraine, before and after 3-6 months of prophylactic scheme (Galcanezumab 120 mg monthly, with a starting dose of 240 mg). All subjects received stimulation over the right-hand dorsum and the right perioral region. Three consecutive repetitions were obtained for each stimulation site. The interstimulus interval varied randomly between 8 and 12 s.
Absolute values of N1, N2 and P2 latencies and amplitudes were compared before and after treatment. For the analysis of LEP amplitude habituation, the LEP amplitudes in the second and third repetition of each stimulation site were expressed as percentages of the amplitudes of the corresponding LEP components recorded in the first sequence.

Results: After treatment the patients reported a significant reduction of the mean number of monthly headache days ($p<0.0001$), monthly drug intake of acute medication ($p<0.0001$), and MIDAS score ($p=0.0019$). No significant differences were found, between pre and post treatment, for the VAS pain rating score, thresholds, LEP latencies and absolute amplitude of N1 potential and N2-P2 complex. A statistically significant modification (normalization) of the amplitude habituation of both N1 ($p=0.001$ after hand stimulation; $p=0.0052$ after face stimulation) and N2-P2 ($p=0.0019$ after hand stimulation; $p<0.0066$ after face stimulation).

Conclusion: Our main finding is that patients with migraine showed a restore of habituation to repetitive stimuli after a prophylactic treatment with Galcanezumab.
Several hypotheses can explain these results, including the re-modulation of central sensitization associated with the GABA levels modification in anterior cingulate cortex.

Preliminary multicenter efficacy study of a bupivacaine-based treatment using the TX 360® device for anesthetic blockade of the sphenopalatine ganglion, in subjects suffering from episodic cluster headache in the acute phase

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Background: Retrospective observational multicenter study to evaluate the efficacy of bupivacaine 5% with a session administration of 0.3 ml per nostril applied via the TX 360® device on the mucosal surface overlying the nerve endings arising from the sphenopalatine ganglion, in subjects suffering from episodic cluster headache in the acute phase, using as an end-point: the resolution of the "cluster" attacks after treatment.

Methods: From October 2019 to January 2023, 14 patients (13 males and 1 female, aged 39-75 years with a mean of 55.5 years) affected by Cluster Headache (ECH), 13 of the episodic type and 1 of the chronic type according to ICHD-III in the acute phase, who had contraindications relative and absolute to the use of classical prophylactic therapy were included in the study.

Results: After the first treatment 10 patients had complete remission of the "cluster", for another 3 a second treatment was used for the complete resolution of the headache symptoms, showing satisfaction for the rapid improvement of their pain condition. The patient affected by the chronic form, a non-responder to the classic prophylaxis therapy with verapamil and cortisone cycles, did not experience any improvement after two applications.

Conclusion: The anesthetic block of the sphenopalatine ganglion, concerning the results obtained in real life, could become a valid alternative to the classic prophylaxis therapy with verapamil and cortisone, for two relevant aspects: the rapid therapeutic action and the few side effects (more frequent lacrimation shortly after application). This preliminary study encourages the execution of an analytical prospective multicenter observational study, which validates the efficacy results obtained with the use of TX 360® in these patients.

Somatosensory evoked potentials in tension-type headache

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Background: Tension-type headache represents the most prevalent primary headache disorder among the general population, yet its underlying pathophysiological mechanisms remain poorly understood. Both central sensitization processes and aberrant pericranial muscle contractions have been implicated in its etiology. To elucidate the subcortical-cortical excitability levels in tension-type headache, we investigated the somatosensory system excitability in a cohort of individuals with TTH, comparing them to a group of healthy individuals.

Methods: A prospective cohort of 19 TTH patients (9 with episodic and 10 with chronic presentation) along with 20 healthy controls were recruited for this study. All participants underwent somatosensory evoked potential (SSEP) recordings, enabling the calculation of N20-P25 amplitude and its habituation across three sets of 100 responses. Additionally, by applying a band-pass filter (450-750 Hz) to the SSEP signal, we extracted two distinct bursts of high-frequency oscillations (early and late HFOs), reflecting thalamocortical and primary cortical activity, respectively.

Results: The latency and amplitude values of SSEPs, as well as the habituation patterns assessed between the initial two and three sets of 100 responses, demonstrated normal findings in TTH patients, including both the episodic and chronic subgroups. However, TTH patients, regardless of the episodic or chronic nature, exhibited a notable increase in cortical HFO amplitude burst ($p<0.001$) while maintaining normal thalamocortical activity.

Conclusions: Our findings indicate that TTH patients exhibit electrophysiological evidence of central sensitization and show no differences in their habituation pattern compared to controls.

Is an autoimmune disease a contra-indication for the use of monoclonal antibodies as prevention therapy in chronic migraine?

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Background: Autoimmune diseases (AD) are a group of inflammatory disorders characterized by systemic or localized inflammation. The possibility that immunologic responses might play a role in migraine is not new. In these patients headache is very common and could be either a comorbidity or the first manifestation of central nervous system (CNS) involvement. Since the adding of monoclonal antibodies anti-calcitonin gene related protein (anti-CGRP mAb) among the therapeutic options, few studies have explored the effectiveness and tolerability of these drugs in patients with AD and if they could interact with other biological medications, commonly used as disease modifying treatments (DMARDs). In our clinical practice we started selecting patients with these characteristics.

Methods: We present a case series of 4 patients affected by chronic migraine, medication overuse headache and concomitant AD. Patients' headaches were classified according to the International Classification of Headache Disorders (ICHD3) and all fulfilled the diagnostic criteria for a specific AD (two Bechet Disease, one Sjogren Disease and one Systemic sclerosis). In agreement with the referring rheumatologist and with AIFA guidelines, they started a preventive treatment with anti-CGRP mAbs.

Results: The median average of migraine attacks at the beginning of anti-CGRP mAbs therapy was 25 (range 15-30) days per month. The last follow up at 6 months showed a reduction of this burden, with median average of 12 (range 3-22) days affected by migraine and a reduction in the use of acute medications. During this period, none of the patients experimented a clinical or laboratory recrudescence/relapse of the undergoing AD and none of them showed interaction with DMARD treatments.

Conclusion: The use of anti-CGRP mAbs appears to be a reasonable choice as preventive treatment in patients with primary chronic migraine headache and concomitant AD. In our case series we observed no adverse interactions and a significant reduction in the days affected by headache.

An evolving machine-learning-based algorithm to early predict response to anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies in patients with migraine

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Background: The study aimed to determine whether machine-learning (ML)-based models can predict 3-, 6-, and 12-month responses to monoclonal antibodies (mAbs) against the CGRP or its receptor (anti-CGRP/R) in patients with migraine using early predictors and to create a prediction tool.

Methods: We prospectively collected data from patients with migraine receiving anti-CGRP/R mAbs for 12 months. Demographic data and monthly clinical variables were collected, including monthly headache days (MHD), monthly days with acute medication use (AMD), number of analgesics and Headache Impact Test-6 (HIT-6) score. Response rates were categorized as <25%, 25-50%, 50-75%, and >75% reduction in MHD. ML models were trained using the random forest algorithm. The ML models were optimized to maximize the average F1-score (harmonic mean of the precision and recall). Along with the F-1 score, the performance of the ML models was evaluated using standard evaluation metrics, including accuracy, precision, and area under the receiver operating characteristic curve (AUC-ROC). Sequential backward feature selection was employed to identify the most relevant predictors for each model. Each model was given 11 baseline data inputs (type of anti-CGRP/R mAb, age, gender, migraine diagnosis, disease duration, aura, MHD, AMD, HIT-6 score, number of analgesics and chronicization onset) and month-based predictors for months 1, 3 and 6.

Results: We included 336 patients treated with anti-CGRP/R mAbs. We are developing 6 models to predict the response rates for months 3, 6, and 12 using early predictors. ML-based models yielded predictions with an F1 score range of 0.42-0.71 and an AUC-ROC score range of 0.44-0.72. Shapley Additive explanations (SHAP) summary plots were generated to interpret the contribution of each feature for each model's output. Based on these findings, a response prediction tool was developed.

Conclusion: The response prediction tool utilizing ML-based models holds promise in the prediction of treatment outcomes for patients with migraine undergoing anti-CGRP/R mAbs treatment, potentially aiding in clinical decision-making and cost-optimization.

Phenotyping interictal migraine patients according to clinical and psychophysical characteristics

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Background: This study aims to 1) identify different migraine phenotypes according to clinical and psychophysical characteristics, and 2) assess the clinical validity of the different migraine phenotypes.

Methods: This observational study included Episodic (EM) and Chronic Migraine (CM) patients assessed in the interictal phase and was divided into two parts. In part 1, headache frequency, disability, cervical active range of motion (AROM), pressure-pain threshold (PPT) over temporalis, two cervical areas (C1/C4 vertebral segments), and two distal pain-free areas (hand/leg) were assessed and used to subgroup migraine patients into different Clusters. In part 2 clinical characteristics (multiple questionnaires), somatosensory function [comprehensive quantitative sensory testing (QST)], and cervical musculoskeletal impairments (cervical musculoskeletal assessment) were assessed and compared across headache clusters and a group of 56 healthy controls matched for sex and age.

Results: Part 1: 98 patients were included, and three clusters were identified. Cluster-2.1 No Psychophysical Impairments (NPI, 18%), Cluster-2.2 Increase Pain Sensitivity (IPS, 45%), and Cluster-2.3 Increased Pain Sensitivity and Cervical Musculoskeletal Dysfunctions (IPS-CMD, 37%). Cluster-2.1 had a higher percentage of men compared to clusters-2.2 and 2.3 ($p=0.009$). Cluster-2.3 had higher headache frequency, and disability compared to Cluster-2.2, and higher disability compared to Cluster-2.1 (all, $p<0.010$). Cluster-2.3 had reduced AROM in all directions compared to Clusters-2.1 and 2.2 ($p<0.029$). Clusters-2.2 and 2.3 have lower PPT values in all areas compared to Cluster-1.1 ($p<0.001$).
Part 2: Cluster-2.3 (IPS-CMD) had 1) longer disease duration, higher headache frequency, disability, and psychological burden vs. Cluster-2.2 (IPS) (all, $p<0.027$) and 2) higher headache-related disability, neck-related disability, and higher symptoms of sensitization vs. Cluster-2.1 (NPI) (all, $p<0.018$). Cluster-2.3 (IPS-CMD) had reduced cervical active and passive range of motion and reduced functionality of deep cervical flexors vs. Controls, Custer-2.1 (NPI), and Cluster 2.2 (IPS) (all, $p<0.034$). Cluster-2.2 (IPS) and 2.3 (IPS-CMD) had reduced QST values vs. controls ($p<0.001$) and Cluster-2.1 ($p<0.039$).

Conclusion: In the interictal phase, three clinically relevant clusters could be identified, with one group showing no psychophysical impairment, one increased pain sensitivity, and one increased pain sensitivity and cervical musculoskeletal dysfunctions.

Modulation of the inflammatory events and neuronal activation after inhibition of PEA hydrolysis: study in an animal model of migraine

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Background: N-palmitoylethanolamide (PEA) is an endogenous congener of the endocannabinoid anandamide with diverse biological functions, including neuromodulatory activity in the central nervous system. In a previous study, we reported that administration of ARN726, an inhibitor of the enzyme N-acylethanolamine acid amidase (NAAA), which is involved in the degradation of PEA, significantly reversed nitroglycerin (NTG)-induced trigeminal hyperalgesia and reduced serum calcitonin gene-related peptide (CGRP) levels and cytokine gene expression in migraine-specific brain areas. Here, we further assessed the anti-inflammatory effects of endogenous PEA, using ARN726, by evaluating gene and protein expression of interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha in specific cranial areas in the animal model of migraine, based on NTG administration. We also investigated the modulation of NTG-induced neuronal activation in the caudal trigeminal nucleus by flow cytometer examination of c-Fos neurons positive in the high cervical spinal cord (CSC, C1–C2 level).

Methods: Sprague Dawley male rats were treated with the NAAA inhibitor, ARN726 (3mg/kg, i.p) 2 hours after NTG (10mg/kg, i.p) or vehicle injection. Four hours after NTG/vehicle administration all rats were sacrificed; the CSC and TG were extracted for the assessment of gene expression and protein levels of TNF-alpha and IL-6. A second set of rats was used to evaluate NeuN/Fos-labeled events in the cervical spinal cord by the Fluorescence-activated cell sorting (FACS)-based method.

Results: Treatment with ARN726 significantly reduced TNF-alpha protein levels induced by NTG administration in TG, compared with the control group. The inhibitor also significantly reduced IL-6 protein and mRNA levels in the CSC and protein levels in the TG. Inhibition of PEA hydrolysis also significantly reduced the percentage of NTG-induced NeuN/Fos-labeled neurons at the CSC level.

Conclusions: The study shows for the first time that the anti-inflammatory activity of endogenous PEA, whose levels are increased through the use of an inhibitor of its catabolism, is associated with the modulation of c-Fos protein at the CSC level in an animal model of migraine.

Altered neurovascular coupling within visual cortex in patients with migraine with aura: a multidelay-3D-pseudocontinous-ASL study

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Background: Converging evidence have identified functional abnormalities of occipital cortex in patients with migraine with aura (MwA). However, several concerns remain about the mechanisms underlying the "tendency" of the visual cortex to allow the beginning of aura phenomenon. Considering that the aura phenomenon triggers are associated with increased global (such as physical activity, stressors and sleep abnormalities) or local (such as bright light visual stimulations) cerebral energy demands, it could be argued that the vascular supply is unable to satisfy the increased energy requirement. Indeed, we aimed to evaluate whether a dysfunctional neurovascular coupling of visual areas could characterize patients with MwA.

Methods: Twenty-three patients with MwA and 25 patients with MwoA, naïve for commonly prescribed preventive migraine medications, were recruited. Finally, twenty subjects with less than a few spontaneous non-throbbing headaches per year were recruited as HC. All patients and HC underwent a 3-Tesla MRI. As CBF and ReHo maps were obtained and registered to the MNI space, 100 bilateral cortical regions were derived on the MNI template using a functional local-global parcellation A quantitative estimation of the neurovascular coupling (NVC) for each subject (and each ASL scan) was obtained by calculating the correlation coefficient between the z-scored ReHo map and the z-scored CBF maps.

Results: We observed a reduced neurovascular coupling in the occipital cortex (ROI 27 and 30) in patients with MwA compared with both patients with MwoA and HC ($p<0.001$). Similarly, no differences were observed in rCBF comparing patients with MwA with patients with MwoA with the exception of significantly increased rCBF of ROI 27 and 30 within the visual network in patients with MwA when compared with patients with MwoA ($p<0.001$) but not healthy controls.

Conclusion: The inadequate neurovascular coupling observed in the visual network of patients with MwA could represent the "missing-link" between the exposure to trigger factors increasing brain energy demand and the development of MwA attacks. We speculate that preventive strategies as antiepileptic drugs exert their antimigraine activity by inhibiting the cortical hyperexcitability probably restoring the trade-off between brain energy demands and rCBF within the visual network.

Treatment with Onabotulinum Toxin Type A restores α dysfunctional connectivity in patients with chronic migraine

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Background: OnabotulinumtoxinA (OBTA, Botox®) is indicated as a prophylaxis treatment of chronic migraine (CM), a disabling neurological condition characterized by a disruption of both peripheral and central nociceptive networks. Several physiological and neuroimaging studies have shown a considerable modulatory action of BTA on central nervous system structures. However, studies in the case of migraine are extremely limited. In this study we aimed to evaluate, by means of high-density EEG (HD-EEG), the longitudinal changes in brain functional connectivity (FC) in adult CM patients treated with OBTA.

Methods: This ongoing prospective cohort study included 10 adult patients diagnosed with CM according to the International Headache Society criteria (IHS ICHD-3, 2018) and initiating OBTA treatment according to clinical practice. Patients underwent clinical scales (Migraine Disability Assessment Scale, MIDAS; Migraine Interictal Burden Scale, MIBS-4; and Headache Impact Test, HIT-6) at enrollment (T0) and at three months (T1) from the start of treatment with OBTA. Resting-state HD-EEG was recorded using a 64-channel system in CM patients at T0 and T1, and in 15 healthy controls (HC). A source reconstruction method was used to identify brain regions activity. Cortical FC in θ, α and β bands was analyzed based on weighted phase-lag index (wPLI). Possible band-specific FC changes between HCs and CM patients at T0 and T1 were assessed using network-based statistics.

Results: Compared to HCs, at T0 CM patients showed hypoconnected network in α band ($t=2.2$ $p=0.03$), mainly involving temporo-parieto-occipital areas. Compared to T0, At T1 CM patients showed higher FC in α frequency band in a similar network ($t=2.4$, $p=0.01$). No functional differences emerged between HCs and CM patients at T1. Finally, compared to T0, at T1 both the number of days with migraine per month ($p<0.01$) and the disability of migraine assessed with MIDAS score ($p=0.03$) and HIT-6 ($p=0.04$) were reduced in CM patients.

Conclusions: This study found that CM patients presented disrupted FC in α band in temporo-parieto-occipital-areas that was restored by OBTA treatment, confirming a considerable central modulatory action of BTA.

Three one-year cycles with CGRP-targeting monoclonal antibodies in patients with chronic migraine: from effectiveness and tolerability assessment to the *floor effect*

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Background: In our Country, monoclonal antibodies targeting CGRP (mAbs) are subsidized for one year with a mandatory interruption period of at least 1 month. Few data are available on their effectiveness during multiple cycles and related suspension periods. We thus assessed mAbs effectiveness and tolerability across 3 consecutive 1-year cycles, namely C1, C2 and C3.

Methods: We started with a baseline cohort of 84 patients with chronic migraine (CM): 72.6% females, 52.2±11.4 years, 90.5% with medication overuse headache. Of them, 25% prematurely stopped the treatment due to lack of efficacy, 14% were lost to follow-up and 6% presented sustained efficacy thus not completing the three mAbs cycles. We analysed the 46 patients who completed the three 1-year cycles (T0 to $T1_{end}$ for C1, S1-$T2_{end}$ for C2, S2-$T3_{end}$ for C3), separated by a suspension period of at least 3 months (S1, S2). Co-primary outcomes were: changes in monthly migraine days (MMDs) during each cycle compared to baseline (namely the 3 months prior to each cycle) and during the related suspensions.

Results: MMDs presented an early reduction that was maintained during each 1-year cycles (C1 T0 22.2±5.1, $T1_{end}$ 6.7±4.1; C2 S1 17.5±5.9, $T2_{end}$ 7.7±4.2; C3 S2 14.0±5.5, $T3_{end}$ 8.0±4.4, factorTIME $p<0.001$, factorGROUP=0.303). Remarkably, at the end of each cycle MMDs reached similar values ($p=1.000$) with nearly half of patients still presenting more than 8 MMDs (C1 57.8%, C2 48.9%, C3 44.4%). During the suspension periods MMDs worsened, but were still lower compared to pre-treatment values (S1 and S2 $p<0.001$, $T1_{end}$ vs T0 $p=0.035$; $T2_{end}$ vs T0 $p<0.001$). No serious adverse events and no discontinuation for adverse events were reported during the whole study period, mild adverse events were reported by 66.7% patients, predominantly constipation, injection site reactions or fatigue.

Conclusion: In our cohort of CM patients, mAbs determined an early and sustained MMDs reduction in each 1-year cycle, with a good tolerability. MMDs comparable values at the end of all cycles suggested a possible *floor effect*, a concept worth of further in-depth analysis. MMDs significantly worsened during suspension periods, still without reaching pretreatment level.

Acute treatments and monoclonal antibodies acting on the CGRP Pathway: a real-world study

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Background: Optimizing acute treatment is essential in the management of migraine. One of the aims of migraine preventive treatments is to improve response to acute migraine treatments. However, this aspect of migraine prevention is poorly studied. The aim of the present study was to assess whether monoclonal antibodies targeting the CGRP pathway (CGRP-MoAbs) can improve response to acute treatments and perceived efficacy of acute treatments.

Methods: Consecutive patients with chronic or episodic migraine from the Headache Centers of Avezzano-L'Aquila and Naples, were included from March 2021 to December 2022. We included and followed up to 6 months patients starting treatment with any CGRP-mAb (erenumab, fremanezumab, or galcanezumab) at the baseline visit. All patients filled out the Migraine Treatment Optimization Questionnaire (MTOQ) – a validated self-administered instrument to assess response to acute treatments – at the start and 6 months after the start of treatment with CGRP-mAbs. Higher MTOQ scores correspond to better acute treatment optimization. During the study period, they completed a headache diary, where they reported the number of migraine days and acute drug intakes.

Results: We included 65 patients (84.7% women; 73.8% with chronic migraine), with a median age of 46 [interquartile range (IQR) 40–55] years. Median mTOQ score increased from 6 (IQR 3-10) at baseline, to 13 (IQR 10-13) after 6 months ($p<0.001$), while median migraine days decreased from 30 (IQR 24-60) at baseline, to 19 (IQR 10-24) after 6 months ($p<0.001$). Median monthly intake of medication doses decreased from 40 (IQR 24-70) at baseline, to 15 (IQR 9.5-30) at 6 months ($p<0.001$). Higher scores on the mTOQ did not correlate with lower use of acute treatments ($p=0.059$, Spearman's correlation).

Conclusion: Our study shows that 6 months of preventive treatment with CGRP-MoAbs led to a significant optimization of acute treatments, paralleled decreased monthly migraine days and acute treatment intake use.

Efficacy, tolerability and safety of monoclonal antibodies blocking calcitonin gene-related peptide or its receptor in drug resistant migraine: long term (>52 weeks) real life data

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Background: Monoclonal antibodies blocking calcitonin gene-related peptide (or its receptor (anti-CGRP (R) mAbs) are the first drugs developed with a selective mechanism of action for migraine, which may offer an advantage in terms of efficacy and tolerability, resulting in greater adherence to treatment. The aim of this real-life observational study was to evaluate the response to anti-CGRP/-R mAb therapy, in a follow-up over 52 weeks, thus evaluating also the persistence of efficacy and tolerability over time.

Methods: We enrolled a sample of patients with high frequency episodic migraine (EM) or chronic migraine (CM), with or without overuse of symptomatic drugs, consecutively admitted to Headache Center of the University of Pisa, from May 2020 to May 2022; they were all eligible for treatment with anti CGRP(R) mAbs according to regulatory authorities. We considered as efficacy end points the reduction in monthly migraine days by 50% (responders) and decrease in the MIDAS questionnaire score, at 3 and 6 months.

Results: 138 patients (22% male and 78% female) aged between 18 and 70 years were enrolled, diagnosed as EM in 27% and CM in 72%; 41% had also symptomatic drugs overuse. All patients were drug resistant, with prior treatment failures >4 (range 4-8). The proportion of responders was 56% at 3 months, 72% at 6 months. A 50% reduction in the MIDAS>o = score was already observed in 132 patients at the third month. 8 patients stopped treatment: 2 of them due to an adverse event (allergic reaction and constipation) and 6 due to lack of efficacy. The remaining 130 patients continued the treatment with a protracted follow-up between 12 and 30 months, maintaining a good response and absence of adverse events.

Conclusion: The increasing proportion of responder patients between 3 and 6 months, in association with high tolerability, suggests that we can observe a late response and we can make an estimate of efficacy only after a few months.
Even in a real-life context, anti-CGRP (R) mAb represent a therapeutic strategy with an excellent efficacy, tolerability and safety profile, even in multi drug resistant patients, up to 30 months of treatment.

Rimegepant for acute treatment of migraine in triptan-ineligibile or resistant patients. A real-life experience

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Background: Since April 2022, the European Commission has granted marketing authorization for rimegepant in the acute treatment and prophylaxis of episodic migraine without and with aura. Rimegepant has an antagonistic action for calcitonin gene-related peptide (CGRP) receptor without vasoconstrictive properties and with a safety profile in the over 65-age population. This first gepant molecule allows the treatment of subjects for whom triptans are contraindicated for age and/or vascular comorbidity.

Methods: All records of patients with migraine without and with aura visited in the headache clinic from January 2020 to 30 June 2023 were evaluated to identify subjects with contraindications to the use of triptans: age over 65 years, cerebro-cardio-vascular events, mild/moderate uncontrolled or severe hypertension, stenotic arterial disease.
Starting in February 2023, we proposed treatment with rimegepant (for at least two consecutive migraine attacks) to the triptan-ineligible patients who came to the clinic. Among the remaining visited migraineurs, eligible and already treated with triptans, those with resistance (defined as ineffectiveness to at least two triptans administered orally) were selected too.

Results: Migraine patients with contraindications to triptans were found to be 75 (9% of all investigated records). 80% by age over 65 years, and the remaining 30% have in descending order: TIA/stroke, arterial stenosis/dissection, moderate/severe or uncontrolled arterial hypertension, and ischemic heart disease. No severe hepatic impairment was found.
From February to June 2023, the patients treated with rimegepant were 16 divided as follows: migraine without aura (12), migraine with typical aura (2), with brainstem aura (2). The triptan-resistant were 4 (25%). The triptan-ineligibile were 12 (75%); of these 7 were over-65; the remaining 5, aged 46-60, had the following medical histories: TIA, PFO, supra-aortic trunk dissection, CADASIL, carotid stent, thrombocythemia. No pharmacological interactions were registered. Side effects of rimegepant were mild. Efficacy values were dispersed.

Conclusion: In a selected small group of migraine patients with contraindications to the use of triptans, rimegepant is well tolerated. Effectiveness is too variable from patient to patient to define a trend in such a small sample. In the few patients with resistance to triptans, rimegepant does not seem to be an alternative.

Instrumental assessment of physiotherapy and Onabolulinumtoxin-A on pressure pain threshold, cervical and headache parameters in chronic migraine

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Background: The present study is based on a considerable amount of literature that highlights the key aspect of musculoskeletal dysfunctions in the trigeminal sensitization and, consequently, in the increase of frequency and intensity of migraine. The purpose of the present study was to compare the effect of the physiotherapy to Onabolulinumtoxin-A, and their combination, in relation to pressure pain threshold (PPT), cervical and headache parameters in patients with chronic migraine.

Methods: Two observational studies were conducted in patients with chronic migraine. Each study involved 30 chronic migraine participants, and in each study the participants were distributed into three groups of treatments for three months: Onabolulinumtoxin-A only (BoNT-A), physiotherapy only (PT), and onabolulinumtoxin-A plus physiotherapy (BoNT-A+PT). The first study investigated the following outcomes: the postural assessment software SAPO for the forward head posture and the CROM goniometer for the cervical range of motion. While, the second study assessed the PPT on five muscles in the trigeminocervical area (namely, trapezius, levator scapulae, temporalis, sub-occipitalis, and scalenus medius) and one muscle outside of the area, (i.e., tensor fasciae latae). Each study also evaluated the headache parameters, i.e., frequency of migraine, duration of attack and pain intensity.

Results: The first study reported a statistically significant change in all parameters taken into consideration after the combined treatment BoNT-A+PT. BoNT-A alone seems to be more useful than PT alone in the reduction of pain intensity ($p = 0.01$), while PT alone seems to be more useful than BoNT-A alone in the improvement of cervical parameters ($p=0.002$). In the second study the combined treatment BoNT-A+PT was more useful than the two monotherapies in the improvement of PPT and pain intensity improved only after BoNT-A+PT ($p=0.007$) and after BoNT-A alone ($p=0.01$).

Conclusion: The results of these two studies suggest that the combination of pharmacological and non-pharmacological treatment was more useful than a mono-therapy alone for the improvement of PPT, cervical and headache parameters.

Disability, burden, and symptoms related to sensitization in migraine patients are associated with headache frequency

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Background: This observational study assessed the difference in disability, quality of life, psychological burden, and sensitization between migraine patients with low-frequency headache (LFEM, 1-8 headache days/month), high-frequency headache (HFEM, 9-14 headache days/months), and patients with chronic migraine CM (> 14 headache days/months).

Methods: Migraine patients were divided into three groups according to headache frequency (LFEM, HFEM, CM). Headache-related disability was assessed with the Headache Disability Index questionnaire; neck-related disability was assessed with Neck Disability Index; physical and mental dimensions of quality of life were assessed with Medical Outcomes Study Short Form-36 Physical and Mental; anxiety and depression were assessed with Hospital Anxiety and Depression Scale Anxiety and Depression; symptoms related to sensitization were assessed with Central Sensitization Inventory. Differences among migraine groups were assessed using the Chi-Quadro test, ANOVA, or Kruskal Wallis as appropriate.

Results: 197 patients were included (97 LFEM, 68 HFEM, 32 CM). Patients with HFEM and CM differed from patients with LFEM showing a worse headache-related (HFEM, $p=0.001$; CM, $p<0.001$) and neck-related disability (HFEM, $p=0.009$; CM, $p=0.003$), worse level of physical (HFEM, $p=0.001$; CM, $p=0.001$) and mental (HFEM, $p=0.001$; CM, $p<0.001$) quality of life, higher level of depression (HFEM, $p=0.024$; CM, $p=0.009$), and increase presence of symptoms related to sensitization (HFEM, $p=0.003$; CM, $p<0.001$). No differences were found in any variables between patients with HFEM and patients with CM ($p> 0.05$).

Conclusion: Patients with high-frequency episodic migraine and chronic migraine could be considered in the same segment of the migraine population, with similar degrees of disability, psychological burden, and sensitization-related symptoms.

Efficacy of Mindfulness added to treatment as usual in patients with Chronic Migraine and Medication Overuse Headache: a randomized clinical trial, early results

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Background: To assess the efficacy of a six-session mindfulness-based treatment added to treatment as usual (TaU) on headache frequency reduction and medication intake.

Methods: This is a phase-III single blind RCT single-center study, carried out at the third-level Italian headache center IRCCS "C. Besta". Patients were enrolled between November 2018 and December 2021, and followed-up for 12 months. 177 patients with Chronic Migraine and Medication Overuse Headache (CM and MOH) were randomized 1:1 to either TaU or mindfulness added to TaU (TaU+MIND). Exclusion criteria were: psychiatric comorbidities; pregnancy; secondary headaches; withdrawal from MOH at least twice in the previous two years; previous experience with mindfulness. TaU consisted of withdrawal from overused drugs, patients' education, and prescription of prophylaxis. Patients attending mindfulness sessions were taught to focus their attention on the present and enhance awareness of body sensations, which enabled tackling the pain-pill automatism, and were encouraged to engage in a 7-10 minute/day self-practice. The primary endpoint was the achievement, at 12 months of ≥50% headache frequency reduction compared to baseline. Secondary endpoints included medication intake.

Results: Out of the 177 participants (median age 47.9 years [Q1-Q3: 40.1-54.2]; 19 [11.3%] males; median CM duration 14.6 years [Q1-Q3: 4.9-22.2]) 89 were randomized to TaU and 88 to TaU+MIND. Patients in the TaU+MIND group outperformed those in TaU for the primary endpoint, achievement of ≥50% headache frequency reduction (78.4% vs 48.3%; $p<0.0001$). They also showed superiority in some secondary endpoints, namely headache frequency and medication intake.

Psychological profiles and clinical characteristics of migraine patients with early life traumas

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Background: Early traumatic experiences and current stressful events seem to be associated to the development and perpetuation of chronic pain syndromes and to dependence-related behaviors. The present study was aimed to evaluate the impact of childhood traumas in a large sample of subjects with migraine in terms of psychological profiles and clinical characteristics.

Methods: A sample of patients with chronic migraine with medication overuse (CM+MO) (n = 200; age: 47.6±10.9) or episodic migraine (EM) (n = 198; age: 39.1±11.1) was enrolled and evaluated for migraine characteristics. Patients received a psychological assessment including self-report questionnaires and, for a subgroup, a clinical interview based on DSM-V criteria for psychopathology and personality disorders.

Results: Thirty-five percent (n=135) of participants reported childhood traumas (CT group), with a higher prevalence in the CM+MO (41%) than in the EM (28%) group (p=0.006). CT individuals had significantly more days of migraine attacks per month (17.8±11.3 vs 14.1±10.7, p = 0.002), more days with medication intake (16.7±12.4 vs 13.5±10.1, p = 0.007) and more doses per month (26.5±26.2 vs 20.4±29.0, p = 0.04) when compared with patients without CT (wCT group). The CT group was also characterized by a significantly higher anxious (8.0±4.0 vs 5.9±3.8, p = 0.001) and depressive (7.4±4.8 vs 5.2±4.0, p = 0.001) symptomatology, alexithymic levels (47.3±12.7 vs 44.0±12.9, p = 0.04), and a higher prevalence of severe (66% vs 34%, p = 0.001) and very severe (66% vs 34%, p = 0.001) current stressful life-events than the wCT group. Moreover, the CT group had a higher prevalence of patients with personality disorders (62% vs 40%, p = 0.001), specifically belonging to Cluster C (60% vs 34%, p = 0.001), as well as Axis I psychopathologies (94% vs 75%, p = 0.001) than the wCT group.

Conclusion: Childhood trauma can have a critical impact on the clinical and psychological characteristics of migraineurs. Patients with childhood trauma are characterized by a more complicated form of migraine associated with psychopathology and personality disorders. These findings have important practical implications and suggest that clinicians should treat patients who have experienced childhood trauma also from a psychological perspective because of the high risk of poor prognosis.

Headache Center and Territorial Pharmacy: a new alliance to reduce the costs of migraine chronicity

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Background: In the era of monoclonal antibodies for the treatment of chronic and high-frequency migraines, and their impressive results on disability, the search for unrecognized patients always plays a most important role. For this reason, we started a collaboration between our Headache Center and the Territorial Pharmacy. First of all, we decided to monitor the trend of the use of monoclonal antibodies and subsequently to identify the abusers of triptans via registry of ATC codes. Moreover, in order to confirm the positive real-life data of monoclonal antibodies and their persistence, we decided to verify the reduction in the use of triptans, and therefore the direct pharmacological costs in the population receiving these drugs.

Methods: Starting from the AREAS software, an E-Health Integrated Platform that supports the Hospital and Territorial Pharmacy, we extracted data regarding the population that uses monoclonal antibodies within our ASL. Furthermore, taking advantage of the Big Data from Cineca, patients with a consumption of more than 15 triptans/month were selected within a population of 630,000 inhabitants of the ASL Roma 3. Subsequently, an email was sent to the General Practitioner about his/her patient with overuse of triptans, with indications for a priority access to the local Headache Center.

Results: Preliminary data showed that only a very small number of the potential population who could benefit from monoclonal antibodies actually use them. In the territory of more than 630,000 inhabitants (ASL Roma 3), chronic migraineurs were approximately 12,500 (2% of the whole), of these only 345 subjects (2.5%) were taking treatment with monoclonal antibodies with a ratio M/F 1/5. Of all patients, 30% were with Erenumab, 31% with Fremanezumab, 38% with Galcanezumab. Efficacy of therapy has been shown by the very low incidence of shift between therapies only 5% predominantly between Erenumab versus the others. This poor penetration of monoclonal antibodies in the population, leads to the persistence of disability and high direct and indirect costs among chronic migraine sufferers, despite the presence of highly effective treatments.

Conclusion: Awareness campaigns and the research of patients in the population, carried out with the collaboration of the Territorial Pharmacy, can help to identify the submerged migraine population not otherwise identifiable.

Italian version of the Headache Disability Inventory: cross-cultural adaptation, validity, and reliability

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Background: To translate and cross-cultural adapt the Headache Disability Inventory (HDI) into Italian and study its reliability and validity.

Methods: 123 subjects with primary and secondary headaches were included. Translation was performed following international guidelines. Structural validity (Confirmatory Factor Analysis [CFA]), internal consistency (Cronbach's alpha), test retest reliability (Intraclass Correlation Coefficient [ICC]), measurement error (Standard Error of the Measurement [SEM], Minimal Detectable Change [MDC]) and construct validity (Hypothesis Testing) were studied.

Results: The translation into Italian was performed without issue. CFA supported the structural validity, confirming a two-factor structure (i.e., emotional and functional). Each subscale presented high internal consistency (alpha=0.872 and 0.866 for emotional and functional subscale, respectively), excellent and good test retest reliability (ICC=0.929 and 0.884 for emotional and functional subscale, respectively), and low measurement error (SEM=3.6 points, MDC=10.0 points for emotional subscale; SEM=3.8 points, MDC=10.7 points for emotional subscale). Construct validity was satisfactory for the emotional subscale and moderate for the functional subscale as 85.7% and 57.1% of *a-priori* hypotheses was met, respectively.

Conclusion: The HDI was successfully translated into Italian with good psychometric properties. HDI can be used in daily clinical practice and research to assess the functional and emotional impact of primary and secondary headaches.

Gender-related stress factors and emotional perception in migraine: a structured online interview in migraine patients vs controls

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Background: Personalized medicine attempts to foresee the outcome of migraine based on specific risk factors. Migraine is markedly prevalent in women (Al-Hassany et al., 2020). Gender related differences in migraine phenotype have been rarely assessed, due to the low number of males generally included in the study groups (Mestres et al., 2022). This was a multi-center observational cross-sectional study aimed: 1. To establish gender related differences in work status, relationships, violence history, perceived stress and emotional regulation, in migraine patients (MG) vs controls (CG); 2. To understand the role of stress/emotional factors in determining sex-related differences in migraine features; 3. To identify variables characterizing genders within the MG.

Methods: The study was designed as an online interview, sent by e@mail to 500 consecutive patients (age 18-75, education ≥13 y) at the time of the first visit to 5 Tertiary Headache Centers (adhering to the Italian Headache Society - SISC). Criteria for inclusion in the study was a diagnosis for migraine without aura and/or with aura or and chronic migraine, according to IHS criteria (2018). The same interview was sent to a similar number of healthy subjects. The survey was divided into 3 *sections*: *Sec. A:* personal/social/work information; Sec. *B*: Perceived Stress Scale (PSS) (Cohen et al., 1993), Romance Quality Scale (RQS) (Ponti et al., 2010), Emotion Regulation Questionnaire (ERS) (Gross et al., 2003), Beck Anxiety Inventory (BAI) (Beck et al. 1988), Body Perception Questionnaire (BPQ) (Porges et al., 2018); *Sec C:* exclusive for MG: scores of migraine severity/last 3 months.

Results: Overall, 202 MG and 202 CG filled the entire protocol, gender and age were equally distributed between groups. *Sec A*: the prevalence of fulltime stable work activity was higher in MG, more prevalent in men even compared to the whole group. *Violence* scores were equally distributed among groups, more prominent in women in the MG group and overall but not in the CG group.

Sec B: BPQ score was lower in MG and in men, independent of diagnosis. PSS score was similar between groups but higher in women, independent of diagnosis. BAI score was similar between groups, significantly increased in women, independent of diagnosis. ERS was similar between MG and CG, predominantly in men; males with migraine had lower ERS scores, with a significant interaction regarding diagnosis and gender. RQS scores showed that perception of conflict within the relationship was higher in MG, interaction between gender and diagnosis was not significant; the perception of emotional support within the couple was reduced in MG and in women. Other RSQ scores were similar between genders, diagnosis and groups. Pain sensitivity scores were higher in MG and slightly in women, not significant.
Sec C: Migraine features (Vas/3 months/related disability) and frequency of attacks did not show significant difference between genders, except for the subjective impression of headache intensity (average/last 6 months), significantly different between genders, higher in women. The history of violence determined more severe features of migraine, independent of gender. The subjective perception of migraine does not correlate with any behavioral scores in both genders. Discriminant factors for gender in MG was reduced body perception and increased emotional suppression.

Conclusion: The present study failed to identify specific emotional and stress factors, attributable to distinct gender-related migraine profiles. The many aspects differentiating 2 genders, as perceived stress, emotional suppression, body awareness, history of violence and romantic conflicts, did not imply different clinical profiles between women and men with migraine. Some critical aspects emerged from these data, such as history of violence and problematic romantic relationships were prevalent in migraine, independent of gender.

Perceived ease-of-usability and local tolerability using CGRP monoclonal antibodies autoinjectors versus syringes: an online questionnaire-based study in migraine patients

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Background: Monoclonal antibodies acting on the CGRP pathway (CGRP-mAbs) are characterized by subcutaneous administration via autoinjector pens or prefilled syringes. Unfortunately, significant local tolerability concerns about injection site pain may degrade patient comfort, increase the fear and stress of dose administration and negatively impact patient adherence. The aim of the present cross-sectional study was to assess the experience of patients with migraine using either CGRP-mAbs prefilled syringes or autoinjector pens, regarding local tolerability and ease of usability.

Methods: An electronic questionnaire was created using "Google questionnaires" and sent to all patients treated with CGRP-mAbs referring to the Headache Centre of the University of Campania "Luigi Vanvitelli" to collect: i) demographic and clinical parameters such as age, headache duration, frequency of attacks, ongoing preventive CGRP-mAbs treatment and interictal cutaneous allodynia; ii) data related to CGRP-mAbs administration as ISP (Injection Site Pain), site of injection, local reactions at administration site, simplicity of administration and administration modality; iii) data related to putative previous onabotulinumtoxin-A administration as ISP.

Results: No significant differences were found among groups in data related to ease-of-usability and local tolerability of CGRP-mAbs regarding simplicity and modality of administration, ISP and other reactions at the sites of administration. Nevertheless, we identified young women with chronic migraine as the phenotype more prone to experience ISP during the CGRP-mAbs treatment. Among 96 patients who previously received at least 3 OnabotulinumtoxinA administrations, injections site pain was significantly higher with Onabotulinumtoxin-A compared to CGRP-mAbs.

Conclusion: Devices used for CGRP-mAbs administration are each characterized by several strengths and downsides, balancing each other so that no differences in easy-of-usability and local tolerability can be observed. The cranial localization of the administration as well as the higher number of injections could explain the difference in terms of ISP with Onabotulinumtoxin-A. These findings may also arise economic and ecological implications, considering the lower impact on costs and environmental pollution of prefilled syringes compared to more expensive and polluting plastic autoinjector pens. Furthermore, since ISP represents a reason for discontinuation of Onabotulinumtoxin-A therapy, this data should be considered by the authorities regulating the modalities of access to therapy with CGRP-mAbs.

Non responders to anti-CGRP/R monoclonal antibodies: unmet needs and challenges in the management of drug-resistant migraine

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Background: To describe the outcome of patients who withdraw anti-calcitonin gene-related peptide monoclonal antibodies (CGRP/R mAb) and the related causes, evaluate the effectiveness during treatment, and characterize patients who do not respond to anti-CGRP/R.

Methods: We conducted a prospective analysis on all consecutive outpatients who started erenumab, galcanezumab, or fremanezumab. In February 2023, we assessed the follow-up of patients that withdrawn the first anti-CGRP/R mAb. We documented whether they had subsequent follow-up after the last mAb administration and if they initiated a new treatment. The primary outcomes were to describe the reasons for anti-CGRP mAbs withdraw and the follow up thereafter. The secondary outcomes were to evaluate the multi-assessed response to mAbs during treatment. The patients were divided in the overall population (*i.e.,* withdrawn for any reason) and then a subgroup that discontinued solely due to ineffectiveness.

Results: A total of 472 patients were treated with at least one dose of anti-CGRP/R mAbs, and 136 (28.8%) discontinued treatment for various reasons. Among them, 46.3% received erenumab, 14.7% received fremanezumab, and 39% received galcanezumab. Almost all patients have chronic migraine (91.9%) and 81.6% medication overuse. The majority of patients withdrawn treatment due to ineffectiveness (n=96, 70.6%), followed by lost to follow-up during therapy (18, 13.1%) and adverse events (13, 9.6%). Three patient each (3, 2.2%) withdrawal treatment for personal choice or for pregnancy. One patient discontinued for no compliance to treatment (0.7%), and 3 (2.2%) for physician decision (not better accountable in other categories).
Overall, 106 (77.9%) patients discontinued treatment during the first 12-month follow-up. At the first follow-up after anti-CGRP/R withdrawn, 66 (48.5%) patients started a new pharmacological treatment (i.e., switching anti-CGRP mAbs, OnabotulinumtoxinA, anticonvulsants, others), 54 (39.7%) patients were lost to follow-up and 16 (11.8%) decided to not start other treatments.

Conclusion: Managing patients who do not respond to anti-CGRP treatment remains a challenge, necessitating tailored management strategies to optimize response or timely identification of non-responders to provide appropriate treatments.

How PCS score can influence clinical response to monoclonal antibodies against CGRP: a single center three years real-life experience

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Background: Catastrophic thought, defined as "an exaggerated negative mental set brought to bear during actual or anticipated painful experience", plays a crucial role in pain chronification, especially in migraine patients. We aimed to evaluate how pain catastrophizing, measured using the Italian version of the "Pain Catastrophizing Scale (PCS)", could influence clinical response to anti-CGRP monoclonal antibodies (Erenumab, Galcanezumab, and Fremanezumab) in patients with chronic migraine with or without abuse. We are furthermore interested in evaluating a possible relationship between tendency to ruminate (measured by Rumination subscale) and response to therapy.

Methods: We collected sociodemographic and clinical data from 20 consecutive patients attending our headache clinic from July 2021 since now. Patients were diagnosed as chronic migraine with or without MOH, according to ICDH-III criteria. All patients in the court were randomly assigned between Galcanezumab (120 mg), Erenumab (140 mg) and Fremanezumab (125 mg), respecting AIFA and EAN guidelines. PCS was measured at the beginning of therapy (T0) and repeated at three (T1) and six months (T2). Clinical response was measured as both as a >50% attacks reduction per month as by reduction in the HIT-6 "Headache Impact Test-6" scale and the MIDAS "Migraine Disability Assessment Test" scoring. Comorbid depression was assessed by BDI II "Back InventoryII" scale. All patients were treated by a psychologist. We utilized the Spearman's and Pearson's tests to analyze PCS and Rumination correlation with the other variables included. Here are reported T0 data.

Results: The study included 20 patients (3 men and 17 women) with or without medication overuse. Migraine impact was moderate (HIT-6≥56) except for three cases. Disability is severe in the whole sample except for one patient (MIDAS 12). We also observe mild to severe depression (BI II ≥ 10). PCS and rumination are mildly correlated with HIT6 (0.65 and 0.58, respectively) but lowly with BDI II (0.49 and 0.39, respectively). While for the leftover variables (i.e., Sex, Age) no correlation was found.

Conclusion: In our court, composed by patients with chronic migraine, PCS and in particular Rumination subscale seems not to be correlated to depression, measured by BDI II scale but show a mild correlation with HIT6 score. In this real-life setting, rumination can predict clinical response to monoclonal anti-CGRP Ab, regardless of depression burden.

Teleconsultation in Headache Centre can reduce emergency department and in-hospital admissions

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Background: Headaches are one of the main causes of admission to the emergency room, requiring neurological consultation in most cases. Patients who come to the emergency department for headache at hospitals, whether or not they have a neurological specialist, are also often subjected to instrumental examinations, with an increase in length of stay and healthcare costs, especially in cases of primary headache that could be managed on an outpatient basis. This is why the presence of territory headache centres is increasingly necessary, in order to guarantee an optimal diagnostic and therapeutic pathway for this type of patient. Since remote assistance has become commonplace in outpatient medical practice, due to the needs arising from the SARS-CoV-2 pandemic, headache centres can also make use of remote consultation in order to respond more quickly to the needs of the patients being followed.

Methods: We evaluated the role of teleconsultation in the headache centre by comparing emergency room admissions, hospitalisations and brain CT scans for headache in the last year, compared to the average of the three years before the pandemic.

Results: In the last year (March 2022-February 2023) there were 550 admissions to the ED compared to an average of 713 (-23%) admissions over the same period in the years 2017-2019; admissions were 58 vs 99 (-41%), while brain CT scans performed were 306 vs 321 (-5%).

Conclusion: The adoption of teleconsultation at the Headache Centre can be a useful means of responding earlier and more precisely to the needs of headache patients, reducing the number of accesses to emergency rooms, hospital admissions and avoidable instrumental examinations, with an improvement in care in clinical and economic terms.

Workplace disability improves with anti-CGRP monoclonal antibody therapies

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Background: High-frequency episodic migraine and chronic migraine carry an important disability burden with a significant influence on working life related to absenteeism and presenteeism in the workplace.
Anti-GCRP monoclonal antibodies emerged with an impressive improvement on the frequency and the disability of migraine. Aim of the study was to evaluate workplace disability before and after anti-CGRP monoclonal therapy.

Methods: Patients with a diagnosis of high-frequency episodic migraine or chronic migraine in accordance to ICHD-3 criteria were enrolled and they were treated with anti-GCRP monoclonal antibodies for one year according to AIFA criteria. We used MIDAS to calculate the disability burden and the days of workplace absenteeism and presenteeism before (t0) and after 12 months anti-CGRP monoclonal therapy (t1).

Results: We enrolled 62 patients (61.3% chronic migraine and 38.7% high-frequency episodic migraine; 74.2% F and 25.8% M; mean age 46±10 y.o.), and we treated them with erenumab (36.5%), fremanezumab (47.6%) or galcanezumab (15.9%). There was a significant reduction of MIDAS at t1 (20±28) vs t0 (95±39). Absenteeism and presenteeism reduced significantly from t0 to t1 (absenteeism: 7 [1-19] days at t0 vs 1 [0-3] days at t1 [p=0.002]; presenteeism: 32 [19-47] days at t0 vs 8 [0-21] days at t1 of presenteeism [p0<0.001]).

Conclusion: Anti-CGRP monoclonal antibodies improve workplace absenteeism and presenteeism.

Neuropsychological effects in migraine patients treated with Erenumab

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Background: Migraine is one of the most disabling disorders in the world, associated with poor quality of life. Migraine prevention strategies have increasingly evolved since monoclonal antibodies against calcitonin gene-related peptide (CGRP), or its receptor, were identified. CGRP is the ideal target of monoclonal antibodies (mAbs). In particular, erenumab is the mAb that has demonstrated good therapeutic efficacy in reducing pain intensity and high tolerability.

Methods: In this study, we aimed to investigate the efficacy of erenumab on both cognitive performance and psychological well-being. This was a pilot study with a retrospective design that included 14 subjects (2 males and 12 females), with a mean age of 52.29 ± 9.62 years, who attended the Headache and Migraine Outpatient Clinic of the IRCCS Bonino-Pulejo Neurolesi in Messina. The assessment consisted of measuring cognitive and psychological functioning.

Results: Comparing clinical and psychometric test scores between baseline and follow-up, we found a significant improvement in both cognitive performance and quality of life. We also observed a decrease in migraine disability.

Conclusion: This pilot study describes the effect of erenumab on cognitive functioning and psychological well-being in a sample of migraine patients. These aspects have been poorly addressed in previous studies on therapy by CGRP, which have generally focused on the efficacy of physical symptoms. Literature data reported discordant results about the migraine effect on cognitive functioning. Many migraineurs often complain of intellectual impairment, particularly deficits in attention and memory, but also confusion during sudden stabbing migraine probably attributable to physical symptoms, such as pain, nausea and photophobia, that decreases cognitive efficiency.
Our results demonstrated an improvement in overall cognitive performance and quality of life in migraine patients taking erenumab.

Elements for an efficient and effective organization: onabotulinumtoxinA (OnabotA) outpatient

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Background: Migraine is a common and incapacitating neurological condition that can progress from an episodic to a chronic form. The management of chronic migraine (CM) by health professionals can be challenging [1].
For more than 10 years now onabotulinumtoxinA (OnabotA) has been licensed in Italy for preventive treatment of CM [2], but, despite the long approval, many Headache Centers still today find both organizational and practical difficulties in the application of this effective and safe therapy. We have deepened, through an initial test, the possible organizational and managerial issues of different Headache Centers/headache outpatients that can be found in the administration of OnabotA.

Methods: A group of 28 Italian neurologists, with a special interest in migraine, was invited to give answers to 9 questions regarding the organizational issues of using OnabotA for the treatment of CM in their hospitals (Time 0, T0). After T0, specialists did an active workshop to analize the different issues regarding the organization of an efficient and effective OnabotA outpatient in order to find useful solutions.
The same questions will be administered after three months (Time 1, T1) to assess the efficacy of the workshop.

Results: The 17.9% of respondents said they did not have OnabotA in their hospital for migraine. Although 82% responded that they had OnabotA available, almost 40% of them responded that they do not administer the toxin autonomously. The main reason for not administering the toxin independently was the lack of experience. Moreover, in 50% of cases it was found that the OnabotA outpatient did not have any dedicated hours and days and in most cases (60%) there was no nursing staff support.

Conclusion: Even today, more than 10 years after PREEMPT studies and the placing on the market of OnabotA for CM, much remains to be done to optimize its use in different hospitals ant headache outpatients in Italy.

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Real-world effectiveness of Anti-CGRP Monoclonal antibodies compared to OnabotulinumtoxinA. The RAMO study: early results

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Background: Chronic migraine (CM) is a disabling condition with huge impact on the quality of life. OnabotulinumtoxinA (BoNT-A) is an effective treatment for CM. Recently, monoclonal antibodies (mAbs) against calcitonin gene-related peptide (anti-CGRP) pathways have also been approved. Aim of this study is to compare the effectiveness and safety of anti-CGRP mAbs and BoNT-A after 6 and 12 months of treatment.

Methods: We enrolled patients from the IRCCS Neurologic Institute C. Besta and Bio-Medic Campus University. Inclusion criteria: diagnosis of CM, received anti-CGRP mAbs or BoNT-A, with at least 6 months follow-up, age 18-65y, ≥2 preventive treatment failures, starting MIDAS ≥11. Exclusion criteria: serious psychiatric diseases, received BoNT-A before anti-CGRP mAbs treatment (for mAbs arm). Study outcomes: difference from baseline in monthly migraine days (MHD), number of monthly acute medications (MAM) and MIDAS. Safety assessment: report of serious adverse events (SAE), treatment discontinuation. Wilcoxon rank-sum and Fisher's exact tests were used for the analyses ($p<0.05$).

Results: At the time of this interim analysis, we screened 122 patients: 92 included, 25 mAbs arm, 67 BoNT-A arm. Population: mean age 51.1 (8.6) y, 80 female, 90 medication overuse (non-significant differences between groups). At baseline the BoNT-A group presented significantly higher mean MHD (23.0[6.3] vs 17.4[32.2]), MAM (24.1[13.7] vs 16.5 [2.8]), and MIDAS (93.0[66.8] vs 55.6[36.8]) compared to the mAbs group. MHD reduction was significantly greater in the mAbs group (-12.4[4.8] vs -9.0[8.8]) at 6 months compared to BoNT-A. Adverse events (AE) discontinuation: 1 (4.8%) patient mAbs arm, 3 (4.5%) patients BoNT-A arm.

Conclusion: Our preliminary results show a comparable effectiveness between mAbs and BoNT-A at 12-month follow-up, with significantly higher efficacy for mAbs at 6 months. Discontinuation due to AE were similar. From these preliminary data the effectiveness and sustainability of the two treatments appear to be overlapping.

Perineural Greater Occipital Nerve block effect in a difficult-to-treat migraine population: a *real-life* study

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Background: Despite the development of new antimigraine drugs, prophylactic therapy may have suboptimal results especially in chronic patients with analgesics overuse. Greater occipital nerve block (GON-B) is commonly used in migraine prophylaxis although the lack of a standardized method and efficacy data. In this light, we investigated the effect of GON-B in a migraine population, mainly composed by difficult-to-treat patients.

Methods: In this *real-life* retrospective study, we enrolled 73 migraine patients presenting to our tertiary Headache Centre. Bilateral GON-B was performed injecting a solution of betamethasone and lidocaine in the perineural GON space. Patients were clinically evaluated at baseline (t-0) and three months later (t-3): during the period following injection, they had to fill in a 30-day headache diary recording number and duration of attacks, headache intensity, associated symptoms and the number of acute medication intake.

Results: We recruited 65 women and 8 men; the median age was 55 years. The years lived with disability was 31.3±15.7. At t-0, 50 patients were affected by chronic migraine while 38 presented a medication overuse headache (MOH). The mean number of monthly headache days (MHDs) was 18.6±8.1, the mean number of monthly acute medications (MAMs) was 19.3±18.1. GON-B effect was evident since the first days after injection: during the first month (t-1), the MHDs were 11.3 ($p<0.001$), and the MAMs were 11.1 ($p<0.001$). Similar results were observed in MOH patients. At t-2 and t-3 follow-up, there was a slightly lower but still significant benefit for both MHDs and MAMs ($p<0.001$). Three patients reported minor adverse events (pain and redness at the injection site).

Conclusion: Perineural GON-B was found to be effective in our *real-life* study as a rapid, inexpensive, and safe prophylactic treatment in very difficult-to-treat migraine patients. This observational study represents a stimulus for future randomized studies to confirm its efficacy. Furthermore, based on its rapid effect, it could be interesting to evaluate GON-B use in association with other slower acting prophylactic therapies.

Psychological profiles of super responders and non-responders to CGRP-monoclonal antibodies: data from a 6-month follow-up

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Background: Migraine preventive therapy targeting the calcitonin gene-related peptide (CGRP) pathway has been shown to be effective in treating difficult-to-treat patients, such as those who have previously failed multiple preventive treatments. Interestingly, these "difficult-to-treat" patients are usually understood to be particularly challenging, characterized by the presence of a high number of psychiatric comorbidities and personality. The aim of this study was to evaluate the psychological predictors of a super response to anti-CGRP monoclonal antibodies (mAbs) in a 6-month follow-up in chronic migraine (CM) or episodic migraine (EM).

Methods: One hundred and sixteen patients (age: 48.2±10.5, F: 77%) with CM or EM who had already failed at least three preventive therapies underwent treatment with CGRP-targeting mAbs. At baseline (T0), patients received a full psychological evaluation comprising mood, anxiety, and personality disorders as well as childhood traumas, current stressors and alexithymia. Patients were then followed up at 6 months for their clinical condition.

Results: At the 6-month follow-up, 41% of patients (age: 49.7±8.8, F: 81%) reported a reduction of at least 75% in monthly migraine days (MMD) (Super Responder, SR); whereas 16% (age: 49.6±11.9, F: 74%) a ≤25% MMD reduction with respect to T0 (Non Responders, NR). When compared to SR, NR patients were characterized by a higher prevalence of anxiety (90% vs 57%, p=.012) and personality disorders (94% vs 34%, p=.003), in particular those belonging to Cluster C (avoidant, dependent, and obsessive-compulsive) (74% vs 30%, p=.001). They also showed a higher number of very serious current stressors (2.0±3.1 vs 0.2±0.7, p<.001) as well as more alexithymic traits (53.6±13.4 vs 43.5±12.9, p=.005). The SR and NR groups were instead similar as regards to mood disorders and childhood traumas.

Conclusions: We confirm the marked effectiveness of CGRP-targeting mAbs also in patients with difficult-to-treat forms of migraine and a high burden of psychological comorbidities. Our results, although preliminary, show that patients who achieve two extreme responses (super response vs. absolute nonresponse) to mAbs also significantly differ in their psychological profiles. In particular, our data highlight the impact of an "anxious-fearful" personality, anxiety, current stressors and alexithymic traits in those particularly refractory to many preventive treatments, including mAbs.

Reduction of caregiver stress burden after 12 months of galcanezumab therapy

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Background: Migraine is a chronic disease that can be very disabling and affect patients and their loved ones. Monoclonal antibodies targeting the CGRP pathway have been shown to reduce the frequency and severity of migraines in just a few weeks of treatment. In a previous study, we found that treating patients with galcanezumab for 6 months not only improved migraine but also reduced the distress of their caregivers and improved their reciprocity.

Methods: We evaluated patient-caregiver pairs at our headache center before and after 6 and 12 months of galcanezumab treatment. Patients kept detailed records of their monthly migraine days, medication use, and pain intensity in a headache diary and quarterly completed Headache Impact Test (HIT-6), and Migraine Disability Assessment Scale (MIDAS). Both patients and caregivers completed the Mutuality Scale to assess their relationship, and caregivers also completed the Relatives' Stress Scale.

Results: 10 dyads were evaluated. Caregivers were mainly males (9 M, 1 F), mean age 55.7 +15.21 yrs old, half of them had a full-time job and spent a mean of 7.6 +4.33 hours/day with their partner. Only 1 caregiver suffered from ischemic cardiopathy. In parallel to the patient's clinical improvement, the caregiver burden reduced. RSS significantly improved at both T6 and T12 compared to baseline, respectively T0 21.06 + 8.05, T6 13 + 8.9, T12 12.7+ 7.78 (p= 0.030). The MS of the dyads did not significantly change.

Conclusion: This preliminary study evidenced that also at 12 months, galcanezumab could significantly improve not only the patient's migraine but also the caregiver's burden, confirming our previous findings after 6 months of follow-up. The significant increase of the MS in caregivers at T6 observed in our previous work was not confirmed in this study, probably due to the small sample size.

Investigating the role of CGRP and Orexin-A in episodic Cluster Headache: a pilot study

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Background: Cluster headache (CH) is a primary headache characterized by intense pain typically located around the peri-orbital and temporal regions, lasting from 15 to 180 minutes, associated with autonomic-trigeminal symptoms. Calcitonin Gene Related Peptide (CGRP) and Orexin-A (OxA) are key neuropeptides influencing nociception and pain modulation. This pilot study aims to evaluate their plasmatic levels in a cohort of patients affected by episodic cluster headache (eCH) and the possible correlation with clinical-demographic characteristics.

Methods: Fourteen consecutive patients with an eCH diagnosis (5 active, 9 in remission; mean age 45.14 ± 11.67 years) underwent plasmatic dosage of CGRP and OxA during the interictal phase, along with the collection of clinical data and results of 6 self-administered questionnaires (HIT-6, CHIQ, STAI Y1/Y2, MEQ, BDI, PSQI). The results were then compared with 41 migrainous patients (24 with chronic migraine, CM; 17 with high frequency episodic migraine, EHFM) and 16 controls.

Results: No differences in the plasmatic levels of the neuropetides were found between eCH and control group (7.66 ± 1.72 pg/ml vs. 30.78 ± 60.6 pg/ml; $p = 0.15$).
However, when comparing these values between eCH and the group of migraine subjects, the latter had significantly higher levels of CGRP (7.66 ± 1.72 pg/ml vs. 138.8 ± 159.38 pg/ml; $p < 0.001$). Furthermore, it is interesting to note a direct correlation between CGRP levels and the scores of the STAI Y1/2 and BDI questionnaires. Finally, the state anxiety score (STAI Y1) emerged as the only significant predictor of CGRP concentration in eCH patients.

Conclusion: Neuropeptides were not found to be predictors of the active phase of the disease. Our results, though exploratory, confirm that neither plasmatic CGRP nor OxA differentiate interictal eCH patients from control subjects as they do in comparison with CM and HFEM patients. Therefore, as CH patients show a poorer response to target therapies as compared to migraine patients, there is need to investigate new biomarkers in larger cohorts of CH patients and compare the obtained data with those of migraine patients.

Predictors of early and sustained efficacy of monoclonal antibodies therapy in migraine: the central role of baseline plasmatic GCRP

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Background: Migraine represents nowadays one of the leading causes of disability and loss of working days in the world. Innovative therapies targeting the CGRP signaling opened and established a new era in preventive treatment of migraine. Post marketing efficacy evidence are convincing and the neurobiological context of CGRP modulation is a field of growing interest though its relationship with clinical results is still scarcely investigated.

Methods: We enrolled 41 patients (34 F, 7 M; age 52.16 ± 12.47 years; 24 CM, 17 EM) who started mAbs therapy (7 Erenumab, 17 Galcanezumab and 17 Fremanezumab). During the first visit (T0) they underwent plasmatic CGRP, Orexin-A (OxA) and PACAP-38 measurement and collection of clinical-anamnestic information. The clinical course was re-evaluated at 3 months (T3) and 6 months (T6), based on monthly migraine days (MMD), monthly medication use, mean pain intensity (NRS) and MIDAS. Data were analysed by linear regression to develop a predictive model of treatment response based on T0 clinical and biochemical characteristics.

Results: Higher CGRP plasmatic concentration at T0 emerged as a unique independent predictor of a less favorable therapeutic response at T3 and T6 through direct correlation with MMD (100 pg/ml per 2,1 MMD at T6; $p = 0.002$). Through multivariate analysis we found a similar correlation also with monthly medication use and MIDAS both at T3 and T6. Moreover, MMD decrease at T6 (ratio to T0) was inversely correlated with plasmatic CGRP at T0 (- 100 pg/ml per 6% MMD decrease at T6; $p = 0.015$).

Conclusion: The neurobiological setting may be crucial in the variability of clinical response to mAbs therapy both in the short-term and midterm (first and second trimester). Though further data are needed to generalise these results, the present study confirms our previous findings about the predictive role of baseline GCRP plasmatic concentration in the context of preventive anti-CGRP therapy.

Connectivity study of Galcanezumab therapy on drug resistant migraine sample

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Background: The critical role of calcitonin gene-related peptide (CGRP) in the activation of the trigemino-vascular system, sterile inflammation, and subsequent headache has been underlined by recent developments in migraine research. As an "oscillopathy," migraine is characterized by abnormal cortical rhythms that could be a factor in the onset of symptoms such as cortical spreading depression and hypothalamic activity. In the occipital brain of migraine sufferers, abnormal response to visual stimuli and altered connection patterns have been noted.

Methods: We studied the effects of a 3-month course of Galcanezumab therapy on a group of 20 patients with migraines who had not responded to traditional therapies, and we compared them to a control group of 10 healthy people. Using a 64-electrode setup based on the extended 10-20 system, we acquired electroencephalographic (EEG) data. The Steady State Visual Evoked Potentials (SSVEPs) during multiple research phases, namely T0 (basal visit), T1, and T2 (after three months), were then assessed to further evaluate the EEG data. In addition, we conducted localized tests on the specific channels exhibiting enhanced network efficiency to determine whether the overall alteration is attributed to specific regions of interest.

Results: Galcanezumab demonstrated the ability to enhance network integration and reduce both node coherence and network segregation in the theta and alpha frequency bands. The differences between T0 and T2 and T1 and T2 tend to be more intense, more numerous and for these differences the more intense links tend to connect the frontal and the occipital cortex. The localized tests conducted on the specific frontal and occipital channels revealed significant differences in communication efficiency within these specific regions.

Conclusion: Our findings support Galcanezumab effectiveness in improving the overall performance of the communication system. Specifically, we observed significant enhancements in interaction and coherence between the occipital and frontal networks. These results suggest that the observed global alterations in the network may be influenced by these specific regions of interest. Our study contributes to a better understanding of its overall impact, highlighting the potential therapeutic benefits of Galcanezumab in optimizing network efficiency and processing within relevant brain regions.

Monocytes differentiation and inflammatory profile in episodic and chronic migraine: association with disease severity

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Background: Neuroinflammation may play a role in migraine pathogenesis, although conflicting data are present in the literature. Studies examining differences in peripheral inflammatory markers between episodic (EM) and chronic migraine (CM) patients did not provide a definite consensus. The primary outcome of the present study was to evaluate cytokines gene expression in total monocytes of EM, chronic migraine with medication overuse headache (CM) patients, and healthy controls (HCs).

Methods: We enrolled 50 EM patients (41.6±10.4 years, 75% female, 6.4±3.7 MMDs), 34 CM patients (46.5±11.3 years, 85% female, 22.6±6.3 MMDs), and 30 healthy controls (HCs, 42.9±14.8, 67% female). We assessed in peripheral monocytes the interictal gene expression of pro-inflammatory (IL-1β and TNF-α) and anti-inflammatory (IL-10) cytokines (rtPCR - Relative Quantification). In a subgroup of patients (18 EM, 24 CM and 17 HC), we also analysed the percentage distribution of M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes in the two main classes of monocytes (classic/non-classic) by means of Fluorescence-activated cell sorting (FACS).

Results: IL-1β and TNF-α expression was higher in EM (IL-1β: 1.17±0.3, TNF-α: 1.11±0.3) and CM (IL-1β: 1.82±1.0, TNF-α: 1.11±0.27) when compared to HCs (IL-1β: 0.39±0.1, TNF-α: 0.39±0.2) (p=0.001). In addition, expression of IL-1β and TNF-α was higher in CM when compared to EM (p=0.001). IL-10 expression was lower in EM (0.81±0.3) and CM (0.64±0.2) when compared to HCs (1.54±0.6, p=0.001), without differences between EM and CM (p=0.132). M1 and M2 percentage events in non-classical and classical monocytes were higher in CM when compared to EM and HCs (p=0.001 for all comparisons).

Conclusion: Our cohort of migraine patients was characterized by a more pro-inflammatory oriented profile, as demonstrated by: i) increased expression of IL-1β and TNF-α; ii) inhibited expression of IL-10. In addition, monocytes distribution showed an overlap of pro-inflammatory and anti-inflammatory activity. Further evaluation will be necessary to understand the clinical significance.

Combining monoclonal antibodies for different diseases: a multicenter study on safety and effectiveness

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Background: No data are available on the safety and efficacy of monoclonal antibodies (MoAb) when used in combination for different diseases. The aim of this multicenter study was to evaluate the 6-month effectiveness and tolerability of MoAb targeting the calcitonin gene-related peptide (CGRP-MoAbs) when combined with other MoAb for different diseases.

Methods: Outpatients of the "Italian Headache Registry" (RICe), treated with CGRP-MoAbs for migraine, while simultaneously assuming monoclonal antibodies for other pathologies, were screened and included if they had a 6-month follow-up after the start of the therapy with the two co-prescribed drugs. Effectiveness outcomes for migraine included reduction from baseline of Monthly Headache Days (MHDs), Migraine Disability Assessment (MIDAS) and HIT-6 questionnaire total scores. The Patients' Global Impression of Change (PGIC) scale was used to quantify the patient's evaluation of the efficacy of treatments. Safety outcomes included the observation of side effects different from those expected in monotherapy.

Results: 26 patients (21 women and 5 men; mean age±SD, 50.3±9.7) were included. In most of cases (n=16; 61%) the CGRP-MoAb (erenumab, galcanezumab or fremanezumab) was added to a previously ongoing treatment with another MoAb (namely adalimumab, ocrelizumab, omalizumab, natalizumab, ustekinumab, risankizumab, tocilizumab, etanabercept, denosumab, certolizumab, evolocumab) for psoriatic arthritis (n=6; 23%), osteoporosis (n=6; 23%), ankylosing spondylitis (n=4; 15%), rheumatoid arthritis (n=3; 11%), multiple sclerosis (n=2; 8%), asthma (n=2; 8%), ulcerative colitis (n=1; 4%), vasculitis (n=1; 4%) and dyslipidemia (n=1; 4%). MHDs (20.7±6.1 vs 11.8±8.0; p<0001), MIDAS scores (75.0±41.9 vs 30.3±27.7; p=0.001) and HIT-6 scores (66.5±10.5 vs 53.4±8.7; p=0.002) significantly decrease from baseline to 6 months. The PGIC score was high

both for anti-CGRP mAbs (mean±SD 5.48±2.6) and other MoAbs (mean±SD 5.5±2.9). The introduction of the second MoAb resulted in mild gastrointestinal symptoms with the co-prescription of evolocumab and erenumab and in mild alopecia with the co-prescription of galcanezumab and ustekinumab.

Conclusions: Combing different MoAbs may be considered safe and effective. Each patient needs to be considered on an individual basis for mild side effects following the combination.

Anti-CGRP monoclonal antibodies are effective and safe prophylactic treatment for patients older than 60 years

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Background: The efficacy of anti-CGRP monoclonal antibodies (mAbs) in migraine prevention is well consolidated, yet data regarding patients aged ≥65 years are limited, especially in the real-life setting. Aim of the present study was to evaluate clinical outcome – efficacy and safety – in patients over 60 years of age in treatment with anti-CGRP mAbs.

Methods: This retrospective study was performed at the ASST Spedali Civili of Brescia, between November 2019 and November 2022. All patients had a diagnosis of migraine according to the International Classification of Headache Disorders III (ICHD-III) and currently in prophylactic treatment with anti-CGRP mAbs. The primary endpoints were to evaluate the reduction of monthly headache days (MHDs), monthly migraine days (MMDs) and clinical disability according to MIDAS score in patients older than 60 years after a follow-up at 3 (T3) and 6 months (T6). The secondary endpoint was to evaluate safety and tolerability.

Results: Twenty patients were enrolled with an average age of 63 years (SD 2.5, range 60-67) of which 11 with a diagnosis of chronic migraine. Eleven patients (55%) documented at least one comorbidity (cardiovascular, autoimmune or psychiatric). According to the type of mAbs, 8 patients were in treatment with fremanezumab, 12 with galcanezumab and 8 with erenumab (140 mg). At baseline, mean MHDs was 17.3 (7.2), MMDs 9.5 (5.2), mean analgesics consumption was 16.2 (18.8) and the MIDAS score was of 95 (69.2).
At T3, 70% of patients obtained a reduction of MHDs >=50%. A significant reduction in MHDs (6.5±3.8 $p<0.0001$), MMDs (1.7±1.5; $p<0.0001$), mean analgesic consumption (4.3±3.4; $p=0.0008$) and MIDAS score (19.9±18.9 $p<0.0001$) was found at T3.
These results were also confirmed after six months of follow up. In particular, MHDs (8.4±7.7 $p<0.0001$), MMDs (2.1±3.6; $p<0.0001$), mean analgesic consumption (6.3±11.2; $p<0.0001$) and MIDAS score (17.3±15.7 $p<0.0001$) were statistically significant compared to baseline. At T6, 80% of patients documented a MHDs reduction ≥50%.
Concerning tolerability and side effects, only 3 patients experienced constipation.

Conclusion: Anti-CGRP mAbs are an effective and well tolerated prophylactic treatment to be considered also in the elderly population.

Sleep quality in migraine patients treated with anti-CGRP monoclonal antibodies – a real-life study

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Introduction: Both migraine and sleep disorders are highly prevalent and burdensome neurological diseases, which are frequently associated and can influence one another. Patients with migraine frequently report worse sleep quality than the general population. Our aim was to assess sleep quality in patients with migraine before and after 3 months of treatment with anti-calcitonin gene related peptide (CGRP) (galcanezumab, fremanezumab) or anti-CGRP-receptor (R) (erenumab) monoclonal antibodies (mAbs).

Methods: In this monocentric retrospective study, we recruited 50 consecutive migraine patients who started treatment with anti-CGRP(R) mAbs from May 2020 to July 2022. Patients were evaluated at baseline and after three months of therapy, considering changes in migraine frequency (mean migraine days, MMD) and in sleep quality (Pittsburgh Sleep Quality Index, PSQI). Patients with a 50% or greater reduction in MMD were considered responders.

Results: Median age was 48 (41-59), with 35 (70%) female patients. Thirty-eight patients (76%) had chronic migraine. Median mean migraine days was 21 (14-30). Twenty patients started treatment with erenumab, twenty-two with galcanezumab and eight with fremanezumab. At baseline, sleep quality was poor (PSQI median score 6 (5-10)). After three months, thirty-three patients (66%) were responders. Median scores of PSQI were significantly reduced to 5 (4-7), (p 0.001). Comparing responders to non-responders, we found no significant differences evaluating sleep quality, neither at baseline (PSQI R 6 (5-9) vs PSQI NR 8 (5-10), p 0,360) or after treatment (PSQI 5 (4-8) vs PSQI 6 (5-7), p 0,481). However, sleep quality was significantly improved both in responders (PSQI t0 6 (5-9) vs t1 5 (4-8) p 0.002) and non-responders (PSQI t0 8 (5-10) vs t1 6 (5-7), p 0.013).

Conclusion: After three months of treatment with anti-CGRP(R) mAbs, we observed a significant improvement in sleep quality in patients with migraine who were overall poor sleepers, although it was not enough to define a good sleep quality. The improvement was observed both in responders and non-responders. More longitudinal studies are needed to assess the impact of anti-CGRP(R) mAbs on sleep quality and sleep disorders.

Beneficial effect of correcting vitamin D deficiency on migraine course: data from an observational study

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Background: Migraine is a complex disorder affecting approximately 11% of the adult population worldwide, with an increasing social and economic burden.
Recent evidence supports the role of dysfunction of immune modulation in pathophysiology of migraine and the beneficial effect of immunomodulatory nutrients in controlling migraine symptoms. Several studies found the association between low vitamin D levels and migraine, and vitamin D has also been reported to be effective in migraine prophylaxis.
Our prospective study investigated vitamin D deficiency in a cohort of migraine outpatients and the effect of vitamin D supplementation on migraine course.

Methods: In Episodic or Chronic adult migraineurs attending Headache outpatient clinic (January-December 2022), vitamin D levels were assessed and deficiency (< 30 ng/mL) promptly supplemented. 'Low' or 'high' frequency episodic migraine was defined as having 0-4 and 5-15 monthly migraine days, respectively. 'Favorable course' of migraine was considered: for episodic migraine if transition from 'high' to 'low' frequency occurred or if a "low" frequency pattern was maintained for at least one year, for chronic migraine if at least a 70% reduction in monthly migraine days was reported.

Results: Out of 118 migraineurs, 81 (69%) had vitamin D deficiency (64 female, mean age 47±14), 54 (67%) had high-frequency or chronic migraine, while 27 (33%) low-frequency migraine.
Sixty-eight (84%) patients received vitamin D supplementation, 61 (90%) of them presented a 'favorable' migraine course (62% plus prophylaxis): 26 low-frequency migraineurs, who remained 1-year stable (96%, 8 of them on migraine prophylaxis), and 35 (65%) high-frequency or chronic migraineurs (6 without prophylaxis). Out of 13 patients not supplemented, 11 (85%) presented an unfavorable course. Among migraineurs with normal vitamin D (33 female, mean age 48 ± 15), 30 (81%) had a statistically significant more 'favorable' migraine course (53% on prophylaxis) compared to migraineurs with deficiency before supplementation ($p<0.00001$), but not after supplementation.

Conclusion: Maintaining normal blood levels of vitamin D is associated with a more favorable course of migraine, regardless of prophylaxis. Assessment of vitamin D should be routinely performed in migraineurs, and deficiency promptly corrected. Vitamin-D supplementation could be considered as an effective, additional strategy in migraine prophylaxis.

Long-term efficacy of monoclonal antibodies anti-CGRP

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Objectives: Aim of the present study was to evaluate the efficacy of monoclonal antibodies in chronic migraine prevention following two cycles of treatment (i.e. 24 months).

Materials and Methods: This retrospective study was conducted at the Headache Centre - ASST Spedali Civili of Brescia. Data were collected between January 2019 and May 2023. Inclusion criteria were the following: age ≥ 18 years old, chronic migraine, 24 months treatment with an anti-CGRP monoclonal antibody (galcanezumab 240 mg, fremanezumab 225 mg and erenumab 70 or 140 mg). The following variables were evaluated: mean monthly headache days (MHDs), mean monthly migraine days (MMDs), analgesics consumption, triptan consumption, and pain intensity (Numerical Rating Scale – NRS). Patients were assessed quarterly. For the present study data are reported at baseline (T0), at the end of the first treatment cycle (T12) and at the end of the second cycle (T24).

Results: Twenty-three patients were enrolled, of whom 18 (78.2%) females. Mean age at baseline was 45.0 years (±9.4; range 26-60). On average, disease duration was 34.0 (±12.0) years. Sixteen (69.6%) were in treatment with Erenumab, 7 with Galcanezumab (30.4%) and none (0%) with Fremanezumab. Compared to baseline, at T12 and at T24 a statistically significant reduction in MHDs (22.0±7.00 vs 8.22± 4.71 vs 8.57± 7.76; $p<0.001$), MMDs (10.0±7.16 vs 4.05±3.47 vs 2.18±2.90; $p<0.001$), monthly analgesics consumption (26.0±18.72 vs 8.09±4.28 vs 7.77± 6.92 $p<0.001$), triptan consumption (12.9±9.16 vs 4.68±4.56 vs 4.05± 4.04 $p<0.001$) and pain intensity (NRS - 7.29±0.95 vs 6.24±0.99 vs 5.90± 1.30; $p<0.001$) was observed. No severe adverse events were reported throughout the long-term follow-up.

Discussion: Anti-CGRP monoclonal antibodies are a safe and effective prophylactic treatment in patients with chronic migraine, also during the second treatment cycle.

Conclusion: Our real-life data supports previous studies regarding the efficacy and tolerability of anti-CGRP monoclonal antibodies as a prophylactic treatment in patients with chronic migraine. In particular, a stable and prolonged clinical response was observed, throughout the second treatment cycle.

Effect of PEAFLOSIN® and Salvia Miltiorrhiza extract in pure catamenial migraine and menstruation-related migraine without aura

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Background: Menstrual migraine affects women of reproductive age during their menstrual cycles. It is characterized by migraine attacks on the days of the menstrual cycle. There are 2 subtypes: pure menstrual migraine (PMM), much less frequent, occurs exclusively during the days of menstruation, while migraine related to menstruation (MRM) occurs both cycle-related and monthly for other non-hormonal triggers. Use of nutraceuticals for mitigation of menstrual attacks is well known. Peaflosin is a patented antioxidant and anti-inflammatory complex containing PEA, curcumin from turmeric and piperine from black pepper, enhanced by the extract of Salvia Miltiorrhiza (Dolvedol).

Methods: Since January 2023 we have selected 15 women aged between 22 and 37 years, 5 with PMM and 10 with MRM; all with severe dysmenorrhea evaluated with Numeric Rating Scale (NRS 0-10), the number of symptomatic drugs taken during the period of the cycle was also taken into account (N. Pain Killer PK), both for menstrual pain and for migraine. also: the number of days with migraine with headache diary and separately the intensity of headache and menstrual pain with NRS. Three menstrual cycles treated only with triptans or NSAIDs for dysmenorrhea or migraine considered compared with another 3 months treated with the same therapy associated with Dolvedol 400 mg bid, started from -2 days after the cycle for the whole menstrual cycle.

Results: The mean number of days with migraine during the first trimester menstrual cycle was 3.5 days (range 2-5), the mean number of PKs was 5.6 (range 3-10) the mean NRS for migraine pain was 8.6 (range 7-10) that for dysmenorrhea 7.6 (range 6-9). From the comparison there is a significant difference between the group treated in prevention with Dolvedol 400 bid versus the baseline with an improvement in all parameters such as: mean number of days with headache p 0.04; no. PKs used p 0.028; NRS Migraine p 0.003 and NRS Dysmenorrhea p 0.04.

Conclusion: With all the limitations typical of observational studies and the small sample size, this study seems to show that the association PEAFLOSIN® and Salvia Miltiorrhiza extract contained in Dolvedol may play a role in improving the quality of life of patients with menstrual migraine and menstruation-related migraine.

Medication Overuse Headache (MOH) among Migraine patients: A Comparative Study of different treatment strategies

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Background: Medication Overuse Headache (MOH) is a condition that occurs when individuals excessively use symptomatic medications, leading to the chronicization of headaches in those with a pre-existing diagnosis of a primary headache disorder (e.g., Migraine). Current European guidelines for managing MOH recommend patient education, withdrawal of overused medication, and preventive treatment. Despite these recommendations, the introduction of novel anti-CGRP monoclonal antibodies (mAbs) has prompted the need for further data comparing different treatment strategies.

Methods: To investigate potential differences in clinical outcomes with various treatment approaches, we retrospectively divided 54 migraine patients with a concomitant MOH into three treatment groups: a) inpatient withdrawal only; b) outpatient treatment with mAbs only; c) inpatient withdrawal combined with mAbs treatment. We collected a comprehensive set of clinical data, headache diaries, and demographics at baseline and at three months follow-up.

Results: Out of the 54 enrolled patients, 18 underwent inpatient withdrawal, 22 received mAb treatment as outpatients, and 13 underwent inpatient withdrawal combined with mAb treatment. At baseline, there were no statistically significant differences between the groups in terms of age, sex, Monthly Migraine Days (MMD_T0), and Monthly Medication Usage (MMU_T0). All three treatment strategies proved to be effective, but no significant differences in clinical outcomes were found, as measured by variation in MMD and MMU at three months follow up among groups (One-way Anova). Additionally, from the analysis, age emerged as a predictor of the change in MMD from baseline to three months after treatment (linear regression, $p=0.049$).

Conclusion: This study aimed to compare the effectiveness of different treatment strategies for MOH in migraine patients. The results have demonstrated that all three treatment approaches - inpatient withdrawal only, outpatient treatment with mAbs only, and inpatient withdrawal combined with mAbs treatment - have proven to be effective in managing MOH. In this study, treatment with mAbs in combination with drug withdrawal produced similar clinical outcomes to treatment with mAbs alone. However, to comprehensively delineate the role of drug withdrawal in Migraine patients with MOH in the anti-CGRP era, further research remains imperative.

Psychiatric comorbidity in patients eligible for anti-CGRP monoclonal antibodies

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Background: Migraine is associated with a higher risk of comorbid psychiatric disorders, approximately twice as high compared to the non-migraine population. Mood, anxiety, and sleep disorders, as well as personality traits or clear-cut personality disorders, are primarily associated with migraine. Subjects with migraine and comorbid psychiatric conditions tend to experience more severe attacks, respond unsatisfactorily to conventional pharmacological therapies, and have a higher risk of developing chronic form of migraine and medication overuse headache. The aim of this study was to describe the psychopathological characteristics of migraine patients eligible for anti-CGRP monoclonal antibody therapy, who are non-responsive to several conventional pharmacological treatments.

Methods: We included 30 patients eligible for monoclonal antibody therapy who were attending the Headache Center of the Neurological Clinic at the Perugia University Hospital. Subjects underwent psychiatric evaluation at the Section of Psychiatry, University Hospital of Perugia. Particularly, we assessed the presence/absence of psychiatric disorders (SCID-5-CV), including personality disorders (SCID-5-PD), as well as the presence and severity of depressive symptoms (BDI-II and HAM-D), anxiety symptoms (HAM-A, STAI-Y), hypomanic/manic symptoms (MDQ), sleep disturbances (ISI).

Results: Diagnostic criteria for at least one psychiatric disorder were met in 34.5% of the included subjects. Particularly, 6.7% met the criteria for personality disorder; 27.8% met criteria for at least one disorder at the SCID-5-CV). Furthermore, 43.3% showed pathological personality traits. 34.5% of patients had moderate to severe depression according to the BDI-II (cut-off >18, mean score 15.03 ± 11,700) and 27.6% at the HAM-D. 17% of patients had moderate to severe anxiety at the HAM-A; 78.6% had a score >40 at least at one of STAI-Y1 and STAI-Y2 tests (mean STAI-Y1 42.46±11.971, mean STAY-Y2 45.36±11.470), underpinning clinically significant state and trait anxiety. 34.5% of patients showed moderate to severe insomnia on the ISI test (cut-off>14, mean score 9.69±7.226).

Conclusion: Psychopathology is highly prevalent in subjects with migraine who do not respond to conventional treatment. This confirms the frequent association between migraine and psychiatric disorders, also suggesting a possible role of psychopathological features in treatment response.

Analysis of the endocannabinoid system before and after anti-CGRP monoclonal antibodies: a real-life prospective study

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Background: Migraine treatment has been revolutionized by the introduction of anti-CGRP monoclonal antibodies (mABs). Most patients achieve a 50% response after 3 months of treatment, while a minority achieve it after 6 months or more. As the endocannabinoid system has been implicated in the pathophysiology of migraine, we tested the hypothesis that this therapeutical approach might induce changes in the levels of endocannabinoids and endocannabinoid-like modulators.

Methods: We conducted a prospective, real-life study to describe the clinical characteristics and to analyze blood levels of endocannabinoids and non-cannabinoid lipid mediators by UPLC-MS/MS in patients with high-frequency episodic migraine (HFEM), chronic migraine (CM), or medication overuse headache (MOH) before and after anti-CGRP mABs. Participants underwent a baseline visit (T_0), a follow-up visit 3 months (T_3), and 6 months (T_6) after starting mABs. In each study visit, subjects underwent a peripheral blood collection and performed a face-to-face semi-structured interview.

Results: We recruited 25 patients: mean age 47.88 years; F 22; M 3; diagnosis: HFEM 6, CM 19, MOH 16. They received mABs at the baseline: erenumab 15, fremanezumab 6, galcanezumab 4. The mean BMI was 23.85. Clinical characteristics at baseline were: mean migraine days (MMD) 15.04; mean headache days 18.96; visual analogue scale 8.64; MIDAS 119.6; HIT6 70.32; monthly analgesic intake 18.44. Considering MMD, 13/19 patients obtained a ≥ 50% response after 3 months of therapy, while 7/11 achieved it after 6 months. To date, preliminary blood test results of 7 patients are available. Globally, endocannabinoids and congeners show a reduction after 3 months and 6 months of mAbs. Anandamide (AEA), Oleoylethanolamide (OEA), Docosahexaenoyl Ethanolamide (DHEA), Linoleoyl Ethanolamide (LEA) show a statistically significant reduction at 6 months.

Conclusion: Endocannabinoids, such as AEA, are known to activate CB1 receptors expressed at the presynaptic level, inhibiting CGRP release in peripheral nerve fibers. mABs block either the receptor or the CGRP peptide, so adaptation of the endocannabinoid system is likely to occur in subjects on therapy. Our results show that the clinical efficacy of mABs is paralleled by changes in the peripheral levels of lipid neuromodulators that might be a consequence of the reduced inhibitory requirement on CGRP release.

Botulinum toxin as an effective treatment in anti-CGRP monoclonal antibodies failure

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Background: Anti-CGRP monoclonal antibodies (anti-CGRPAb) represent a highly effective prophylactic treatment for chronic migraineurs, but in some rare cases they are ineffective. Our case series aims to determine whether patients that did not respond to anti-CGRPAb could benefit from OnabotulinumtoxinA (BoNT/A) treatment.

Methods: We collected data from eight chronic migraineurs that attended our headache tertiary center and did not benefit from anti-CGRPAb treatment. Before this therapy, six of them had never been previously treated with BoNT/A, whereas three patients had already made use of it without achieving a good control over headache symptoms. After anti-CGRPAb failure, all these patients underwent at least one BoNT/A treatment according to the PREEMPT protocol. We compared the reduction in migraine days, intensity, and symptomatic medication intake obtained before and after anti-CGRPAb therapy and BoNT/A treatment.

Results: These patients did not benefit from anti-CGRPab therapy in terms of days of headache (19.566±8.546 days vs 19.111±9.584; p=0.977), pain intensity (NRS 7.444±0.527 vs 7.000±1.000; p=0.346) and the number of symptomatic intake (46.667±58.496 assumptions vs 48.667±59.569; p=0.675). All of them started BoNT/A therapy after discontinuing anti-CGRPAb; there was a significant reduction in migraine frequency (21.67±6.65 vs 9.000±5.701 days per month, p=0.002) and symptomatic medication intake (48.667±59.569 vs 19.000±23.749, p=0.022) while pain intensity NRS did not improve significantly (7.444±1.236 vs 6.222±1.481, p=0.057).

Conclusion: BoNT/A improved migraine frequency and symptomatic drug intake; the difference in pain intensity resulted in borderline significance. It is not well established on which basis pharmacological resistance to anti-CGRPAb exists, but in these cases BoNT/A seems to be effective by bypassing a purely CGRP-mediated pathogenetic mechanism of pain, thus being a good rescue therapy in resistant headache management. BoNT/A could be useful in chronic migraineurs when anti-CGRPAbs are ineffective.

Improving the treatment of cervicogenic headache by combining physiotherapy with immersive virtual reality

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Background: Cervicogenic headache (CH) is a pathological condition related to disorders of the cervical spine. Current guidelines for the treatment of CH advise conservative physiotherapy approaches, although the potential of Virtual Reality (VR), as an additional therapeutic tool for the neuro-rehabilitation of patients affected by CH has been poorly studied so far. The purpose of this study is to explore the potential of VR, on top of physiotherapy, to improve neuro-rehabilitation in CH.

Methods: We firstly evaluated, by an observational case-control study, the efficacy of implementing VR, in addition to the physiotherapy, for the neuro-rehabilitation of CH assessing changes in cervical spine disorders related to the onset of the headache. Secondly, we discussed the feasibility in clinical setting and the compliance of the patient. To this end we recruited 24 participants, who were randomized into two arms of intervention (1:1) receiving either physiotherapy alone or the physiotherapy + VR. In the latter group, the physiotherapy treatment was preceded by the VR experience. Each participants underwent two evaluations, at the enrollment and at the follow-up after 5 weeks (4-6 weeks). The immersive experience was analyzed through ITC-Sense of Presence Inventory (ITC-SOPI) scale and the Neck Disability Index (NDI) scale was used to score the level of disability. The statistical analysis was carried out using the Rstudio software.

Results: Both groups showed an improvement regarding the disability of the participants in their everyday-life activity, specifically physiotherapy stand-alone (*p value* = 0.013; baseline = 9.54, follow-up = 6.18), even if physiotherapy + VR group did not achieve statistical significance (*p value* = 0.08; baseline = 5.3, follow up = 3.6). Regarding the immersive experience, through the analysis of ITC-SOPI score, it emerged that all the participants expressed positively interest in the use of the virtual reality viewer, especially its usability and the environmental involvement.

Conclusion: We found that VR seems to be a usable, well-accepted and promising tool to combine with physiotherapy for the neuro-rehabilitation of CH. These results encourage a clinical application, although larger data for validation are warranted.

Multicentric study of effectiveness in prophylaxis of Episodic Tension-Type Headache and Migraine without aura using a combination of Pea 300 mg + Boswelia Akkba 10 mg + Feverfew (parthenolides 0.2 mg) + Griffonia (5 HTP 24 mg) + Niacin 10 mg + Riboflavin 1.4 mg each tablet (NATAWELL®) compared with Amitriptiline

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Background: Multicentred Analytical observational study with comparison group to evaluate the effectiveness of a nutraceutical "complex" Natawell® (NW) against Amitriptyline (AM) in the prophylaxis therapy of patients with ETTH and MWoA, using as an end-point: pain modification (NRS scale), reduction in the number of attacks/month and the consumption of analgesics/month.

Methods: Selected patients with ETTH and MWoA according to ICHD-III, who required prophylactic therapy; in total 400: 200 ETHH and 200 MWoA. One hundred patients with ETTH on NW therapy (1 cps morning and evening) compared with 100 on AM therapy (20 mg evening). One hundred patients with MWoA on NW therapy (1 cps morning and evening), compared with 100 on AM therapy (20 mg evening). The comparison took place at T1 (60 days) and T2 (120 days) of treatment.

Results: In ETTH patients treated with NW and AM the results were, respectively: the mean number of attacks decreased by 5 and 4.5 episodes/month (P=0.031); the NRS score was reduced by an average of 3.1 and 3.2 with no significant difference between the two groups; no significant difference was also observed with respect to the consumption of analgesics with an average decrease of 4.8 and 4.7 respectively. In MWoA patients treated with NW and AM the results were, respectively: the mean number of attacks decreased by 4.6 and 4.9 episodes/month without significant differences between the two groups; the absolute reduction in NRS score was less pronounced in the NW group (2.7 vs 3.7; P<0.001); with respect to the absolute reduction in analgesic use, a significant difference was observed between groups (4.5 vs 6.6; P<0.001).

Conclusion: Both NW and AM groups, in the forms of ETTH and MWoA, showed a statistically significant reduction from T0 to T2 for all the end-points considered. The results obtained in the various end-points highlight the effectiveness of prophylaxis with the nutraceutical "complex" NATAWELL®, which through the synergistic action of various molecules manages to reduce: the number of attacks per month, the pain score and the consumption of analgesics.

Slow responders instead of late responders: assessing the time to response to anti-CGRP/R monoclonal antibodies

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Background: Although the response to anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) is usually rapid, occurring sometimes within the first weeks, recent evidence suggests that some patients no responders at three months (≤50% response in monthly headache days, MHDs) might achieve responder status at six months. However, it is still unclear whether these patients have no response at all at three months or if they already achieve a clinically meaningful response at 3 months, without reaching the 50% cutoff, and improve over time. In this study, we evaluated whether late responders are actually slow responders to anti-CGRP mAbs.

Methods: We performed a prospective analysis on all patients that started erenumab, galcanezumab, or fremanezumab, including out-patients with a potential 6-month follow-up. Based on observational studies on late responders, response was defined as a ≥50% reduction from baseline in MHDs at 3 and 6 months. The response rate was then evaluated using different intervals (0-9; 10-19; 20-29; 30-49; ≥50%) to assess responses at three months. The primary outcomes were the number of potential late responders and to evaluate how many patients defined as late responders have a response ≥30% at three months (slow responders).

Results: Overall, we include 332 patients and among them 283 (85.2%) continued treatment for six months. Patients achieving response status were 63.6% (180/283) at six months. In particular, 40 (14.1%) patients non responders at three months achieve response status at six months, 140 (49.5%) persisted in response, 77 (27.2%) continued to be non responders and 26 (9.2%) lost the responder status. However, among the 40 patients defined as late responders, 21 (47.5%) had already achieved a response ≥30% at three months with 14 (35.0%) of them with a 40-49% response. Remarkably, 8 (20%) with almost no response at three months (0 to 9%) achieved a 50% response rate at six months.

Conclusion: The majority of patients designed as late responders are instead slow responders, starting a meaningful response to anti-CGRP at three months and improving over time. Nevertheless, to maximize response to treatment in all patients, we recommend evaluating the treatment after a minimum of three to six months.

Underlining the role of indotest in a rare Hemicrania continua-like headache

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Background: Hemicrania continua is a rare type of headache included in chapter 3.4 of ICHD-3, belonging to indomethacin-responsive headache disorders; for a definite diagnosis a complete diagnostic work-up is mandatory.

Methods and Results: A 91-year-old woman presented to our Centre because of the onset, in the previous 3 months, of severe headache in the left fronto-orbital region, irradiated ipsilaterally, with a continuous trend from onset, burning quality (poorly definable), moderate-severe intensity, never experienced before, with daily exacerbations, 10 times/day, with stabbing and unbearable intensity, lasting a few minutes, with no nausea or vomiting and no phono-photo-osmophobia.
Pain showed no postural changes, it was not associated with restlessness and it was minimally aggravated by exertion. No amaurosis or claudication were reported. A few days after the onset, during exacerbations, she noticed slight drooping of the left eyelid, without fluctuations, conjunctival hyperemia, rhinorrhea, or other trigeminal autonomic symptoms; furthermore, she reported fluctuating presence of diplopia. Both brain CT scan without contrast and brain MRI with angiography revealed no alterations; also, no ophthalmologic abnormalities were found; serum ESR and PCR were negative.
When the patient came to our attention, she was initially started on high-dose IV indomethacin with only partial response; this therapy was suggested by the diagnostic hypothesis of a persistent unilateral headache, with ipsilateral trigeminal-autonomic fluctuations and signs, such as Hemicrania Continua according to ICHD-3 criteria (not completely fitted). The presence of diplopia led us to suspect an inflammatory genesis, but a high-dose steroid trial was, again, unsuccessful. Therefore, we performed a new contrast-enhanced brain MRI with angiography and a cerebral CT angiography which were analyzed by the neuroradiologist who recognised a minimal arterial flow signal in the posterior portion of the left cavernous sinus and concomitant slight asymmetry of cavernous sinuses (left opacified earlier than right), findings suggestive of a small carotid cavernous fistula. The patient refused X-ray angiography and, at a 6-month follow-up, she reported the persistence of pain; a control contrast-enhanced brain MRI with angiography confirmed the diagnosis.

Conclusion: This case underlines the importance of carrying out extensive diagnostic investigations in trigeminal autonomic cephalalgias, particularly when ICHD-3 diagnostic criteria are not fully fitted.

Evaluation of the risk of hypertension in patients treated with anti-CGRP monoclonal antibodies in a real-life study

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Background: The calcitonin gene-relate peptide is critically involved in the homeostatic regulation of the systemic blood pressure in pathological conditions [1]. Meanwhile, the monoclonal antibodies (mAbs) blocking the calcitonin gene-related peptide are unquestionable effective in the prevention of migraine [2]. Despite this, the development of hypertension has been detected in some patients [3]. The aim of the present study is to explore the rate of hypertension incoming in patients treated with mAbs against the CGRP.

Methods: For the present study patients receiving an anti-CGRP mAb (erenumab, galcanezumab or fremanezumab) for migraine prevention were consecutively enrolled at the headache center of Modena. Visits were scheduled every 3 months and during every visit the systolic blood pressure (SBP) as well as the diastolic blood pressure (DBP) were collected, up to 1 year.

Results: Globally, no significant increases in the SBP and in the DBP were detected compared to the baseline. Additionally, no significant differences were found regarding the SBP and DBP comparing different mAbs. Globally, 5.7% of the patients developed a significant increase in their BP, thus necessitating the introduction of an anti-hypertensive treatment or the change of a pre-existing one. Patients with a pre-existing hypertension were more likely to have a significant increase in the blood pressure.

Conclusion: The risk of developing hypertension during the treatment with anti-CGRP mAb seems low. Anyway, patients with a pre-existing hypertension should be cautiously monitored because they are more likely to develop hypertension.

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In vivo biological activity of the dual FAAH/MAGL inhibitor AKU-005: evaluation in a model of trigeminal hyperalgesia

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Background: Several preclinical studies support that modulation of the endocannabinoid system (ECs) by inhibitors of enzymes involved in endocannabinoid hydrolysis may reduce the mechanisms underlying migraine-related pain. The dual MAGL-FAAH inhibitor AKU-005 shows a strong inhibitory effect *in vitro*. Here, we tested for the first time the pharmacological activity of AKU-005 in the animal model of migraine based on the administration of nitroglycerin (NTG) to validate its effect *in vivo*.

Methods: Male rats were treated with AKU-005 (0.5 mg/kg, i.p.) or vehicle 3 hours after receiving NTG (10 mg/kg, i.p.) or NTG vehicle. One hour later rats were then subjected to the open field test followed by the orofacial formalin test. We also assessed serum levels of calcitonin gene-related peptide (CGRP), gene expression of pro-inflammatory cytokines and CGRP and levels of endocannabinoids and related lipids in specific central and peripheral areas.

Results: The results showed that AKU-005 reduces NTG-induced hyperalgesia during the orofacial formalin test but did not influence NTG-induced changes in the open field test. Furthermore, AKU-005 significantly reduced the gene expression of CGRP, TNF-alpha, and IL-6 in the trigeminal ganglia, cervical spinal cord, medulla, and CGRP serum levels. Surprisingly, AKU-005 caused no change in cranial levels of endocannabinoids and related lipids.

Conclusions: These results indicate that AKU-005 has significant anti-migraine effects in the NTG model, which are mediated by the suppression of inflammatory events and reduction of CGRP release. The data show that this dual inhibitor *in vivo* can induce changes in alternative pathways that are not closely related to the modulation of ECs in specific brain regions.

Migraine and dementia: what correlation?

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Background: Migraine is a primary headache with significant impact on patients' social and work lives. Dementia is the most common neurological disease in elderly patients. According to the *International Journal of Geriatric Psychiatry*, migraine, the most common disorder overall, is an important risk factor for dementia, particularly for Alzheimer's disease.

Methods: Between January and December 2022, 67 patients (40 F, 27 M) were discharged from the Alzheimer Unit of the ASP IDR S. Margherita di Pavia (mean age 74.6 + 10.7; range 53-92). At the time of admission, an anamnestic questionnaire was administered to patients and/or caregivers (family members who were aware of the state of health prior to the initial cognitive impairment) on the presence of headache according to the IHS criteria (ICDH-III).

Results: Of 67 patients, 39 (30 F and 9 M) (mean age 71.9 + 9.8) had in the past headaches of 25 migraine without aura (24 F, 1 M) and 14 episodic or chronic tension-type headache (13 M, 1 F), only 5 patients a mixed form. 20 patients had received preventive pharmacological treatment with prophylactic therapy, while 19 had received symptomatic therapy. Only 8 of these had been visited at Headache Centres. Of the 39 patients, 34 presented a clinical picture of mixed dementia (mainly vascular) and 5 dementia of the Alzheimer type.

Conclusion: Our study highlights that migraine attacks can influence lifestyle such as variations in sleep-wake rhythm (particularly insomnia), sedentary lifestyle and poor social interaction (all risk factors related to cardiovascular disease) also play a role in the onset of senile dementia and its initial symptoms. Vascular dementia is a decline in cognition due to vascular lesions, while Alzheimer's disease is a neurocognitive disorder. In conclusion, could migraine identify people for high risk of dementia?

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