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ABSTRACTS

Effects of anti-CGRP monoclonal antibodies treatment on anxiety and depression comorbidities: a 12 months real-life study

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Background: Migraine is often associated with psychiatric comorbidities, such as anxiety and depression, which can influence the clinical course of the pathology and the outcome of treatment. Anti-CGRP monoclonal antibodies are a new class of medications for preventive therapy in chronic migraine or high-frequency episodic migraine. The purpose of this study is to evaluate the effect of anti-CGRP therapy on anxiety and depression aspects in migrainous patients during a 1-year treatment period.

Methods: We included patients with chronic refractory migraine or high-frequency episodic refractory migraine eligible for anti-CGRP treatment. Patients received a monthly treatment for 1 year with an anti-CGRP monoclonal antibody (Erenumab 70 mg, Erenumab 140 mg, Galcanezumab 120 mg or Fremanezumab 225 mg). Patients completed a set of validated scales (Hospital Anxiety and Depression Scale [HADS], Beck Depression Inventory II [BDI-II]) at baseline, to evaluate the impact of anxiety and depression symptoms on the quality of life, and then after 3, 6, 9 and 12 months of treatment. Data were compared using the Kruskal-Wallis test.

Results: We enrolled 80 patients (F: 58; M: 22; Erenumab 70 mg: n = 20, Erenumab 140 mg: n = 20, Galcanezumab 120 mg: n = 20, Fremanezumab 225 mg: n = 20). A significant reduction in the scores of the HADS anxiety score and BDI-II between the baseline and 3 month assessment was observed ($p < 0.05$). The HADS depression score showed a reduction trend, but did not reach statistically significance ($p = 0.10$). The average scores remained stable at 6, 9 and 12 months follow-ups.

Conclusion: Anti-CGRP treatment is associated with a long-term improvement both in anxiety and depression-related disability.

Personality profile of patients with chronic migraine treated with CGRPmAb

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Background: Psychiatric comorbidities have been extensively studied in migraine and represent a major risk factor associated with poorer outcome, playing a role in the headache chronicization process at once as cause and consequence of it. Monoclonal antibodies targeting the calcitonin gene-related peptide pathway (CGRPmAb) represent the first disease-specific preventive migraine therapy. Growing evidence suggests that they are effective in the preventive treatment of difficult-to-treat patients.
In this study, we evaluated the personality profile of patients with chronic migraine (CM) treated with CGRPmAb to identify personality disorders (PDs) that may be predictive of the long-term outcome.

Methods: Thirty-eight patients (mean age 48, SD 12 yrs) with CM who had already failed at least 3 preventive therapies received CGRPmAb every 28 days for a period of 12 months. Before the first administration, patients received a full psychological evaluation using the Millon Clinical Multiaxial Inventory-III (MCMI-III), a psychological assessment tool compatible with Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) particularly focused on Axis II disorders (i.e. PDs).

Results: After 12 months, among the 29 patients still under treatment, 15 showed a reduction of at least 50% in headache days/per month (Responders). The most frequent PDs were obsessive-compulsive (26%), dependent (21%) and histrionic (18.4%). When compared to Responders, Non-Responders were characterized by a higher prevalence of histrionic personality (5 vs 1, $p = 0.05$). Among Axis I disorders patients had a high prevalence of anxiety (21%), dysthymia (16%) and major depression (5.3%). Non-Responders were more frequently dysthymic (3 vs 0, $p = 0.05$).

Conclusion: CGRPmAb confirmed their effectiveness in a population of difficult-to-treat chronic migraine. The presence of histrionic personality together with “anxious-fearful” personality trait are negative predictors of treatment outcome.

Clinical differences between migraineurs responders and non-responders to monoclonal antibodies acting on the CGRP pathway

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Background: Calcitonin gene-related peptide (CGRP) is a potent vasodilator for peripheral and cerebral blood vessels [1]. It plays a causative role in migraine attacks since its level is elevated during attacks [2]. It is believed to be a potential biomarker of migraine. Pre-clinical studies have shown that trigeminal activation can induce CGRP release from peri-vascular nerve endings, resulting in pia-vessel dilatation and neurogenic inflammation, leading to migraine. CGRP antagonists can reduce cortical spreading depression in animal models of migraine. Baseline CGRP levels in adult patients are considerably higher than those in healthy controls. During migraine attacks, plasma CGRP levels are elevated in adult and pediatric patients, and their changes correlate with headache intensities. Intravenous infusion of CGRP produces a migraine-like headache in volunteers.
A CGRP receptor antagonist, olcegepant, is effective in treating acute migraine attacks and anti-CGRP or anti-CGRP-receptor monoclonal-antibodies are approved for migraine prevention [3]. Anti-CGRP (Fremanezumab and Galcanezumab) and anti-CGRP receptor (Erenumab and Eptinezumab) are the first monoclonal antibodies (mAbs) validated and specific for migraine prevention. Migraines occurring under prevention with anti-CGRP receptor mAb might be due to CGRP binding to other receptors (e.g., AMY1) with a structure similar to CGRP receptor, while migraine occurring under prevention with anti-CGRP mAbs might be due to other peptides binding to the CGRP receptor.

Methods: Eighty-five patients underwent CGRP-antibody prophylaxis (25 with erenumab, 32 with fremanezumab and 28 with galcanezumab). Five patients discontinued treatment due to ineffectiveness (5.88%) and 1 no longer needed to continue it.

Results and conclusion: Based on the analysis of this small sample, the clinical characteristics of non-responders to anti-CGRP moAbs did not show worse migraine pattern or longer preventative history compared to responders. The clinical markers of non-responders are: overweight/obesity, non-responders to triptans, mechanical hypersensitivity with fibromyalgia, mood and sleep disturbances inadequately treated, dependent personality with analgesic abuse. The sixth patient had chronic migraine without aura, overweight and borderline arterial hypertension. After 1 year treatment with fremanezumab, a ketogenic diet and the introduction of candesatan 4-8mg/day the frequency of attacks was 2-4/month, responsive to triptans and it was not necessary to continue a treatment with monoclonal antibody.

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Preliminary efficacy study in prophylaxes of episodic tension headache and migraine without aura using a combination of PEA, Griffonia, Boswellia, Partenio, Niacina and Riboflavina (Natawell®) compared with amitriptiline

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Background: Open study of efficacy in prophylaxis therapy with a nutraceutical association Natawell (NAT) towards Amitriptyline (AM) in patients with CTE and ESA using as outcome: modification of pain (NRS), number of attacks/month and consumption of analgesics-triptans/month.

Methods: We selected 200 patients with CTE and ESA: 100 CTE and 100 ESA, of these, 50 CTE patients underwent treatment with NATAWELL® (1 cp morning and evening) compared with 50 patients in treatment with AM (20 mg evening); while 50 ESA patients underwent treatment with NAT, compared with 50 in treatment with AM. The comparison took place at T0 and T1 (120 days) of treatment.

Results: In patients with CTE in the groups of NAT and AM: the NRS was reduced by 3.02 points and by 3.5 points respectively; the number of attacks went from 7.82 to 3.1 and from 9.6 to 4.7; the frequency of consumption of analgesics was reduced by an average of 5.02 and 4.9. The percentage of patients in which a reduction in the frequency of attacks was observed equal to or at least 50% of the basal value was 96% in the NAT group and 40% in the AM group.
In patients with ESA respectively in the NAT and AM groups: the NRS was reduced by 3.44 points and by 4.24 points, the number of attacks went from 8.24 to 3.84 and from 9.3 to 4.2; the frequency of consumption of analgesics was reduced by an average of 7.92 to 3 and of 5.48 to 2.92; the percentage of patients in which a reduction in the frequency of attacks was observed equal to at least 50% of the basal value was 72% in the NAT group and 60% in the AM group.

Conclusion: The results confirm the improvement, in patients treated with NATAWELL® in all the outcomes considered in the two forms of primary headaches observed.
No substantial differences were observed in efficacy between the two types of prophylaxis therapy used in both ESA and CTE patients, with the advantage of absence of side effects and increased compliance by patients in the treatment with "the supplement".

Monoclonal anti-CGRP antibodies in post-menopausal woman: a real-life study

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Background: Migraine usually ameliorates after menopause. However, about 10-29% of women still experience migraine attacks after menopause, especially if the menopause is surgical. The use of monoclonal antibodies against the calcitonin gene-related peptide (CGRP) are changing the landscape of migraine treatment. The aim of this study was to explore the effectiveness and safety of anti-CGRP monoclonal antibodies in women in menopause.

Methods: Women affected by either migraine and/or chronic migraine and treated with an anti-CGRP monoclonal antibody for up to one year. Visits were scheduled every 3 months.

Results: Women in menopause displayed a similar response if compared with women in childbearing age. Among women in menopause, the women experiencing a surgical menopause exhibited a similar response if compared to the ones experiencing a physiological menopause. Erenumab and galcanezumab displayed a similar effectiveness in women in menopause. No serious adverse events were registered.

Conclusion: The effectiveness of anti-CGRP monoclonal antibodies is almost the same between women in menopause and women of childbearing age, without appreciable differences between the different antibodies.

Galcanezumab for the treatment of chronic migraine and medication overuse headache. Real-world clinical evidence in a severely impaired patient population

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Background: Galcanezumab is a monoclonal antibody acting against the calcitonin gene-related peptide (CGRP) approved for the preventive treatment of migraine. The aim of this article was to explore its effectiveness and safety of galcanezumab in chronic migraine (CM) with medication overuse headache (MOH).

Methods: Seventy-eight patients were consecutively enrolled at the Modena headache center and followed up for 15 months. Visits were scheduled every 3 months and the following variables were collected: the number of migraine days per month (MDM), the painkillers taken per month (PM), the number of days per month in which the patient took, at least, one painkiller (NDM), the 6-items headache impact test (HIT6), the migraine disability assessment questionnaire (MIDAS) score. Demographic features of the analyzed sample were collected at the baseline and adverse events (AEs) were collected at every visit.

Results: After 12 months, galcanezumab significantly reduced the MDM, the PM, the NDM, the HIT-6 as well as the MIDAS scores (all $p<0.0001$). The greatest amelioration was obtained in the first trimester of treatment. A higher MDM, a higher NRS score at the baseline and a higher number of failed preventive treatments negatively predict the CM relief at the year of treatment. No serious AEs were registered and only 1 drop-out due to AE.

Conclusion: Galcanezumab is effective and safe for the treatment of patients affected by CM and MOH. Patients with a higher impairment at the baseline may find less benefits with galcanezumab.

Psychiatric comorbidity among migraineurs treated with monoclonal antibodies against CGRP-pathway

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Background: Psychiatric comorbidity is one of the most common associated conditions in migraine patients, especially the ones with a medication overuse headache or a chronic migraine. Anxiety-depressive syndrome characterizes many of the most difficult-to-treat migraineurs who were the first ones to be enrolled for treatment with anti CGRP-pathway monoclonal antibodies at our Headache Centre.

Methods: Data were collected from the database of the Headache Centre of the Ospedale dell'Angelo in Mestre. Through the Beck Depression Inventory II (BDI-II) and the Anxiety Hamilton Scale (AHS), we searched for a psychiatric comorbidity among patient who were treated with the available monoclonal antibodies against CGRP (i.e. Galcanezumab or Fremanezumab) or its receptor (i.e. Erenumab). Then, looking at the MIDAS change after six months of therapy, we qualitatively explored the possible influence of the psychiatric comorbidities over the efficacy of the treatment itself.

Results: Fifty-one patients have been treated with monoclonal antibodies (mAbs) against CGRP or CGRP-receptor, during the study period. According to BDI-II and AHS criteria, 14 patients of the sample (27.5%) suffered from depression and/or pathologic anxiety (in 2 cases with panic attacks, as well) as comorbid condition. Thirty-nine patients completed at least a 6-months period of treatment with mAbs: 25.6% of these patients (10/39) fulfilled the criteria for depressive or anxious symptoms, the remaining 74.4% (29/39) did not experience any psychiatric condition. The mean MIDAS-improvement at six months was lower among migraineurs with psychiatric comorbidities (52.4%) than among migraineurs without depressive or anxious symptoms (73.8%). Furthermore, three patients interrupted the treatment: in one case due to a secondary hypertension; in the other two due to inefficacy and they both had psychiatric pathologies.

Conclusion: In patients with depressive or anxiety symptoms, MIDAS improvement after 6 months of therapy appears significantly lower ($p<0.05$). Psychiatric comorbidities seem to have a negative influence on the globally positive effects of migraine prophylactic therapy with monoclonal antibodies against CGRP-pathway, increasing the probability of an early interruption of the treatment due to a lack of efficacy.

Sars-Cov-2 infection and vaccination in migraine patients: does the migraine get worse or stay the same?

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Background: Headache occurs as one of the symptoms of COVID-19 in a percentage that reaches 60% of cases, but a persistent headache for several months, often the expression of a worsening/chronicization of a pre-existing migraine, has also been reported in literature. Many possible pathophysiological mechanisms of this post-infection headache have been postulated, including the increase of circulating pro-inflammatory cytokines and the deranged innate immune signalling, which are implicated in both COVID-19 headache and migraine, or the activation of peripheral trigeminal nerve endings by the SARS-CoV-2 directly. The present study was aimed at verifying any changes in frequency and severity of headaches in migraine patients after Sars-Cov-2 infection and, secondly, after Sars-Cov-2 vaccination.

Methods: In the period December 2021-May 2022, about seven hundred and fifty patients visited the Headache Center of Perugia; during their visits they were questioned about the occurrence of Sars-Cov-2 infection in the past year, as well as their experience after the first, second and third dose of the vaccine for Sars-Cov-2, with particular attention to any changes in the headache pattern.

Results: Seventy-five migraine patients reported Sars-Cov-2 infection in the past six months; of these, 48 patients (64%) reported a persistent worsening of headache, both in terms of frequency (an increase of at least 50% of migraine monthly days) and intensity, in the months following the resolution of the infection. Among these, 14 patients (28%) reported a change pattern from an episodic to a chronic form of migraine and it was necessary to introduce or change their prophylactic therapy. The remaining 27 patients (36%) did not report long-term changes in their usual migraine. It should be noted that among patients who reported a headache worsening after the infection, only 31% were on prophylaxis, unlike the 58% of patients who did not experience any headache changes. Among the prophylaxis, anti-CGRP monoclonal antibodies was the most “protective” against post-infection headache. Regarding the vaccine, although many patients reported headache episodes soon after vaccine inoculation, only a small minority of interviewed patients reported persistent headache worsening after vaccine, independently of which vaccine was administrated.

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.
We aimed to define specific internodal connectivity patterns of the default mode network (DMN) in eCH patients, through advanced brain connectivity analyses with high-density EEG (HD-EEG).

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. Of these 24 patients, 8 were registered only at T0, 10 only at T1, while 6 completed both registrations. 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.

Psychopathological disorders in chronic migraine: Is there an association with the endocannabinoid system?

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Background: The understanding of factors involved in the prognosis of chronic migraine (CM) has become a topic of interest in the current debate. Compelling evidence has suggested a negative prognostic value for psychopathological disorders. Dysfunctions of the endocannabinoid system can underlie several psychiatric disorders. To date, no evidence is available for CM. Hence, the present study aims to evaluate the association existing between psychopathological disorders and endocannabinoid system in CM.

Methods: This study was conducted at the Headache Science and Neurorehabilitation Center of the C. Mondino National Neurological Institute in Pavia, Italy. Thirty-four patients (mean age = 44.9 ± 11.9 years) with a CM diagnosis, operationally defined according to ICHD-III, who failed at least three previous preventive therapies were enrolled and received full psychological evaluation according to DSM-V criteria for mood, anxiety, and personality disorders. Gene expression of enzymes involved in the synthesis and degradation of endocannabinoids and their receptors (CB1 and CB2) was assessed in peripheral blood mononuclear cells.

Results: Among enrolled patients, 53% (n = 18) presented mood disorders (MD), 79% (n = 27) anxiety disorders (AD), and 53% (n = 18) resulted positive for personality (PD) disorders (Cluster C - predominantly obsessive-compulsive disorder). We detected interesting associations between these psychopathological disturbances and mRNA levels of cannabinoid receptors. Specifically, higher CB1 (2.97 ± 2.05 vs 1.66 ± 1.00, p = .018) and NAPE (2.09 ± 0.62 vs 1.63 ± 0.50, p = .04) receptor gene expression was found in the group of patients with MD when compared to the non-MD group. The AD group had higher levels of FAAH, the hydrolase that degrades anandamide, when compared with the non-AD group (2.09 ± 0.62 vs 1.63 ± 0.50, p = .04). Finally, a lower CB1 gene expression (1.48 ± 0.78 vs 2.52 ± 1.76, p = .027) was detected in the PD group when compared to the non-PD group.

Conclusion: These preliminary findings provide knowledge regarding the association existing between psychopathological disorders and alterations in the endocannabinoid activity in CM.

The virtual "Enfacement Illusion" on pain perception in patients suffering from chronic migraine: preliminary data from a randomized controlled trial

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Background: Given the limited efficacy of pharmacological treatments for chronic migraine (CM), new non-pharmacological therapeutic strategies have gained increasing attention. Body ownership illusions have been proposed as a non-pharmacological strategy for pain relief. Here we report the preliminary data from a randomized controlled trial (RCT) evaluating the efficacy in reducing pain perception of the enfacement illusion of a happy face observed through an immersive virtual reality (VR) system in patients with CM.

Methods: Here we present the output of the interim analysis of data from a double-blind RCT involving patients with CM randomly assigned to the experimental or the control intervention. The experimental group was exposed to the enfacement illusion; whereas the control group was exposed to a pleasant immersive VR environment. Both conditions consisted in three VR sessions (about 20 minutes) during a one-week period. At baseline (T0) and at the end of the intervention (T1), the patients filled in behavioral measures related to their emotional and psychological state, and body image perception. Before and after each VR session, we assessed the level of pain (Visual Analogue Scale, VAS), the body image perception, and the affective state of the patients.

Results: Twenty-five CM patients were evaluated. Eleven (39.5±12.6 years) received the experimental treatment and fourteen (44.3±10.7 years) were exposed to the control condition. Patients were comparable from the clinical and psychological point of view. Preliminary data showed a similar pattern for both groups as regards to pain intensity following the intervention with a comparable reduction in VAS score within and across sessions. Interestingly, more pronounced benefits were found for the experimental group than the control group in terms of changes in the affective state between T0 and T1.

Discussion: Even if preliminary, the results of this study seem to support the effectiveness of body ownership illusions as a cognitive behavioral intervention acting not only on pain relief but also on the affective state in patients with CM.

Migraine chronification as an allostatic disorder: assessment of the Bologna Allostatic Load Index (BALI)

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Background: The underpinning biologics of migraine chronification are not well understood. We aim to investigate the role of the cumulative burden of stress, namely the allostatic load, in migraine chronification.

Methods: This was a cross-sectional study. The allostatic load was measured with a composite multi-system score (BALI: Bologna Allostatic Load Index), evaluating 20 biomarkers representing four physiological systems: immune, metabolic, cardiovascular, and neuroendocrinological systems. BALI score was subdivided into high-score and low-score based on the distribution in controls. Migraine patients were included and subclassified into low-frequency episodic migraine group (low-EM group), high-frequency episodic migraine group (high-EM group), and chronic migraine group (CM group).

Results: The distribution of BALI high-score increased in parallel with headache attacks monthly frequency: 16% in low-EM group (n=10), 24% in high-EM group (n=12) and 40% in CM group (n=21) (p=0.017). In a multivariable analysis, the Odds Ratio of having a high-score BALI in CM patients (vs. Low-EM patients) was 2.78 (95% CI 1.07-7.22; p=0.036). Individual BALI biomarkers values which were significantly different among migraine subgroups included systolic blood pressure (p=0.018), diastolic blood pressure (p<0.001), and heart rate (p=0.019).

Conclusion: Our study substantiates this emerging concept of migraine chronification as an allostatic disorder.

In-depth profiling of chronic migraine phenotype via peripheral biochemical markers

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Background: Chronic migraine associated with medication overuse headache (CM-MO) represents one of the most disabling phenotypes across the migraine spectrum. The progression from episodic migraine (EM) to CM is still an unclear process. The aim of this study was to better define the phenotype of CM-MO by means of peripheral biochemical markers and specific clinical features.

Methods: We enrolled 13 CM-MO patients, 21 EM patients and 17 healthy controls (HC). In all subjects, we evaluated the expression of miR-34a-5p and miR-382-5p in peripheral blood mononuclear cells (PBMCs), and plasma levels of CGRP and PACAP. Furthermore, we considered the clinical/demographic features and the psychological profile of migraineurs. CM-MO group was also tested 2 months after an in-hospital detoxification protocol.

Results: CGRP and PACAP levels, miR34a-5p and miR-382-5p expression were higher in the CM-MO group when compared to EM and HC ($p < 0.05$ for all comparison). Headache frequency positively correlated with CGRP (Spearman's rho: 0.559, p=0.030), PACAP (Spearman's rho: 0.563, p =0.001) and miR-34a-5p (Spearman's rho: 0.496, p =0.003). Depression was more prevalent in CM-MO patients when compared to the EM group (61.5% vs. 33%, p=0.001). Personality disorders and anxiety were equally distributed between the two groups. In the CM-MO group tested 2 months after detoxification, we found decreased CGRP and PACAP levels (p=0.031 and p=0.008, respectively), as well as a reduction of miR34a-5p expression (p=0.004).

Conclusion: Our findings identify a specific phenotype for CM-MO, which seems to be characterized by an alteration of peripheral biomarkers and of the psychological profile.

Secondary headache in patients with migraine: remember Susac Syndrome. A case report and review of literature

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Background: Susac Syndrome (SuS) is a rare disease characterized by inflammatory microangiopathy presenting with a clinical triad of encephalopathy, branch retinal artery occlusion and hearing loss. Central nervous system involvement often presents with headache, which is estimated to affect up to 80% of SuS patients. The European Susac Consortium consider headache as a possible brain manifestation if it is new, either migrainous or oppressive type, and precedes other symptoms by less than 6 months. The coexistence of a primary headache disorder in patients with SuS is reported in the literature, but it is scarcely documented.

Case Report: A 26-year-old woman presented to the Emergency Room 3 times within a month, with a history of 15 days of severe headache. It started as neck pain and evolved as holocranic, associated with nausea, vomiting, occasional vertigo and three episodes of remitting tingling in the left upper limb. Since she had no focal deficits at neurological examination neither lesion at brain CT, and she had a history of migraine with visual aura, no further investigation was carried out. She was repeatedly discharged with diagnosis of migraine and adviced to undergo a brain MRI on her own. Lastly, she was admitted to our department for persistence of disturbances, in particular headache, described by the woman as unusual compared to her previous migraine attacks. Brain MRI with intravenous contrast revealed multiple small hyperintense foci on T2/FLAIR weighted images, and contrast enhancement, in the supratentorial white matter, cerebellum and brainstem, “snowball”-like lesions of the corpus callosum and leptomeningeal enhancement. Altogether these findings were highly suggestive of SuS and the diagnosis was confirmed after finding retinal and vestibulocochlear involvement with fluorescein angiography and audiometry respectively, despite the absence of vision and hearing complaints.

Conclusion: The lesson from this case of a new onset of “different-from-usual headache” in a migrainous women, is that headache should be taken into account as a presenting symptom of SuS, even in patients affected by primary headache disorders, especially when the classical clinical triad is absent at onset and the risk of missing the diagnosis is highest.

Fremanezumab and Plasmapheresis in a patient with chronic migraine and myasthenia gravis: a case-report of an effective treatment

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Background: Anti-calcitonin-gene-related-peptide (CGRP) antibodies are novel drugs used to treat patients with episodic/chronic migraine (EM/CM) and with no therapeutic response or contraindications of >3 preventive medications such as beta-blockers, antiepileptics, onabotulinumtoxinA, tricyclic antidepressants. We describe a subject suffering from CM and generalized myasthenia gravis (MG), treated with both Fremanezumab and Plasmapheresis (PEX). This case outlines that PEX sessions do not limit the efficacy of the anti-CGRP antibodies.

Methods: We selected patients diagnosed with MG treated with PEX and concomitant CM requiring anti-CGRP antibodies.

Results: We selected a 57-years-old lady suffering from generalized MG and CM; homozygote mutation in MTHFR-gene was also reported.
She was diagnosed with MG in 2012; anti-Ach-Receptor antibodies were detected and thoracic CT was normal. Steroids were progressively stopped due to low benefit and side effects. Due to disease progression, Azathioprine was started, but stopped later due to laboratory test abnormalities. Intravenous immunoglobulin were not administered considering the risk of venous thrombosis in MTHFR-gene-mutation carriers. Since 2015 she is treated with periodic PEX sessions every two months; she also takes Pyridostigmine every 4 hours and Pyridostigmine Retard in the evening.
She also suffered from menstrual migraine with visual aura from her youth. Rizatriptan was useful during attacks. Brain MRI was normal.
In 2020 she noted an increasing frequency in her migraine attacks (> 16 die/month) of medium-high intensity. Rizatriptan, NSAIDs and Paracetamol (20 times/month) were not useful. Prevention with Amitriptyline and Topiramate provided no benefits. B-blockers and OnabotulinumtoxinA were contraindicated in MG.
On March 2022, Fremanezumab 225 mg q.m. was started. After a month, she noted an important benefit with only 5-6 attacks/month requiring no other symptomatic drugs. During this 5-month-long follow-up period, she did not report side effects.

Conclusion: Fremanezumab is a safe and secure medication for patients with CM, while PEX is an effective therapy in MG muscular crises. Although PEX removes serum proteins reducing the efficacy of anti-CGRP antibodies, administrations at adequate time intervals can preserve the efficacy and clinical benefit of both treatments. To our knowledge, this is the first reported case of simultaneous treatment with Fremanezumab and PEX with proven efficacy.

Influence of disability and impact of headache on somatosensory electrocortical responses in patients with medication-overuse headache

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Objectives: Migraine is one of the most disabling neurological diseases, mostly affecting patients in their working age. Medication overuse is a frequent cause of chronic evolvement of migraine. In patients with medication-overuse headache (MOH) a plastic change in cortical somatosensory responses occurs as well as a worsening of disability. It is not yet known the exact connection between functional brain changes and disability in patients with MOH.

Material and methods: We prospectively enrolled 18 MOH patients who completed the Migraine Disability Assessment (MIDAS) questionnaire - the most frequently used questionnaire to assess migraine-related disability -, the Headache Impact Test (HIT-6) - measuring the adverse impact of headache on multiple domains -, and the 12-item Allodynia Symptom Checklist (ASC-12). The same patients underwent a recording of somatosensory evoked potentials (SSEPs) from median nerve stimulation at the wrist. We studied N20-P25 amplitude and habituation as well as high frequency oscillations (HFO) that most directly reflect thalamo-cortical (early) and primarily cortical (late HFO) activation.

Results: In patients with MOH, a higher HIT-6 correlated with a more pronounced habituation deficit ($r=0.519$, $p=0.027$), and a higher ASC-12 ($r=0.729$, $p=0.017$). Furthermore, a higher ASC-12 correlated with a higher late amplitude HFOs ($r=0.676$, $p=0.032$). Electrophysiological responses did not correlate with MIDAS scale score.

Conclusion: Our data show that habituation deficit and high-frequency cortical oscillatory activity of SSEPs may be biomarkers of the impact of headache in daily life and of its associated symptoms.

The effect of therapeutic neuroscience education on clinical characteristics and neurophysiological findings in chronic migraine patients: a feasibility study

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Background: Chronic migraine is the most severe and debilitating migraine form, and despite the novel pharmacological options, still a high proportion of these patients have not reached an improvement in quality of life. For this reason, in recent years there has been an increasing interest towards non-pharmacological therapies, and more than 50% of migraine patients report their use in the management of migraine symptoms. Therapeutic Neuroscience Education (TNE) is an educational approach, aimed at improving knowledge about pain mechanisms, changing wrong beliefs and attitudes, improving coping strategies, with the final goal of improving quality of life.

Methods: Seven chronic migraine patients participated to the present study, in which the goal was to assess the feasibility of a program of TNE in this population. All included patients underwent a clinical, neurophysiological, and somatosensory assessment before entering into a program of TNE for 10 weeks, and then the assessment was replicated in the middle of the TNE program (neurophysiological and somatosensory assessment), and at the end of the TNE program clinical data was collected again. We hypothesized that a TNE program in chronic migraine patients may be feasible and have a positive clinical effect, and that the neurophysiological changes will anticipate clinical improvement, and may then act as biomarkers useful to predict the efficacy of the treatment before the end of the treatment itself.

Results: Patients showed a significant reduction ($p=0.01$) in the number of migraine days per month, and an overall significant reduction of migraine-related disability ($p=0.01$). Neurophysiological assessment showed a general tendency of improvement, with a significant change in nociceptive blink reflex (nBR) ($p=0.04$), and important change in intensity-dependence of auditory evoked potentials (IDAP) ($p=0.06$). Also wind-up ratio (WUR), a somatosensory evaluation, showed a significant change ($p=0.01$) from baseline values.

Conclusion: The results of the present study showed that administering a TNE program in chronic migraine patients is feasible and promising, with no dropouts despite the long protocol. Further, it may help clinicians in addressing a complex condition like chronic migraine, targeting cognitive and lifestyle aspects in order to obtain a clinical benefit.

Trigeminocervical pain sensitivity during the migraine cycle depends on headache frequency

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Background: This study aimed to assess if pain sensitivity in the four phases of the migraine cycle differed between LFEM, HFEM, CM, and healthy controls.

Methods: This was a multicenter, cross-sectional, observational study. Clinical characteristics (diary and time from the last and to the next headache attack), and quantitative sensory tests (QST) (Wind-up pain ratio (WUR), mechanical pinprick pain threshold (MPT), static pressure pain threshold (sPPT) from the trigeminal area and from the upper cervical spine) were recorded. LFEM and HFEM were assessed separately in each migraine phase (ictal, postictal, interictal, preictal) and compared vs. 1) each other's, matched for the phase; 2) CM (ictal LFEM and HFEM were compared vs. ictal CM, while postictal, interictal, preictal LFEM and HFEM were compared vs interictal CM); 3) control. A Bonferroni corrected p-value of 0.017 was used for between-group differences.

Results: A total of 56 controls, 32 CM, 105 LFEM, and 74 HFEM were included. No differences in QST parameters were observed in any phases between LFEM and HFEM. When compared to controls, interictal HFEM had lower trigeminal MPT ($p=0.012$); preictal HFEM had lower trigeminal MPT ($p=0.002$) and lower upper cervical sPPT ($p=0.014$); ictal HFEM had lower trigeminal MPT ($p<0.001$), trigeminal ($p=0.002$) and upper cervical ($p=0.009$) sPPTs, and higher trigeminal WUR ($p=0.002$); postictal HFEM had lower trigeminal MPT ($p=0.001$), trigeminal ($p=0.004$) and upper cervical ($p=0.010$) sPPTs. No differences were observed between HFEM and CM. When compared to controls, interictal LFEM had lower trigeminal MPT ($p<0.001$) and trigeminal ($p=0.002$) and upper cervical ($p=0.016$) sPPTs; preictal LFEM had lower trigeminal MPT ($p=0.003$) and upper cervical sPPT ($p=0.014$); ictal LFEM had lower trigeminal MPT ($p=0.006$); postictal LFEM had lower trigeminal MPT ($p<0.001$) and upper cervical sPPT ($p=0.006$). Ictal LFEM had also higher trigeminal ($p=0.013$) and upper cervical ($p=0.012$) sPPTs when compared to CM.

Conclusion: The results of this study suggested that HFEM patients have a sensory profile matching CM more than to LFEM. When assessing pain sensitivity in migraine populations the timing with respect to headache attacks are of utmost importance and can explain the inconsistency in data reported in the literature.

Ability of a set of trunk acceleration-derived gait indexes to characterize gait imbalance in subjects with migraine

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Background: Subjects suffering from migraine experience static and dynamic balance impairment, which leads to a reduction in anticipatory postural adjustments and an increased risk of falling. The aims of this study were: (i) to assess the ability of 16 gait stability indexes to identify gait instability in subjects with episodic migraine without aura (MO) regardless of age and gait speed and (ii) to investigate their correlations with clinical and kinematic variables.

Methods: Twenty-three walking trials from subjects with MO and 23 age, gender, and gait speed matched healthy subjects (HS) were acquired using a single lumbar-mounted inertial measurement unit. The harmonic ratios, percent recurrence, percent determinism (RQAdet), coefficient of variation, normalized jerk scores, and maximal Lyapunov's exponents for short time series (LLE) were calculated based on trunk acceleration patterns in the anteroposterior (AP), medio-lateral (ML), and vertical (V) directions. Independent sample t-tests, Cohen's d, the area under the receiver operating characteristic curves, and partial Pearson's correlation coefficients between clinical scales and gait parameters excluding the effects of gait speed were calculated.

Results: LLE_{ML} values ≥ 1.04, LLE_{V} values ≥ 1.06, and RQA_{detAP} values ≥ 96.32 characterized MO with 78%, 70%, and 75% probabilities, respectively, regardless of gait speed. LLE_{ML} correlated with the duration of the migraine attacks ($r = 0.48$, $p = 0.01$), VAS ($r = 0.42$, $p = 0.02$), Migraine Disability Assessment Score ($r = 0.38$, $p = 0.03$), Dizziness Handicap Inventory scores ($r = 0.44$, $p = 0.04$). LLE_{V} correlated with Allodynia Symptoms Checklist scores ($r = 0.46$, $p = 0.01$) and pain intensity ($r = 0.42$, $p = 0.02$). RQA_{detAP} correlated with the Activities Balance Confidence scale scores ($r = -0.40$, $p = 0.03$).

Conclusion: LLE can capture the subtle gait imbalance experienced by MO, reflecting a loss of local dynamic stability in ML and V directions, and a reduced ability to respond adequately to small perturbations during gait. As a result of their perceived imbalance, MO increase their gait regularity, particularly in the AP direction, as evidenced by higher RQAdet when compared to HS.

Are patients with resistant or refractory migraine also resistant to acute medication? A cross-sectional study

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Backgrounds: The terms “resistant” and “refractory” identify patients who do not respond to preventive medication. However, it is common experience in headache centers that patients may have multiple failures of acute medication. We evaluated the response to acute migraine medication, their frequency of use, and treatment satisfaction in patients with resistant or refractory migraine (Res/Ref) compared with those with non-resistant, non-refractory migraine (Nres/Nref).

Methods: We included consecutive patients with Res/Ref referring to the Headache Center of Avezzano-L’Aquila, Italy, from March to June 2022; patients were matched by age with a group of patients with Nres/Nref. We assessed demographics, medical history, and history of medication overuse in each patient. We assessed the number of symptomatic drugs taken in the last three months, both overall and by class (non-steroidal anti-inflammatory drugs – NSAIDs and triptans), their relief and patient satisfaction with acute treatment based on questions 5-6-7 of the Headache Under-Response to Treatment (HURT).

Results: We included 50 patients (84% women) with a median age of 49 years (interquartile range – IQR, 40-54) and a median age at migraine onset of 18 (IQR 13-26) years. Twenty-three patients (46%) had Res/Ref and 27 (54%) Nres/Nref. Patients with Res/Ref had a non-significant but clinically relevant higher prevalence of medication overuse history (47.8% vs 18.5%; p=0.056) and used more triptans (4 vs 0 median monthly intakes, p=0.042) than those with Nres/Nref. NSAID use did not differ (4 vs 5 median monthly intakes, p=0.269) between the two groups. Pain relief with NSAIDs (50.0% vs 73.9%; p=0.184) and with triptans (58.3% vs 75.0%; p=0.774) was comparable between the two groups, with a trend towards lower efficacy in the Res/Ref group. With the HURT questionnaire, Res/Ref patients reported feeling less control over their headaches than Nres/Nref (8.7% vs 51.8%; p=0.012), while the reported efficacy of a single dose of drug and fear of adverse events did not differ.

Conclusion: Our data show that Res/Ref patients have unmet needs not only for preventive, but also for acute migraine treatment. Patients with Res/Ref could be the target not only for novel preventatives, but also for novel acute migraine treatments.

Vestibular signs in experimentally induced migraine attacks: a post-hoc, exploratory analysis

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Background: Vestibular migraine (VM) as defined in the ICHD-3 represents one of the most common vestibular syndromes, although its pathophysiology is not fully understood. The acute phase of VM is characterized by transitory oculo-vestibular signs (OVSs) that usually disappear outside of the VM attack. The difficulty in studying spontaneous migraine attacks led to inconsistent results, and we believe that the adoption of human migraine models can help overcome this issue.

Methods: In this post-hoc analysis, we investigated the incidence of OVSs during experimentally induced migraine attacks in 24 episodic migraine patients without VM and 19 healthy controls exposed to sublingual nitroglycerin (NTG 0.9 mg). A comprehensive oculo-vestibular examination was performed at baseline, at migraine-like onset and before hospital discharge (180 minutes after NTG).

Results: Sixteen out of the 24 migraine patients developed a migraine-like attack (66.7%). Three of them (12.5%) developed OVSs during the migraine-like attack. In line with previous results, we described a combination of central (down-beating nystagmus) and peripheral (bilateral deficit of vestibulo-ocular reflex) vestibular signs. Noteworthy, no patients with a negative induction test developed OVSs. No OVSs were detected in healthy subjects at any timepoints. Noteworthy, no subjects complained of vestibular symptoms throughout the study procedures.

Conclusion: Human migraine models may indeed be appropriate tools to evaluate the vestibular dysfunction in migraine and in VM under well-controlled experimental conditions. The present findings represent a starting point to design future ad hoc and well-powered studies to further our knowledge on this topic.

Variability of the cost of antimigraine drugs across different regions of the world. A comparative burgernomics analysis

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Background: Drug prices are quite variable around the world. Here we evaluated the cost of representative antimigraine drugs in several countries with different health systems and reimbursement policies to analyse the variability of the power of purchasing antimigraine drugs in different regions of the world.

Methods: We adopted the Big Mac Index (BMI) as a purchasing power index. BMI was proposed by The Economist in 1986 following the notion that exchange rates should move towards the rate that would equalise the prices of an identical basket of goods and services (in this case, a burger) in any two countries.
We extracted drug prices of generic sumatriptan 50 mg 1 tab, generic topiramate 50 mg 60 tab packaging, and erenumab 70 mg 1 dose from available public registries and private databases. We obtained prices from 11 countries (USA, Argentina, Australia, Brazil, Canada, Denmark, Italy, South Africa, Spain, Sweden and Switzerland), converted them in US Dollar (ECB exchange rate of 19 August 2022) and then calculated the Big Mac Index (BMI) of drugs as the number of how many Big Macs would be needed (burger equivalent) to buy 1 tab of sumatriptan, 1 package of topiramate and a 70-mg dose of erenumab in the different countries.

Results: The burger equivalent for sumatriptan 1 tab is <1 in Australia, Denmark, Switzerland, Brazil, Italy, Spain and Sweden (range varying from 0.18 to 0.99), >1 in US, Argentina and South Africa (range 1.33-1.73). For one package of topiramate the burger equivalent ranges from 2.92 (Sweden) to 12.3 (South Africa). Definitely more ample is the range of the indicator for erenumab, with a minimum of 66.3 in Sweden and a maximum of 163.6 in Argentina.

Conclusion: These findings suggest a quite ample variability of purchasing power for antimigraine drugs across different regions of the world. The WHO Intersectoral Global Action Plan, approved earlier this year, aims at reducing the burden of neurological diseases worldwide by year 2031. One important step in this global plan is the attention to the equity of drug prices in relation to the purchasing power of individual countries.

Idiopathic non-dental facial pain syndromes in children

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Background: The orofacial pain syndromes (OFPs) are a heterogeneous group of syndromes characterized by painful attacks involving the orofacial structures. Following the International Classification of Orofacial Pain (ICOP) they primarily are divided into six groups: OFP attributed to disorders of dentoalveolar and anatomically related structures, myofascial orofacial pain, temporomandibular joint (TMJ) pain, OFP attributed to lesion or disease of the cranial nerves, OFP resembling presentations of primary headaches and idiopathic OFP. The last three groups most frequently come to the attention of neurologists and child neuropsychiatrists. They are often a clinical challenge. Our aim was to describe a clinical paediatric series.

Methods: We retrospectively collected the children's charts admitted to our headache centers (Bari, Palermo, Torino) from 2017 to 2021. Our inclusion criterion was the presence of a pain that occurs "below the orbitomeatal line, anterior to the pinnae and above the neck" following the 3rd ICDH and exclusion criteria were pain included in the first three groups of ICOP and pain syndromes due to the secondary etiologies.

Results: Our sample was composed of 42 subjects (22/20 M/F, in range age 5-17). By ICOP we classified them in: 23 primary headaches involving the facial topography, 2 facial TACs, 1 facial primary stabbing headache, 1 facial linear headache, 6 trochlear migraine, 3 red ear syndrome and 6 atypical facial pain. All patients described a debilitating pain for intensity (moderate/severe), 30 children had episodic attacks and 12 had continuous pain. Almost all received drugs for acute treatment (less than 50% were satisfied), some received non pharmacological treatment, associated with drug therapy.

Conclusion: OFP, although rare in paediatric age, exists and it can be debilitating if unrecognized and untreated, affecting psychophysical well-being of young patients. To our knowledge, this is the first study on a large paediatric OFP series. We underline the specific characteristics of the disorder for the purpose of a more correct and earlier identification during the diagnostic process, already difficult in paediatric age, and to define approach and possible treatment to prevent negative outcomes in adulthood.

Migraine aura and anti- CGRP targeted therapy: an observational case series study

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Background: Monoclonal antibodies blocking calcitonin gene-related peptide or its receptor (anti-CGRP mAbs) are clearly established as the disease-specific preventive treatment for both episodic and chronic migraine. However, poor clinical evidence is available on the potential efficacy of anti-CGRP mAbs for preventive treatment of migraine with aura. The present observational study is aimed to verify the changes in frequency of migraine aura attacks due to anti-CGRP mAbs treatment over one year.

Methods: We retrospectively collected data of twelve migraine patients diagnosed with both migraine with and without aura attending the Headache Centre of the Neurological Clinic of the University of Perugia. Seven were treated for one year with erenumab, two with fremanezumab and three with galcanezumab. Clinical parameters were recorded for each patient at baseline and at each trimester of treatment during one year treatment period, including the number of headache and migraine days/month, number of days with acute drug intake/month, number and characteristics of aura episodes, the scores of Migraine Disability Assessment (MIDAS) and those of Headache Impact Test-6 (HIT-6).

Results: Anti-CGRP mAbs induced a significant decrease in mean headache and migraine without aura days per months, number of days with medication intake, MIDAS and HIT-6 scores ($p<0.0001$). Conversely, they did not influence the frequency of migraine with aura attacks, but they produced a reduction in intensity and duration of headache phases of migraine aura. In addition, patients experienced aura attacks without headache more frequently.

Conclusion: Based on our findings we can postulate that anti-CGRP mAbs are not able to influence neuronal and vascular events related to cortical spreading depression (CSD) considered the pathophysiological substrate of aura, but they can counteract, via their peripheral mechanism of action, the sensitization of trigeminovascular pathway consequent to CSD, and this can explain why migraine aura attacks are unchanged in frequency in our patients, but headache phase is reduced or abolished.

Galcanezumab in unremitting subtype of Hemicrania Continua: a case report

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Introduction: Hemicrania Continua (HC) is a rare disorder belonging to trigeminal autonomic cephalalgias (TACs), together with Cluster Headache and SUNCT. Recent studies have shown that HC shares pathophysiological mechanisms with migraine, in particular the activation of the trigeminal vascular system and the CGRP signaling pathway. Anti-CGRP (R) mAbs are the first specific therapy for episodic and chronic migraine; in particular, Galcanezumab has shown efficacy also in episodic cluster headache patients, but not enough data are available about its use in HC.
We report a woman with a resistant HC, responding to treatment off-label with Galcanezumab.

Case Report: 28-year-old woman with diagnosis of HC in 2019, unremitting subtype, according to ICHD-3 criteria. The patient failed several prophylaxes (Amitriptyline, Topiramate, Gabapentin and Propranolol). A partial and transient response was obtained with Flunarizine, but with low tolerability and significant weigh gain. She was treated with Indomethacin 50 mg daily for 2 weeks and then with Etoricoxib 90 mg daily during the menstruation days, every month. In consideration of long term coxib treatment toxicity (increased risk of ischemic heart disease), partial resistance to canonic treatment and great disability provoked by continuous pain, we decided to administer Galcanezumab. On March 1st she received an initial dose of 240 mg and then 120 mg monthly. At 3 months follow-up she reported a progressive improvement, with only 2 headache episodes in the last month.

Discussion: This case shows that Galcanezumab and maybe the other anti-CGRP drugs can be used in TACs prophylaxis, as well as migraine, considering that CGRP is one of the main molecules implicated in pain genesis. Moreover, these drugs have shown low side effects unlike traditional medication used for prevention of primary headaches (both migraine and TACs). Galcanezumab efficacy has been demonstrated in Cluster Headache, at a higher dose than migraine; in literature we found one case of SUNCT and HC responsive to galcanezumab treatment.

Conclusion: This case confirms the hypothesis that CGRP plays a key role in TACs and further studies are needed to clarify if anti-CGRP drugs can be used routinely in HC prophylaxis.

A 9-years-old girl with a recurrent unilateral head pain in a line-shaped area: a new case of linear headache?

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Background: Linear Headache (LH) has recently been described as a paroxysmal or continuous fixed head pain restricted to a linear trajectory of 5–10 mm in width, linking one endpoint in occipital or occipitocervical region with another endpoint in ipsilateral nasion or forehead region (Lu et al 2016). We describe a case of a young girl with a headache circumscribed in a line-shaped anterior area but not confined to the territory of one nerve. To our knowledge, this could be the first case of this underdescribed type of headache in childhood.

Case report: A 9-year-old girl with recurrent pain in a linear area from the wing of the nose to the right ear. She always reports pain on the same side, with gradual onset, rarely associated with nausea, phono- and photophobia. Paroxysms are stabbing, with throbbing pain and strong intensity. During the interictal phase, she complains of a persistent sensation of discomfort, burning quality. Frequency of headache is not regular, varying in duration from a few minutes to 2-3 days. The girl rarely reported sensitivity when brushing teeth. We prescribed symptomatic treatment for painful attacks with ibuprofen (10 mg/kg) and preventive therapy with carbamazepine 300 mg/die with progressive benefits for two months. Neurological and odontostomatological examinations were normal. Cranium magnetic resonance imaging (MRI) did not report any intracranial abnormalities.

Discussion: The clinical features of this headache resemble other extremely rare pediatric headaches but present important differences. The absence of autonomic signs and duration may contribute to exclude SUNCT or other TACs. The duration and localization of pain could further exclude Epicrania fugax. The characteristics of headache, especially pain location, duration, and absence of autonomic ipsilateral signs, could rule out cluster headache. The clinical characteristics satisfy the previous delineated criteria for Linear Headache despite the atypical localization. However, the involvement of V2 branch trigeminal and the good response to carbamazepine, did not exclude trigeminal neuralgia. Finally, the presence of nausea, phono- and photophobia, frequency, duration and quality of pain is typical of a migraine attack.

Conclusion: Our case has clinical features that might be attributed to atypical facial pain like linear headache or trigeminal neuralgia.

Warning migraine and aura: Do they have a different underlying physiopathological process?

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Background: In a very small percentage of migraine patients, migraine attack is preceded by warning symptoms (sense of hunger, yawning, mood changes or anxiety, hyperosmia, etc). Warning migraine (WM) symptoms never evolve into neurological signs or symptoms typical of the migraine aura. Since Aurastop (a dietary supplement consisting of 5-htp - tanacetum-partenium - magnesium) has been proven effective in acute treatment of aura, if WM shares the same pathophysiology it may respond to the same treatment.

Methods: Twelve patients were selected at the hospital Istituto Clinico Città di Brescia based on WM symptoms present for at least 1 episode every 3 months. All patients (8 females and 4 males, average age 42 years, 25-58) met the diagnosis criteria for episodic migraine and were not in prophylactic therapy. We designed a cross clinical trial in which all patients received Aurastop for the first 3 months within 20 minutes of WM onset. For the following 3 months, the patients received the same formulation bid as in prevention therapy regardless of symptoms onset. All patients were provided with a diary where they could record migraine episodes (frequency, duration, and intensity) and WM symptoms. In addition, they were asked to express a degree of satisfaction from 0 to 10.

Results: After the first 3 months of using Aurastop for acute attacks, the total number of WM symptoms was 25 and the total number of migraine episodes was 225. We have observed a response rate of less than 50% for both duration and disability with an average satisfaction degree of 3/10. After the following 3 months of preventive therapy, the total number of WM symptoms was 4 and the total number of migraine episodes was 104 (a reduction of 84% and 54% respectively). The average satisfaction degree was 8/10.

Conclusion: From our pilot study emerges that the use of Aurastop is ineffective for WM symptoms in acute treatment. In contrast, preventive treatment resulted in a strong reduction in WM symptoms and a good reduction of migraine episodes. Considering that WM symptoms are closely related to migraine without aura and do not respond to Aurastop in acute, probably the two phenomena may underlie different pathophysiologic mechanisms.

Migraine and monoclonal antibodies: efficacy and safety in a real life study. A preliminary analysis

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Background: Migraine headache is the most common neurological disease in the population. In the past, different classes of drugs have been shown to be effective: antidepressants, calcium antagonists, beta blockers and antiepileptics. According to a greater understanding of migraine physiopathology, a new class of drugs has been approved in recent years. Gene-related calcitonin peptide (CGRP) inhibitors have shown high efficacy in both clinical trials and real-life studies. Although these drugs have a very high efficacy rate, in several studies non or partial responders are observed. A possible underlying cause could be anxiety-depressive comorbidity, often present in patients with chronic forms of migraine.

Methods: We conducted a prospective observational study at the hospital Istituto Clinico Città di Brescia. Patients received treatment with anti-CGRP monoclonal antibodies (MAbs) in migraine prevention, according to the supplier's datasheet. For each patient, Migraine Disability Assessment (MIDAS) and monthly migraine days (MMDs) were collected at several time-points: baseline (V0), 3 months (V3) and 12 months (V12). In addition, at V0, each patient underwent a standardized psychometric test using Minnesota Multiphasic Personality Inventory (MMPI).

Results: Forty-eight patients (62.5% female, 50.9 ± 13.0 years) were included. Five patients were lost at follow-up and 3 suspended for side effects or intolerance. At V3, in 40 patients (60.0% female, 49.9 ± 12.8 years), MMDs reduced by 9 days and MIDAS reduced significantly (both $p<.0001$); ≥50% response rate (RR) was 47.5%. At V12 in 34 patients (64.7% female, 50.1 ± 13.8 years), MMDs reduced by 13 days and MIDAS reduced significantly (both $p<.0001$), ≥50% RR was 70.6%. Among patients with a 25-50% RR, about 30% at V12, we observed a more frequent anxious-depressive profile emerging in the MMPI test compared to those with ≥50% RR ($p<.01$).

Conclusion: Our results are in line with the literature. MAbs have a high response rate and are well tolerated in migraine patients. Although further studies are necessary, results indicate that an anxious-depressive profile is more frequent in patients with a suboptimal RR. A multidisciplinary approach and adequate treatment of psychiatric comorbidities could reduce the rate of partial responses to anti-CGRP drugs.

Brain connectivity modifications induced by monoclonal antibodies targeting the CGRP pathway in migraine patients: a prospective HD-EEG, open-label, study

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Background: Monoclonal antibodies targeting the CGRP pathway (mAbs) proved effective and safe as migraine preventive treatment. Due to their molecular weight, mAbs act outside of the blood brain barrier, namely in the peripheral component of the trigeminovascular system. Nonetheless, a reduced sensitization of the first order neuron in the trigeminal ganglion may induce secondary effects at central level. Here we aim to study the changes induced by mAbs treatment in cortical brain connectivity recorded by means of high-density electroencephalography (HD-EEG).

Methods: We plan to perform 5 resting state HD-EEG recordings, at baseline (before mAbs treatment), and then every 3 months for one year. Here we present data regarding 16 migraine patients (age 44.7±10.6, 14 females, 11 with CM) who completed the first three months of mAbs treatment (T3). We aim to study the connectivity changes in the nodes of the default mode network (DMN): the right and left angular gyrus (RANG and LANG), the medial pre-frontal cortex (MPC) and the posterior cingulate cortex (PCC).

Results: At T3, mAbs treatment induced an inter-nodal connectivity reduction between MPC-PCC (p=0.025), MPC-LANG (p=0.020), MPC-RANG (p=0.043), and PCC-LANG (p=0.005). By contrast, the connectivity was enhanced between PCC-RANG (p=0.005) and LANG-RANG (p=0.003). At T3, 7 patients qualified as “Responder” to mAbs (reduction in monthly migraine days of at least 50% when compared to baseline). Responders were characterized by a baseline enhanced connectivity between MPC-PCC (p=0.042) and MPC-RANG (p=0.032), and by a reduced connectivity between LANG-RANG (p=.016).

Conclusion: We described brain connectivity modifications in the DMN of migraine patients after three months of mAbs treatment. We hypothesize that a reduced sensitization of the peripheral component of the trigeminovascular system may account for the observed findings. In addition, Responder patients showed a specific baseline brain connectivity pattern.

A new measure of migraine-related disability across the spectrum of migraine frequency

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Background: Previous data show that high-frequency episodic migraine (EM), carries a disability that is comparable to chronic migraine (CM) according to the Migraine Impact and Disability Assessment Scale (MIDAS) and to the Headache Impact Test (HIT-6) [1]. We recently developed an index to determine headache-related functional disability (HRFD) on patients' headache diaries without the need of disability questionnaires. We aimed to evaluate differences between the HRFD index and MIDAS and HIT-6 across the spectrum of migraine frequency.

Methods: In patients referring to our tertiary headache center, we computed a HRFD-index considering headache occurrence and associated disability level (from 1 to 3) reported on headache diaries during the last 90 days. We categorized patients, according to monthly headache days (MHDs), into: low frequency EM (LFEM, 1–9 MHDs), high frequency EM (HFEM, 10-14 MHDs) and CM (≥15 MHDs). We used Wilcoxon test to compare the median values of MIDAS, HIT-6 and HRFD among those three patient categories.

Results: We included 102 patients (85.3% women) with a median age of 41.5 years (interquartile range [IQR] 30.5-51) years; 9 patients (8.8%) had CM, 13 (12.6%) HFEM, and 80 (78.4%) LFEM. Median MIDAS values were 12, IQR 4-25 in LFEM; 24, IQR 3-70 in HFEM; and 34, IQR 25-100 in CM. HRFD index values were 8.7, IQR 4.7-11.9 in LFEM, 21.1, IQR 15.9-24.4 in HFEM, and 49.6, IQR 35.2-60.4 in CM; $p<0.001$. Median HIT-6 values were 62, IQR 57-65, in LFEM, 62, IQR 54-65 in HFEM, and 66, IQR 58-67 in CM. Median MIDAS score was significantly different between LFEM and CM ($p=0.004$), but not between LFEM and HFEM or between HFEM and CM; between groups comparisons were all significant ($p<0.001$) for HRFD index, while they were all not significant for HIT-6 scores.

Conclusion: The HRFD index, compared with other measures of migraine-related disability, was able to discriminate better the three categories of LFEM, HFEM, and CM, which are characterized by different migraine burden and might be managed differently. The new index might be suitable for the fine-tuned identification of unmet needs in patients with migraine, moreover it can be computed directly by patient diaries thus avoiding the recall bias of questionnaires.

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Non-neuronal TRPA1 encodes mechanical allodynia evoked by neurogenic inflammation and partial nerve injury in rats

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Background: The proalgesic transient receptor potential (TRP) ankyrin 1 (TRPA1) channel, expressed by a subpopulation of primary sensory neurons, has been implicated in various pain models in mice. However, evidence in rats indicates that TRPA1 conveys nociceptive signals elicited by channel agonists but not those associated with tissue inflammation or nerve injury. We explored the TRPA1 role in mechanical allodynia associated with neurogenic inflammation and moderate (partial sciatic nerve ligation, pSNL) or severe (chronic constriction injury, CCI) sciatic nerve injury in rats.

Methods: Acute nociception and mechanical hypersensitivity associated with neurogenic inflammation and sciatic nerve injury (pSNL and CCI) were investigated in rats after TRPA1 pharmacological blockade or genetic silencing, CGRP receptor antagonism. TRPA1 presence and function were analyzed in cultured rat Schwann cells.

Results: Hind paw mechanical allodynia (HPMA), but not acute nociception, evoked by local injection of the TRP vanilloid 1 (TRPV1) agonist, capsaicin, or the TRPA1 agonist, allyl isothiocyanate, was mediated by calcitonin gene related peptide (CGRP) released from peripheral nerve terminals. CGRP-evoked HPMA was sustained by a reactive oxygen species (ROS)-dependent TRPA1 activation, probably in Schwann cells. HPMA evoked by pSNL, but not that evoked by CCI, was mediated by ROS and TRPA1 without the involvement of CGRP.

Conclusion: As found in mice, TRPA1 mediates mechanical allodynia associated with neurogenic inflammation and moderate nerve injury in rats. The channel implication in mechanical hypersensitivity following inflammation and partial nerve damage is a common rodent feature and might be explored in humans.

Evaluation of cerebral vasoreactivity in migraine patients: a transcranial doppler study

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Background: Transcranial Doppler (TCD) is a non-invasive technique, and it can be widely applied for the study of variations of cerebral blood flow. The relationship between systemic endothelial dysfunction and migraine remains debated. Currently, there are several works that correlate with the hypothesis of vascular damage in migraine patients predicting a major probability of cardio and cerebrovascular diseases. The aim of the study was to assess variations of cerebral blood flow and variation of vasoreactivity in patients affected by episodic migraine compared to healthy controls.

Methods: We presented a prospective observational study carried out at the Neurological Clinic at the A.O. Santa Maria (Terni) from October 2021 to December 2021. This study collected data of 49 patients matched by sex and age. The characteristics of enrolled patients were as follows: 27 migraine patients and 22 healthy controls. All patients underwent a clinical examination; specifically, the headache characteristics were collected as well as migraine related disability (MIDAS) and HIT6 scores. They also underwent TCD exam. The following parameters were recorded: pulsatility index (IP), resistance index (IR), systolic speed peak (PSV), telediastolic velocity (VTD), mean velocities of internal carotid artery (ICA), middle (MCA), anterior (ACA) and posterior (PCA) cerebral arteries, vertebral artery (VA) and basilar artery (BA) of both sides. Vasoreactivity index (VI) of the right and left middle cerebral artery was calculated after Valsalva maneuver.

Results: Our study showed, in line with the literature, that the cerebral vasoreactivity measured at the level of the MCA in the interictal phase in migraine patients is lower than in healthy controls. A significant correlation was found between the VI of left and right MCA and the frequency of attacks, MIDAS and HIT6 scores. In fact, the vasoreactivity index is reduced in the presence of some parameters of greater severity of migraine. Higher is the gravity of migraine, greater will be the risk of vascular damage. Therefore, this concept underlines how it is important to start a prophylactic therapy in the case of severe forms of migraine: by improving migraine-related disability, vascular damage could also be reduced.

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Headache as main symptom of primary pseudotumor cerebri syndrome in children: a 5-year retrospective study

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Background: Pseudotumor cerebri syndrome (PTCS) is a rare condition of childhood caused by elevated cerebrospinal fluid (CSF) pressure with no evidence of intracranial mass nor hydrocephalus on neuroimaging, and normal CSF composition. If not treated, it can lead to visual loss. PTCS can be primary (idiopathic intracranial hypertension) or secondary, if a specific cause is recognized (i.e., drugs, abnormalities of the cerebral venous system, or predisposing systemic diseases). Diagnosis is made according to newly proposed Friedman criteria. The mainstay of treatment is acetazolamide, which allows to relieve symptoms and to avoid permanent visual loss when promptly started.

Methods: This retrospective single-center study included all the children aged 0-15 years diagnosed with primary PTCS at the Pediatric Emergency Department of the Regina Margherita Children Hospital of Turin, Italy, between January 2017 and December 2021. Descriptive analysis is reported.

Results: Twelve patients (8 females) were included; mean age at the onset was 9 years and 10 months (standard deviation: 3 years and 7 months); the youngest patient was a 7-month-old infant. Headache was reported by 11/12 patients, along with vomiting (8 patients; 66%), and back or neck pain (4 patients; 33%). Overweight was reported in 6 (50%) patients. Papilledema was observed in all patients and diplopia in 8 of them (66%). Six patients presented unilateral or bilateral VI nerve palsy, and one showed unilateral VII nerve palsy. In 5 patients, brain MRI showed at least one of the four neuroimaging criteria. No patient tested positive for COVID-19.
All patients were treated with acetazolamide (10 mg/kg/day). Symptoms, including headache, resolved in all patients in a median time of 5.5 days (range 1-21 days). Papilledema resolved in all patients and the treatment was discontinued after a median time of 99 days (range 36-272 days) without any complication.

Conclusion: Though primary PTCS is rare, it should be suspected when headache is associated with papilledema, as prompt diagnosis and treatment are fundamental to avoid visual loss. Accurate neurological examination by the emergency pediatrician is mandatory and drives multidisciplinary approach including ophthalmologist, neurologist and neuroradiologist.

The longitudinal modification of affective and fatigue symptoms in a cohort of migraineurs treated with anti-CGRP antibodies

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Background: The comorbidity between migraine and psychiatric disorders was extensively explored. The strongest association was described for depression and anxiety, which showed a bidirectional relationship with migraine. Less is known about fatigue and migraine. It was historically recognized as a dominant feature of migraine and seems to be correlated with symptoms of depression and headache intensity. Depression, anxiety, and fatigue are pivotal elements of migraine-related disability and disease progression. In addition, they may limit migraine traditional prophylaxis and require additional pharmacological and non-pharmacological strategies increasing the risk of treatment complications. Recently, monoclonal antibodies (mAb) directed against the calcitonin gene-related peptide (CGRP) (Eptinezumab, Fremanezumab, and Galcanezumab) or its receptor (CGRPR) (Erenumab) were approved for clinical use as prophylactic drugs for high frequency EM and CM. While the efficacy of anti-CGRP/R mAb on headache pain is well documented, the effect of these drugs on neuro-psychiatric symptoms associated with migraine is still poorly understood. The aim of our study was to evaluate the effects of anti-CGRP/R on comorbid symptoms of depression, anxiety, and fatigue in migraine patients resistant to traditional prophylaxis.

Methods: The study was an open-label prospective study assessing depression, anxiety, and fatigue comorbidities in patients with high frequency (HFEM) and chronic migraine (CM), with or without medication overuse headache (MOH), resistant to traditional prophylaxis and treated with anti-CGRP/R mAbs for 3 months.

Results: Forty-eight patients with HFEM (19%) or CM (81%) with or without MOH (56%) were enrolled. We identified 12 non-responders (25%) and 36 responders (75%), defined on the reduction ≥ 50% of headache frequency. The two groups were highly homogeneous, although non-responders were younger. Disease severity in terms of monthly frequency, migraine-correlated disability, and allodynia was reduced in both groups with different thresholds. However psychiatric comorbidities and fatigue were ameliorated only in responders. Peculiarly fatigue was unmodified in non-responders after 3 months of treatment.

Conclusion: The role of anti-CGRP/R drugs is not limited to the improvement of headache in migraine but may also affect depression, anxiety and fatigue. Fatigue seems to be specifically improved in patients with the best clinical outcome.

The effect of gender related stress in the family and work environment in migraine patients: a pilot study

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Background: Chronic pain conditions have a strong gender connotation, the most represented and disabling, mainly affecting the female sex throughout the lifespan. The complex factors of chronicity are favored by hormonal, genetic and psychopathological variables often related to social, work and relationship problems. In such a way, the never outdated issues of social and occupational distress that characterize the female gender give "gender pain" a broader meaning in the psychological, sociological and legal fields.
The present study aims to detect the impact of stress due to social, family and work conflicts in women and men with migraine.

Methods: An online survey was proposed by Italian migraine experts among patients diagnosed with migraine with aura, without aura, and chronic migraine (IHS2018).
The online survey included: demographic, socioeconomic, and sociodemographic features, BAI Beck Anxiety Inventory (Beck et al.), BPQ Body Perception Questionnaire (Porges), RSQ Romance Quality Scale, CTS Conflict Scale, ERQ Emotional Regulation Questionnaire (Italian Version Balzarotti et al.), PSS Perceived Stress Scale (S. Cohen), Work-Related Stress Scale, and Perception of Migraine Pain.

Results: Preliminary findings on migraine: The exploratory model shows that in women, the intensity of acute headache increases significantly with hyperattendance, whereas the hyperattendance condition appears to decrease the chronicity of headache. The alteration of body perception, related to somatization, appears to be significantly greater in migraine women than in men.

Conclusion: In migraine, there are gender-related differences in psychosocial dynamics, especially with regard to conflict in the partner relationship and work.

Phenotyping migraine patients according to clinical and psychophysical characteristics

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Background: This study aims to identify different phenotypes according to clinical and psychophysical characteristics in migraine patients.

Methods: This multicenter, cross-sectional, observational study was divided into two phases. Experiment 1 included migraine patients assessed during the interictal phases, and Experiment 2 included migraine patients assessed during the ictal and perictal phases. The following variables were assessed: 1) Clinical characteristics: headache frequency, intensity, and duration, use of drugs, headache disability index (HDI); 2) Psychophysical characteristics: a) Cervical musculoskeletal impairments: active range of motion (AROM) in flexion, extension, right/left lateral flexion, right/left rotation; flexion rotation test (FRT) (left/right/total); activation pressure score (APS); the number of active and latent myofascial trigger points (MTrPs) in head/neck muscles; the number of positive cervical vertebral segments (C1, C2) to passive accessory intervertebral movements (PAIVMs). b) Quantitative sensory testing (QST): mechanical pain threshold (MPT) and static pressure pain threshold (sPPT) over the trigeminal area; sPPT and dynamic PPT (dPPT) over the cervical area; sPPTs and MPT over the hand. Hierarchical clustering using the Ward method was performed to estimate the optimal number of clusters and the K-means cluster technique was used to determine the membership of the individual cases into the clusters. Differences across clusters were investigated with the ANOVA, or Kruskal Wallis test as appropriate.

Results:
Experiment 1
A total of 100 patients were included and three major clusters were identified. Cluster I (22 patients), Cluster II (42 patients), and Cluster III (36 patients). Cluster II had reduced headache frequency ($p=0.006$) and lower HDI ($p=0.018$) compared to Cluster I, and reduced headache frequency ($p=0.012$), lower usage of drugs ($p=0.027$), and lower HDI ($p=0.018$) compared to cluster III. Cluster III had lower AROM in all directions compared to Cluster I and II ($p<0.001$), reduced left and right FRT compared to Cluster II ($p<0.001$) and reduced left FRT ($p=0.010$) and APS ($p=0.003$) compared to Cluster I.
Cluster I showed reduced QST results in all tests compared to Cluster II ($p<0.036$) and reduced QST results ($p<0.036$) but not MPT over temporalis ($p=0.093$) compared to cluster III.
Experiment 2
A total of 101 patients were included and three major clusters were identified. Cluster I (10 patients), Cluster II (60 patients), and Cluster III (31 patients). Cluster I had reduced headache frequency ($p=0.018$) and intensity ($p=0.012$) compared to Cluster II, and reduced headache frequency ($p=0.003$), intensity ($p=0.042$), and lower HDI ($p=0.025$) compared to Cluster III. Cluster III had lower AROM and FRT in all directions ($p<0.001$) and lower APS compared to

Cluster II. Cluster III had lower AROM in flexion ($p=0.004$), extension ($p=0.007$), left ($p=0.033$) and right ($p<0.001$) lateral flexion, and right FRT ($p=0.024$) compared to Cluster I. Cluster I showed reduced QST results in all tests compared to Cluster II and Cluster III ($p<0.001$).

Conclusion: When assessing migraine patients in the interictal phase, three different migraine phenotypes could be identified according to clinical and psychophysical characteristics, with one group showing no psychophysical impairment, one increased pain sensitivity, and one increased pain sensitivity and cervical musculoskeletal impairments. These three clusters were also identified when assessing migraine patients in the ictal/pericta phase, supporting the external validity of this subgrouping approach.

The influence of small intestinal bacterial overgrowth (SIBO) in migraine

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Background: Serotonin has a leading role in migraine pathogenesis, its production is due to the assimilation in the small intestine of tryptophan, an essential amino acid.
In case of small intestinal bacterial overgrowth (SIBO), decreases availability of tryptophan in the brain to produce serotonin; moreover, they are find in urines bacterial metabolites of tryptophan digestion, namely indole (indicating fermentative dysbiosis) and skatole (indicating putrefactive dysbiosis). The aim of the study is to investigate the influence of these 2 tryptophan metabolites in a population of migraine patients comorbid with irritable bowel syndrome (IBS).

Methods: Ninety-two migraineurs comorbid with bowel disorders were referred to the gastroenterologist. Of these, 60 were diagnosed with IBS, and tested for urinary indole and skatole. According to values observed, dysbiosis was classified as absent, mild, moderate, or severe for each of the 2 metabolites. In addition, data were collected for each patient about the frequency of headache in the 30 days before the urine test was performed.

Results: Only 59 patients filled in the headache diary. Of these patients, 43 had an episodic migraine (EM; < 15 days/month) and 16 a chronic migraine (CM; ≥ 15 days/month). The mean number of migraine days/month was 12.64±7.26. According to indole: in 2 patients (2 EM) the dysbiosis was absent, in 15 was mild (15 EM), in 28 moderate (21 EM; 8 CM), in 14 severe (5 EM; 9 CM). According to skatole, 56 patients had absence of dysbiosis (40 EM; 16 CM), 2 had mild (2EM), 1 moderate (1 EM), none severe. By a univariate analysis of variance, indole emerged as a significant predictor of headache days ($F= 8.02$; $p<0.001$). In a binary logistic regression, only severe indole dysbiosis emerged as independent predictor for presence of CM ($p=0.017$; $OR= 0.185$; $CI=0.046 – 0.742$).

Conclusion: Indole seems to influence migraine frequency. Comorbidity with IBS in migraineurs should not be considered as a psychosomatic issue but rather as a probable SIBO, responsible for altered serotonergic homeostasis.

Prevalence and severity of long covid syndrome in patients with headache

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Background: Long covid (LC) is defined as the persistence or the onset of COVID-19 related symptoms after the nasopharyngeal swab negativization, not otherwise explainable by other medical condition. It has been observed that its prevalence varies according to the presence of other medical conditions. No data are available for patients with headache (PWH).

Methods: We collected data (demographics and headache clinical parameters, COVID-19 infection, vaccinal status, and LC presence and characteristics) by an online survey published on Italian and USA Facebook groups targeted at PWH. We also collected a non-headache control group among family members of patients.

Results: Three-hundred PWH (250 in Italy, 50 in USA) filled in the survey (164 developed the LC, 136 no); 90 controls (36 LC, 54 no). The difference between groups was significant (χ^2=5.96; p=0.015; OR=1.81). Among PWH we divided migraineurs (259; 156 developed LC, 103 no) from non-migraineurs (41; 8 developed LC, 33 no). Also in this case, the difference between groups was significant (Yates χ^2=22.07; p<0.001; OR=6.25). Finally, between the subgroup under migraine prevention with monoclonal antibodies (MAB) (50; 20 developed LC, 30 no) and not (209; 136 developed LC, 73 no), we also observed a difference (Yates χ^2=9.57; p=0.002; OR=0.36).

Conclusion: LC is more prevalent among migraineurs than controls, while anti-CGRP MAB seems to be protective. LC has a double nature, energetic and inflammatory: similarly, migraine is associated to a neuronal energetic impairment (accounting for LC higher prevalence) while MAB may reduce the inflammatory status of migraineurs, accounting for its protective effect.

Hyperexcitability and dysfunction of cortical excitation/inhibition mechanisms in migraine: a paired pulse TMS study

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Background: Paired-pulse TMS paradigms can be used to test connectivity within the primary motor cortex [1]. Aim of the study was to provide additional information on short intracortical inhibition (SICI) and intracortical facilitation (ICF) using different intensities of the test stimulus (TS) in episodic and chronic migraine (CM, EM) patients.

Methods: We enrolled 24 patients with EM, 13 with CM and 24 healthy subjects. EM and controls were randomly assigned to two groups for assessment of SICI and ICF. While in patients with CM we tested both ICF and SICI during the same experiment. We assessed SICI and ICF at three different suprathreshold intensities of the TS (110%, 130% and 150% of the resting motor threshold). Interstimulus intervals of 2 ms and 10 ms were used for testing SICI and ICF respectively [2].

Results: When testing ICF, maximum increase in conditioned MEP amplitude was observed in EM at the lower stimulation intensity of the TS ($p<0.005$). This intensity was indeed to induce significant facilitation in the CM and healthy subjects. No significant differences were observed as regards SICI.

Conclusion: Our results strengthen the notion of altered tuning of cortical excitability in migraine [3]. The increased ICF cannot be detected at higher stimulation intensities in EM probably due to the induction of homeostatic regulatory mechanisms of cortical excitability that could aim to protect against the risk of neuronal damage. CM have a greater cortical excitability than EM and the homeostatic regulatory mechanisms of cortical excitability are activated early, even at 110% of TS.

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Effectiveness and safety of CGRP-mAbs in menstrual related migraine: a real-world experience

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Background: Menstrual related hormonal fluctuations represent the most common migraine trigger. Menstrual migraine attacks are consistently referred as more disabling, less responsive to symptomatic treatments, longer in duration, and more prone to relapse than non-menstrual migraine attacks. Estrogen fluctuations are involved in migraine attacks worsening during the perimenstrual window through several mechanisms directly or indirectly involving the CGRP pathway. We evaluated whether mAbs blocking CGRP-ligand or receptor (CGRP-mAbs) could represent an effective and safety strategy for menstrual migraine attacks in patients with menstrual related migraine (MRM) with previous treatment failures.

Methods: Forty patients with MRM with at least three previous treatment failures received monthly CGRP-mAbs. At baseline and after six CGRP-mAbs administrations, patients underwent to extensive interviews to assess frequency, duration, intensity and responsiveness to painkillers intake of migraine attacks occurring during the perimenstrual window.

Results: After 6 administrations of CGRP-mAbs, we observed a reduction of menstrual migraine frequency (from 5 to 2 days per month), pain intensity (from 8/10 to 6/10) and attacks duration (from 24 hours to 8 hours) ($p<0.001$). Nevertheless, a significant increase in the percentage of responding to migraine painkillers was observed from 42.5% at baseline to 95% at T1 ($p<0.001$).

Conclusion: CGRP-mAbs could represent a safe and effective preventive therapeutic strategy able to reduce the disabling burden of menstrual migraine attacks frequency, duration, intensity and significantly improve the response to painkillers. These findings could be related to, and further indirectly prove, the greater influence of CGRP-mediated mechanisms in the pathophysiology of menstrual migraine attacks.

Does symptomatic treatment help children and adolescents with chronic migraine?

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Background: Chronic migraine (CM) is defined in the third edition of the International Classification of Headache Disorders (ICHD-3) as the presence of headaches on 15 days or more in a month, at least 8 days showing the migraine phenotype, for more than 3 months. CM affects from 0.6% to 1.8% of children and adolescents and determines a decrease of the quality of life. Aim of this study was to analyze the type of symptomatic drugs used and their efficacy for the treatment of acute migraine attacks in pediatric patients with CM.

Methods: We conducted a prospective study by selecting pediatric patients diagnosed with CM in our Department. We administered a questionnaire to the parents of all our pediatric patients with CM according to ICHD-3; questions were focused on symptomatic drugs used for acute migraine attacks and their effectiveness.

Results: For the final analysis we considered 91 patients with CM. Only two patients responded to the initial therapy with acetaminophen and only 31% improved with ibuprofen. Fifty-three percent of patients had relief with second-line NSAIDs drugs like ketoprofen, indomethacin, naproxen. Fifty-one percent of patients did not respond to more than three drugs and 16% were resistant to all acute treatments. All patients underwent prophylaxis therapy.

Conclusion: In our study we showed that the drugs for acute attack are not very effective in patients with CM and that some patients do not respond to any acute treatment.

Recurrent painful ophthalmoplegic neuropathy in adult: a case report

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Introduction: Recurrent painful ophthalmoplegic neuropathy (RPON), previously known as ophthalmoplegic migraine, is an uncommon condition characterized by recurrent unilateral headache attacks associated with ipsilateral ocular cranial nerve palsy, commonly the IIIrd. The onset is usually in childhood (median age of onset of 8 years).

Case Report: We present the case of a 30-year-old male with recurrent painful ophthalmoplegic neuropathy involving the III right cranial nerve. He experienced four episodes over 12 years characterized by right temporal headache followed 24 hours later by ptosis, mydriasis in the right eye, and double vision. Symptoms lasted for a period between a few weeks to 2 months with progressive improvement, but slight mydriasis remained in the right eye.
He performed multiple cerebral contrast-enhanced MRI showing a lesion suggestive for schwannoma of III right cranial nerve, later identified as partial volume effect. During the last episode, a cerebral MRI was performed showing a thickening of the III right cranial nerve in its proximal intracisternal part with post-contrast enhancement. Intracranial MRA was normal except for superior cerebellar arteries and right cerebral posterior artery running next to the III right cranial nerve, without clear conflict.
Cerebral MRI was repeated 20 days after the beginning of the last episode, with ongoing symptoms, showing the reduction in thickening and contrast enhancement of the III right cranial nerve without complete resolution.
The patient was treated with high dose corticosteroids with improvement in headache and oculomotor deficit. Pain was successfully managed with antiepileptic drugs (pregabalin). Analysis for myelin-associated glycoprotein, sulfatide, and ganglioside antibodies tested negative. Cerebrospinal fluid analysis was proposed to the patient who refused.

Conclusion: Recurrent painful ophthalmoplegic neuropathy typically presents during childhood although growing evidence has shown adult onset. Our case fulfilled the ICHD3 criteria for RPON and showed typical neuroradiological features. Corticosteroids were partially beneficial and antiepileptic drugs useful for pain control. Complete remission of symptoms is usual but residual deficit can be observed as in our case. Finally, neuroradiological follow-up is essential to rule out possible differential diagnosis, in particular an underlining cranial nerve schwannoma.

Real life data on Onabotulinumtoxin A for preventive pediatric chronic migraine

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Background: Chronic migraine affects 9% of pediatric populations. Diagnostic criteria are defined by the IHS, chronic migraine is defined by more than 15 headache days per month lasting more than 3 months. OnabotulinumtoxinA (OBT-A) is the only preventive treatment approved for chronic migraine in adults. To date only few trials and real life studies have focused on the use of OBT-A in pediatric age. The aim of this study is to demonstrate safety, tolerability and effectiveness of OBT-A in a cohort of pediatric chronic migrianeurs.

Methods: Thirty-six chronic migraine patients with first-line-oral-drug failures were enrolled at Headache Center at Bambino Gesù Children's Hospital and treated with OBT-A according to PREEMPT protocol (155 UI-195 UI in 31-39 sites of injection every 12 weeks) for at least 3 cycles. Twenty-six (72.2%) were females. Patients who experienced a reduction in monthly migraine days (MMD) > 50% were considered responders.

Results: Median age of patients was 14.42 ± 1.4 (12-16 years). Based on the presence of contraindications, all patients failed at least one oral drug treatment, of which the most used were amitriptyline (94.4%), topiramate (52.8%) and flunarizine (44.4%). Twenty patients received add-on oral drug with OBT-A. Percentage of responders was 36.7% after first injection, 70.8% after second, 66.7% after third. Patients who received 4 cycles (14) were responders in 71.4% of case. Only one patient discontinued for lack of tolerance. No differences in response to treatment based on gender ($p>0.05$), age ($p>0.05$), MMD before OBT-A treatment ($p>0.05$) and add-on ($p>0.05$). The best response to treatment was obtained in patients with a longer disease duration ($p<0.05$). No side effects were registered.

Conclusion: OBT-A is a safe, well-tolerate and effective treatment in pediatric chronic migraineurs starting from 12 years of age.

Pressure pain threshold in migraineurs treated with anti-CGRP monoclonal antibodies

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Introduction: In migraine, reduction of Pressure Pain Threshold (PPT) is related to peripheral sensitization.

Objectives: To study the neurophysiological effect of anti-CGRP monoclonal antibodies (mAbs) on PPT as modulation of peripheral sensitization in migraineurs.

Methods: We evaluated migraineurs without aura treated with anti-CGRP mAbs. All patients underwent a PPT analysis over craniofacial muscles according to the Andersen's standardized guidelines. Five muscles of the trigemino-cervical-complex and one far from this area were tested. PPT values of all muscles of each area were measured at baseline (t0) and after 3 (t1) and 4 (t2) months after the first injection of the anti-CGRP mAb. Data were compared with PPT in healthy controls. Data were analysed with GraphPad InStat 3.06.

Results: Twenty-two patients (11 migraineurs and 11 healthy controls, mean age 43±15, F=63.6%) were enrolled. Patients suffered from high-frequency episodic migraine (45.5%) or chronic migraine (54.5%). They were treated with erenumab 140 mg (63.6%), fremanezumab (27.3%) or galcanezumab (9.1%). All migraine outcomes improved at t1 and t2 (migraine days/month: 18.2±6.9 t0 vs 8±4.7 t1 vs 6.1±3.8 t2; severe hours/month: 28.1±40.7 t0 vs 1.6±2.9 t1 vs 3.7±5.6 t2; MIDAS: 100±25 t0 vs 21±15.4 t1). At t0, migraineurs showed a significant lower PPT respect to controls in all muscles, except in the left temporalis and procerus. At t1 and t2, PPT increased in all migraineurs' muscles.

Conclusion: PPT in cephalic and extra-cephalic muscles in high-frequency episodic migraine and chronic migraine are lower than healthy controls. Treatment with anti-CGRP mAbs normalizes migraineurs' PPT, that is related to the improvement of headache.

Persistent familial hemiplegic migraine without infarction: the first case studied with perfusion computed tomography

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Background: Familial Hemiplegic Migraine (FHM) is a rare genetic condition in which stroke-like symptoms accompany or follow migraine pain. They can be long-lasting and correlate with a prolonged migraine aura up to a week.

Objectives: Aim of this study was to analyse the first case of a 27-year-old male suffering from FHM with persistent (>1 week lasting) aura who performed a Perfusion Computed Tomography (PCT).

Results: Our patient suffered from migraine since he was 4 years old. Since he was 15, a right hemibody strength deficit and hypoesthesia starting about 15 minutes after the onset of pain and lasting up to 12 hours have been added. Seldom, speech and visual disturbances have also been present. The patient's sister was diagnosed at the Headache Centre as a case of FHM. In 2016 our patient went to the Emergency Room (ER) due to the onset of more severe motor symptoms. The neurological examination objectified a right sensorimotor hemiparesis with pyramidal signs. He performed blood chemistry tests, brain CT and perfusion CT (PCT) within 4.5 hours after the onset, while symptoms were still present. Blood tests and cerebral CT were normal. PCT maps of Mean Transit Time, Time To Pick, Cerebral Blood Volume and Cerebral Blood Flow evidenced no asymmetries between the different areas of the two brain hemispheres. In ER the symptoms partially improved and he was discharged with a diagnosis of migraine with aura. Motor weakness and hypoesthesia of the right limbs persisted for three months. He was evaluated at the Headache Centre of the University of Trieste and he was diagnosed as persistent FHM without infarction. He was treated with lamotrigine 50 mg bid for two months, then lamotrigine was replaced by valproic acid 300 mg bid because of suicidal ideation. The patient improved after one month of lamotrigine therapy and he reached the resolution of aura symptoms after two months of valproic acid treatment. Specific genetic analyses are still ongoing.

Conclusion: For the first time, we describe a case of persistent FHM without infarction. PCT performed during aura symptoms was normal. Lamotrigine and valproic acid were effective.

Therapeutic gain in switching from onabotulinumtoxin A to erenumab in multidrug-resistant chronic migraine with medication overuse

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Objectives: Aim of this study was to assess the therapeutic gain of a direct switch from onabotulinumtoxin A (BoNTA) to erenumab in multidrug-resistant chronic migraine with medication overuse not responding to BoNTA.

Methods: A 21-month prospective study of multidrug-resistant patients affected by chronic migraine with medication overuse not responding to BoNTA and shifting to erenumab was performed. Subjects received at least 4 different ineffective prophylaxes in the past. Three unsuccessful sessions of 195 U of BoNTA were carried out, then BoNTA was shifted to erenumab at the dosage of 70 mg at time 0 (T0), increasable to 140 mg after three months (T1) in case of unsatisfactory efficacy. After six (T2) and twelve months (T3) from the first administration of erenumab patients were re-evaluated. Subjects could not use other prophylactic drugs. Demographic data, previous ineffective prophylactic treatments, medications overused, response rate, headache days, headache duration, symptomatic drugs intake and MIDAS were analyzed with SPSS 24.0.

Results: We enrolled eleven patients (3 males, 8 females, mean age 44±11). Chronic migraine developed 3±1 years before. Subjects previously had used 7±1 ineffective migraine prophylaxes, most frequently being anticonvulsants (100% of cases) and calcium antagonists (91%). Triptans (63.6% of cases), analgesics combinations (18.2%), analgesics in association (9.1%) and non-steroidal anti-inflammatory drugs (9.1%) were symptomatic medications overused. Percentage of patients with a response of 50%, 75% and 100% were 54.6%, 18.2% and 9% respectively. All the headache outcomes (days of headache/month: 20±5 at T0, 7±6 at T3; attacks duration [hour]: 7±1 at T0, 4±2 at T3; symptomatic drugs/month: 23±7 at T0, 9±6 at T3; MIDAS: 95±38 at T0, 44±40 at T3) improved from T0 to T3. Out of the six patients responders, 3 switched from erenumab 70 to 140 mg with further improvement (days of headache/month: 12±6 at T1, 7±1 at T3; symptomatic drugs/month: 10±2 at T1, 7±2 at T3; MIDAS: 44±15 at T1, 31±8 at T3).

Conclusion: Multidrug-refractory chronic migraine with medication overuse not responding to BoNTA improve by switching from BoNTA to erenumab. Erenumab 140 mg was more effective than 70 mg.

Cannabidiol as a potential treatment for migraine: preliminary data in an animal model

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Background: Clinical and preclinical data have suggested a deregulation of the endocannabinoid system in migraine pain. Furthermore, modulation of this system may reduce trigeminal excitability. Cannabidiol (CBD), a phytocannabinoid devoid of psychoactive effects found in *Cannabis Sativa*, has recently gained much attention due to its antioxidant, anti-inflammatory and analgesic properties.

Aim: 1) To evaluate accumulation of CBD in cranial areas that are involved in migraine pain in rats treated chronically; 2) To test whether a single CBD administration reduces hyperalgesia in an animal model specific for migraine.

Methods: Four sets of male Sprague-Dawley rats (n=5 for each experimental group) received CBD 15 mg or 30 mg/kg for 5 consecutive days. Rats were sacrificed 1 h or 24 h after the last administration and the meninges, medulla, cervical spinal cord and trigeminal ganglia were quickly dissected out to evaluate CBD levels by online-SPE LC-MS/MS. In another set of rats (6-7 per group), we tested the effect of a single dose of CBD (15mg/Kg, i.p.) in the nitroglycerin (NTG)-based animal model of migraine. Rats were treated with CBD or its vehicle, 3 h after NTG or vehicle injection and were exposed to the orofacial formalin test 1h later.

Results: We found elevated levels of CBD in all areas under evaluation after chronic treatment. As expected, the levels were higher 1 h after the last treatments, than after 24 hours, thus suggesting that CBD does not accumulate in these tissues. Interestingly, the single acute administration of CBD significantly reduced NTG-induced trigeminal hyperalgesia.

Conclusion: These data offer key information on the distribution of CBD in the meninges and in central and peripheral nervous system areas involved in migraine pain. They also suggest the capability of the compound to modulate migraine-related nociceptive transmission.

Discontinuation after one-year of treatment with anti-CGRP antibodies did not provide long-term sustained response without therapy

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Background: The general recommendation indicates to discontinue treatment with oral preventive medication for migraine. Although there is no evidence to support this practice, most guidelines recommend a pause in the treatment with anti-calcitonin gene related protein (CGRP) pathway monoclonal antibodies monoclonal antibodies (mAbs) after 12 to 18 months of continuous treatment. The Italian Medicines Agency (*AIFA*) set a mandatory regulation to stop anti-CGRP mAbs administration after 12-months of treatment. Herein, we assess the long-term effects of discontinuation and retreatment of anti-CGRP mAbs in resistant chronic migraine (CM) patients.

Methods: In this monocentric prospective cohort study, we enrolled 53 severe (resistant to ≥3 preventive treatments) CM patients (96.2% with medication-overuse [MO]), treated with erenumab, galcanezumab or fremanezumab for 12-months, who discontinued and re-started the treatment. The primary outcome was the estimation of the sustained clinical response after six months of discontinuation. The clinical effectiveness was assessed using monthly migraine days (MMDs), response rates and acute medications use. Secondary outcomes were the evaluation of the effect of re-treatment up to three months, using the same parameters reported for the primary outcome.

Results: After 6 months of discontinuation only 8 patients (15.1%) achieved a sustained response without treatment. Most patients (34, 64.2%) had restarted treatment, mainly after the mandatory period of discontinuation (3 months). Patients with a sustained response compared to patients who restarted therapy showed less MMDs (10.6±7.8 vs 3.8±2.4, p=0.010) and days with analgesic use (9.8±7.7 vs 3.6 ±2.6, p=0.014) and lower MIDAS score (24.2±24.6 vs 7.8±16.3, p=0.001) at month-12 of treatment, respectively. Patients re-treated for 3 months (n=39, 73.5%), reported an amelioration in all outcome measures recovering a clinical response similar to that observed at the end of initial treatment. However, 6 patients (15.3%) did not show any amelioration during retreatment, and in one patient treatment was withdrawn.

Conclusion: Discontinuing treatment after 12 months did not provide long term benefits and appeared unnecessary in most patients. Two small subgroups of patients reported sustained benefit during discontinuation or, contrariwise, a worsening in MMDs during the second treatment cycle.

Switching OnabotulinumtoxinA and Monoclonal Antibodies Anti-CGRP in severe, drugs-resistant chronic migraine

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Background: Clinical evidence supported the use of topiramate and OnabotulinumtoxinA (BTX-A) as preventative treatment for chronic migraine (CM). More recently, anti-calcitonin gene relate peptide (CGRP) monoclonal antibodies (mAbs) have been approved for the treatment of CM. Whereas a comparison between topiramate and anti-CGRP mAbs has been performed a similar comparison between anti-CGRP mAbs and BTX-A is lacking, However, the challenging management of CM would benefit of additional information on BTX-A and anti-CGRP mAbs effectiveness. Herein, we assess the long-term therapeutic impact of anti-CGRP mAbs in severe, drugs-resistant patients with CM with no or partial response to BTX-A.

Methods: A retrospective, cohort study, enrolling 78 severe CM patients (>80% with medication-overuse [MO]), resistant to ≥3 preventative treatments, and treated with BTX and then with anti-CGRP mAbs. The study consisted of two observational periods of 9 months. A varying non-observational period of at least 6-months occurred after the last BTX treatment. The primary endpoints were the absolute change from baseline in monthly headache days (MHDs), response rates and persistence in MO at 3-, 6- and 9-months follow-up in the two cohorts separately. The secondary endpoint was the change in acute medications use per month (absolute number and days). Finally, we performed a last observation carried forward analysis for primary and secondary endpoints.

Results: After nine months of treatment, retention rate ranged from 91.0% to 62.2% in the BTX-A cohort and from 96.2%, to 76.9% in the anti-CGRP mAbs cohort. Approximatively 20% of patients discontinued both treatments due to inefficacy. After 9 months of treatment, 22.4% with BTX-A and 65.0% with anti-CGRP mAbs achieved a ≥50% response. Two patients were migraine-free in the CGRP cohort. BTX-A and anti-CGRP mAbs reduced MHDs at month-9 by -5.0 and -12.0, respectively, and decreased the number of MO patients at month-9 (75.5% and 25% persisted in MO, respectively). Only two patients discontinued treatments due to AEs.

Conclusion: Our findings in drugs-resistant CM patients indicate that patients who discontinued BTX-A undergoing anti-CGRP mAbs treatment showed a substantial clinical improvement in migraine related outcomes. Stopping BTX-A in patients with no response/partial response after the first two cycles and switching to an anti-CGRP mAb appears a viable option.

Periorbital nociception in a progressive multiple sclerosis mouse model is dependent on TRPA1 channel activation

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Background: The transient receptor potential ankyrin 1 (TRPA1) is involved in acute and chronic pain generation, and its activation is mediated by several exogenous and endogenous agonists such as hydrogen peroxide (H_2O_2) and 4-hydroxynonenal (4-HNE) that are increased in mouse and rat models of periorbital and facial nociception, such as migraine-like behaviour. TRPA1 activation leads to calcitonin gene-related peptide (CGRP) release, an endogenous compound related to headache development. Headache can be present in several pathologies, including progressive multiple sclerosis (PMS). Our purpose was to study the development of periorbital mechanical allodynia (PMA) in a PMS-EAE model and to explore the role of TRPA1 in this behaviour.

Methods: To induce PMS-EAE in mice, emulsion of MOG_{35-55} was administered by a subcutaneous (s.c.) injection in the flank region of female mice. Subsequently, all animals received a dose of 300 ng of pertussis toxin, which was re-administered 48 h after the induction. PMA was assessed on days 3, 5, 7, 9, 11, 13, and 14 after PMS-EAE induction. The modulation of PMA in PMS-EAE induced mice was tested in *Trpa1*$^{-/-}$ mice and after the administration of: 5-HT receptor agonist (sumatriptan), CGRP receptor antagonist (olcegepant), TRPA1 antagonists (A967079, HC-030031, metamizole and propyphenazone), the antioxidant α-lipoic acid and the NADPH oxidase (NOX) inhibitor apocynin.

Results: PMS-EAE-induced mice developed PMA from day 7 to 14 post-induction. *Trpa1*$^{-/-}$ mice showed a reduced PMA respect to wildtype mice, moreover the systemic administration of sumatriptan, olcegepant, TRPA1 antagonists were able to reduce PMA until 2 hours after administration. PMS-EAE-induced mice showed an increase in oxidative markers (4-HNE, H_2O_2) and NADPH oxidase activity in the trigeminal ganglia, and treatment with α-lipoic acid and apocynin was able to reduce PMA.

Conclusion: These results suggest that the generation of TRPA1 endogenous agonists in the PMS-EAE mouse model may sensitise TRPA1 in trigeminal nociceptors and release CGRP to elicit PMA. TRPA1 channel seems a valuable therapeutic target for PMS-EAE-induced PMA.

A case report of a MINOCA in a patient receiving erenumab and sumatriptan and a review of the current literature

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Background: Anti-calcitonin gene-related peptide (CGRP) antibodies, including erenumab, have recently come into use for migraine. We describe a case report of a myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) in a chronic migraineur treated with erenumab 140 mg and sumatriptan 100 mg. A 55-years-old man started erenumab in October 2021; he had a daily migraine with the use of 7 sumatriptans per day. After 6 months, he was hospitalized for acute chest pain with the subsequent cardiac MRI diagnosis of MINOCA. He was taking 4 sumatriptans daily. Erenumab and sumatriptan were immediately discontinued.
He had no risk factors for MINOCA. Several cases of MINOCA have already been described during triptan therapy and this side effect is indicated in their Summary of Product Characteristics. Nonetheless our patient had been overusing sumatriptan for several years without adverse events (AEs). Because CGRP can mediate vasodilation, its inhibition could theoretically attenuate compensatory vasodilation during ischemic conditions, but this mechanism is uncertain. Therefore, we ran a search.

Methods: A literature review using PubMed and clinicaltrials.gov was performed to highlight any clinical correlation between erenumab and MINOCA.

Results: In a pooled analysis of vascular safety in randomized clinical trials (RCT) of erenumab, AEs were adjudicated by an independent committee. Two patients had MI during open-label treatment. The authors concluded that there was no evidence of association between erenumab and vascular events; MIs that occurred could have had plausible alternative etiologies.
An exercise treadmill safety study in patients with chronic stable angina showed no aggravation of ischemia in erenumab patients vs placebo.
However, an analysis of spontaneous reports of AEs recorded by the Food and Drug Administration identified six cardiovascular disproportionality signals, including MI. Furthermore, we found a recent case report of MINOCA during erenumab.

Conclusion: Our case report is confusing due to the patient's abuse of triptans, and our literature search is not conclusive because, while RCT have shown that erenumab is safe, some “safety concerns” are emerging in the “real world”. However, as clinicians, we believe that caution should be exercised in prescribing anti-CGRP antibodies and that a robust post-marketing surveillance is required.

Influence of barometric pressure on the onset of a new period of cluster headache

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Background: A relationship between atmospheric variables and the onset of a new period of cluster headache (CH) has been rarely investigated.

Methods: Patients who received a diagnosis of CH according to the ICHD criteria between April 2004 and October 2021 were instructed to promptly contact the Headache Centre on the first day of a new active phase onset and the data were prospectively collected in their clinical sheet. CH was diagnosed in 161 among the 4411 outpatients who referred for a first evaluation: 144 subjects (m: 105, 72.9%; f: 39, 27.1%; ratio m/f: 2.7; average age at CH onset: 37.4±15.3; average age at first evaluation: 46.8±15.0) received the diagnosis of 3.1.1 *episodic CH* (n=117) or 3.1.2 *chronic CH* (n=13); 14 presented an isolated active phase and, therefore, a third-level diagnosis was hampered; 17 were excluded because of lack of information (n=13) or modified diagnosis in further controls (n=4). Data concerning the day of appearance of a new active phase, time of onset of the attacks within the cluster and clinical features of the crises were prospectively collected.

Results: The average barometric pressure (BP) values recorded on the first day of the attack of the last active phase of 123 episodic CH patients were considered: the values were divided according to the month of onset and then processed by calculating the average of the pressures of the month in question and standard deviation. The pressures most represented were in the ranges between 1012-1017.9 mbar (n=48) and 1018-1023 mbar (n=27). The high standard deviation values prevent the identification of a pressure range significantly correlated to the onset of the cluster, both in the comparison between months and within the same month. However, the daily recordings of BP showed a sinusal trend, with minimum value detected in two peaks (04:00 pm and 04:00 am), roughly corresponding to the peaks of onset of the attack in the series evaluated but with no statistical significance.

Conclusion: The relationship between the daily variation of the barometric pressure and the appearance of a new active phase or a single attack requires further studies on a larger number of cases.

Relationship between cluster headache and lunar phases: a prospective study

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Background: Since ancient times, the moon has been associated with some aspects of human life and several human pathologies, such as epilepsy or mental disorders. Despite modern scepticism, the possible effects of the moon on humans continue to obtain popular support. Episodic cluster headache (CH) is characterized by a typical pattern of the attacks, frequently with regular periodicity in the same patient and, therefore, could represents a good model to investigate the influence of lunar phases on the onset of new cluster periods.

Methods: Patients who received a diagnosis of CH according to the ICHD criteria between April 2004 and October 2021 were instructed to promptly contact the Headache Centre on the first day of a new active phase onset and the data were prospectively collected in their clinical sheet. CH was diagnosed in 161 among the 4411 outpatients who referred for a first evaluation: 144 subjects (m: 105, 72.9%; f: 39, 27.1%; ratio m/f: 2.7; average age at CH onset: 37.4±15.3; average age at first evaluation: 46.8±15.0) received the diagnosis of 3.1.1 *episodic CH* (n=117) and 3.1.2 *chronic CH* (n=13); 14 presented an isolated active phase and, therefore, a third-level diagnosis was hampered; 17 were excluded because of lack of information (n=13) or modified diagnosis in further controls (n=4). Data concerning the day of appearance of a new active phase, time of onset of the attacks within the cluster and clinical features of the crises were prospectively collected.

Results: In 123 cases the exact day of the onset of last cluster was defined with certainty, allowing to correlate it with the relative moon phase and the percentage of the disk illuminated. New cluster period most frequently occurred during the following phases: growing gibbous (n=27, 22.0%); waning (n=28; 22.8%); increasing (n=25, 20.3%), waning gibbous (n=21; 17.1%) and when the moon is illuminated for <10% (n=32, 26.0%) or >90% (n=25, 20.3%) of its surface. In both cases no statistical significance was reached.

Conclusion: There is no statistical evidence supporting a relationship between lunar phases or fraction of illuminated moon and the onset of cluster periods.

Ten years of follow-up in a sample of pediatric migrainous children admitted at an Emergency Department: preliminary reports

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Background: Despite its high prevalence, the clinical course of pediatric migraine is not clearly known and several studies may present conflicting results. We present the findings of a 10-year follow-up study involving children with severe migrainous pain admitted to our Emergency Department. Our aim was to determine the long-term outcome of severe migraine headaches for intensity and to identify possible predictors of prognosis.

Methods: Forty-eight of 80 subjects (60%) with migraine headaches (mean age 8 years with a range of 4-14 years, 50% females), who attended the baseline examination of a population admitted for headache to the Emergency Department in the first half of the year in 2012, were eligible for follow-up in 2022. We included in our study only patients diagnosed with migraine, according to the diagnostic criteria of the International Classification of Headaches. All were contacted by telephone and after a short informative interview and after acquiring informed consent, a semi-structured questionnaire was sent to them by email. The association between several possible prognostic factors and the long-term persistence of migraine headaches was explored using logistic regression analysis.

Results: Of the 48 subjects with migraine headaches at baseline, 31 (65%) had persistent migraine, 17 (35%) had experienced remission. The preliminary results showed that the presence of neurologic disorders in the parents and sleep disorders significantly predicted the 10-year persistence of migraine headaches ($p>0.01$).

Conclusion: Migraine in children has a favorable long-term prognosis at ten years of follow-up because about 35% resisted the attacks despite the severe attacks that led them to the emergency room. Familial neurological comorbidity and sleep disorders were unfavorable factors for predicting a good outcome. To our knowledge, this was the first study conducted on a selected paediatric population upon admission to the emergency room. Therefore, due to the increasingly frequent use of the Emergency Department for the management of severe hemicrania attacks, further long-term follow-up studies conducted on pediatric patients hospitalized in ED are needed. This would give us a better knowledge of the evolution of severe migraine disorders and therefore a better therapeutic management in the clinic.

Clinical phenotypes in migraine and in migraine chronicization: Principal component analysis in the Italian National Headache Registry (RICe)

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Background: The clinical heterogeneity of migraine has always raised the need of classification and identification of phenotypical subgroups to help the clinicians in the diagnostic-therapeutic process. This issue could be particularly important when considering chronic migraine (CM) and medication overuse headache (MOH) due to their high socio-economic impact. Migraine diagnostic criteria (ICHD-3) mainly focus on attack characteristics; the use of nationwide databases enables to refine the characterization of patient subgroups through a wider range of clinical and demographic features.

Methods: A principal component analysis (PCA) was performed on the clinical data of 1238 patients diagnosed with migraine with or without aura, CM or MOH and included in the Italian Registry of Headaches (RICe Study) between April 2020 and March 2021.

Results: Through PCA applied to categorical variables, we extracted 3 components: the first inversely correlated the diagnosis of CM and MOH with the presence of migraine diagnostic criteria, identifying a phenotype less attributable to the typical migraine presentation; the second directly correlated diagnostic categories (CM and MOH) with the migraine diagnostic features, describing a group of "typical" patients; the third one identified direct correlations between initial localization of pain and the presence of migraine characteristics such as worsening in case of physical activity, high pain intensity and allodynia. Considering the quantitative variables, 2 components were extracted: the first related to age, BMI and monthly migraine days (MMD); the second was strongly correlated with the level of pain intensity (NRS scale).

Conclusion: Some relevant clinical phenotypes were identified in a large migraine Italian population involved in the RICe Study. A group of patients suffering from CM or MOH would be less identifiable through the migraine diagnostic characteristics, resulting in problems of underdiagnosis or wrong diagnosis. Another group presents a significant association between BMI, age, and MMD, thus revealing possible risk factors for chronification. PCA emerges as a useful approach to handle large number of variables in migraine clinical research. Further studies are needed to evaluate the association between these phenotypes and other relevant characteristics, including the level of disability or the response to preventive and therapeutic interventions.

Neuropeptides modulation during monoclonal antibodies therapy in migraine: a pilot study investigating the role of CGRP, Orexin-A and PACAP

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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 a new era in preventive treatment of migraine. In particular, anti-CGRP (Fremanezumab and Galcanezumab) and anti-CGRP receptor (Erenumab) monoclonal antibodies (mAbs) represented the first validated and specific migraine prevention therapy. Post marketing efficacy data are accumulating worldwide but, at the same time, the neurobiological context of CGRP modulation and its relationship with clinical results was scarcely investigated.

Methods: This is a pilot study of CGRP, Orexin-A (OrxA) and PACAP plasmatic variations in relation with clinical outcome during "anti-CGRP" therapy. We enrolled fifty-five consecutive migraine patients (episodic or chronic) who were eligible for mAbs preventive treatment based on AIFA reimbursement criteria. Sixteen of them underwent plasmatic CGRP, OrxA and PACAP dosing at the start of treatment and after six months. A group of sixteen age and sex matched non migraineur volunteers was enrolled, the same blood sampling procedure was performed in this group. A comprehensive set of clinical and demographic data was collected at baseline and at three and six months follow-up in migraine patients.

Results: Treatment efficacy on both pain and functional outcome was confirmed: NRS, MIDAS, mean monthly migraine days (MMD) and migraine attack treatment use were significantly reduced after 6 months ($p<0.001$). OrxA emerged as an inverse independent predictor of clinical response (NRS, MIDAS, MMD and medication use; $p<0.05$ in multivariate analysis). Basal CGRP level inversely correlated with 6 months clinical outcome ($p<0.001$ in correlation with MMD, MIDAS and medication number reductions). Concerning comparison with control group, OrxA and PACAP levels were significantly higher in patients at baseline ($p<0.05$ and $p< 0.001$ respectively).

Conclusion: Though further studies are needed, this work deepens insights into neuropeptides modulation during anti-CGRP therapy in migraine patients. We suggest a possible association between OrxA and clinical outcomes even in the context of CGRP signaling inhibition while the role of baseline CGRP as a predictor of efficacy needs to be further investigated.

TRPA1: a key mediator of headache-related cephalic allodynia in a mouse model of relapsing–remitting multiple sclerosis

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Background: Multiple sclerosis (MS) is characterized by a chronic demyelinating and inflammatory process that results in several debilitating symptoms, including different types of pain. It has been reported that primary headaches are more frequent in patients with MS than in the general population. However, the underlying mechanisms that trigger or worsen headaches in MS patients are poorly understood. The transient receptor potential ankyrin 1 (TRPA1) is a pain detecting ion channel involved in different model of pain. It is activated by endogenous substances and by-products of oxidative stress (4-hydroxynonenal, 4-HNE, and hydrogen peroxide H_2O_2) which play a critical role in many neurodegenerative diseases, including MS. TRPA1 activation in primary sensory neurons evokes the peripheral release of the calcitonin gene–related peptide (CGRP), the primary mediator of migraine and headache. Here we evaluated the development of periorbital mechanical allodynia (PMA) in a relapsing–remitting multiple sclerosis (RR-EAE) model and the mechanisms involved in this nociceptive behaviour.

Methods: RR-EAE was induced by a subcutaneous injection of $MOG_{35–55}$ antigen mixed with Quillaja saponin solution in C57BL/6J female mice. The RR-EAE clinical signs were assessed once a week over an experimental period of 35 days. The modulation of PMA in RR-EAE induced mice was tested after the administration of: 5-HT receptor agonist (sumatriptan), CGRP receptor antagonist (olcegepant), TRPA1 antagonists (A967079, HC-030031), antioxidant (α-lipoic acid) and NADPH oxidase (NOX) inhibitor (apocynin).

Results: RR-EAE induced mice developed PMA (day 1-35). At day 35 after RR-EAE induction olcegepant and sumatriptan reduced PMA. Genetic deletion or pharmacological blockade of TRPA1 attenuated PMA associated with RR-EAE. The levels of oxidative stress biomarkers (4-HNE and H_2O_2) and superoxide dismutase and NOX activities were increased in the trigeminal ganglia of RR-EAE mice. The treatment with apocynin or a-lipoic acid attenuated PMA.

Conclusion: This study suggests a relationship between TRPA1 and the development of PMA in a mouse model of RR-EAE. TRPA1, presumably activated by endogenous oxidative stress, evokes release of CGRP from trigeminal neurons thus inducing PMA. These findings reveal TRPA1 as suitable therapeutic target for the development of new drugs in the treatment of headache symptoms in RR-MS patients.

Idiopathic non-dental facial pain syndromes: a clinical study

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Background: The orofacial pain syndromes (OFPs) are an heterogenous group of syndromes characterized by painful attacks localized in facial and oral structures. The International Classification of Orofacial Pain (ICOP), divides OFPs into six major groups. The first, the second and the third are disorders of dentoalveolar and anatomically related structures. The remaining groups (non-dental facial pain, NDFP) correspond to the cranial neuralgias, facial pain syndromes resembling the primary headache syndromes. They are often a clinical challenge because the symptoms may be very common with other disorders. Thus, the diagnostic path involves a complex algorithm, which includes several specialized tests. Our aim was to describe the difficulties encountered by these patients during the diagnostic-therapeutic pathway.

Methods: The study was based on the responses to a survey questionnaire that was administered to 346 patients (265 female and 81 male) affected by OFP using a free online tool, with the aim to determine pain characteristic and diagnostic-therapeutic care pathways. Male and female of 18 years and older who declared to be affected by OFP were included in this study. All the patients were member of a no-profit association.

Results: The population sample was subdivided in age range (18-35 ys: 17.2%; 36-55 ys: 55.0%; > 55 ys: 27.8%). Most of the patients declared to be affected by OFP for over 3 years. The sample presented one OFP diagnosis in 60% of cases, more than one in 36.2%, while 3.8% was not classified. The trigeminal neuralgia resulted more represented, followed by the cluster headaches and migraine. About 70% of patients did not have pain remission, showing a persisting background pain, autonomic cranial signs during the pain attack ranged between 45-65%. Subjects (70.9%) consulted at least two different specialists. Almost all received drug treatments, 26.1% received more than four drugs, but 39.7% remained unsatisfied and 50.8% received non pharmacological treatment, associated with drug therapy.

Conclusion: To our knowledge, this was the first study on a OFP population not selected by a third-level specialized center. This allowed a more real-life view of the suffering of orofacial pain subjects. Furthermore, the medical approach often resulted unsatisfied.

Italian multicenter study of acute headache in children under six years of age in the Emergency Departments: predictive red flags of life-threatening disease

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Background: Headache is one of the main neurological disorders causing admission to the pediatric emergency departments (ED). Age under 6 years (i.e. preschool-age) makes diagnosis challenging and is generally considered a "red flag" that requires neuroimaging, mainly computed tomography (CT). In this study we characterize preschool-age children with headache admitted to the ED, identifying the features associated to hospitalization and to potentially life-threatening disease (i.e. neoplastic, cerebrovascular, inflammatory/infectious and intracranial hypertension).

Methods: This is a multicentre retrospective study involving 14 Italian Children's Hospitals. Preschool-age patients with new-onset non-traumatic headache seen in the ED were included (January 1, 2017-December 31, 2018). Clinical characteristics and exams performed were recorded.

Patients were divided into two subgroups: hospitalized and discharged. To identify features associated with hospitalization, a logistic regression analysis was performed. Among hospitalized patients, variables linked to potentially life-threatening disease were investigated.

Results: A total of 1455 patients were included. Median age was 55 months (IQR 45-65) and 846 (58%) were males. Three hundred and twenty-five patients had comorbidities and family history of headache was reported in 375. Main associated symptoms were: fever in 562 (38.6%), vomiting in 487 (33.5%) and neurological symptoms/signs (i.e. papilledema, ophthalmoparesis, nystagmus, ataxia and dizziness) in 142 (9.8%). Neuroimaging studies were performed in 187 (13%) patients: CT in 169, magnetic resonance imaging (MRI) in 16 and both in 2. 95 patients (6.5%) were hospitalized and had a higher prevalence of neurological symptoms or signs. Headache attributed to non-intracranial infection was the most frequent subtype. Hospitalized and discharged group were compared and variables predicting hospitalization resulted ophthalmoparesis, ataxia, nocturnal awaking, neurological symptoms/signs and vomiting. Thirty-four of the 95 hospitalized patients had potentially life-threatening disease and showed a higher frequency of neurological symptoms and signs, asthenia, nocturnal awakening and vomiting. Only ataxia and vomiting were predicted of life-threatening disease at regression multivariate analysis.

Conclusion: Age <6 years does not represent “per se” a risk factor of a life-threatening disease and neurological examination should be carried out before considering neuroimaging. In this age subgroup, headache due to life-threatening diseases is rare (2.3%) and we found predictive variables that should be carefully evaluated in order to obtain a prompt diagnosis and treatment.

HEADWORK as innovative tool for monitoring MABs efficacy in migraine and their influence on work activity

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Background: Monoclonal antibodies (MABs) have been a game changer in the treatment of migraine since their approval. Their efficacy is generally assessed with disease related metrics, but there is an increasing need to evaluate the impact of disease treatment on the global burden on patients and society. HEADWORK (HW) is a new evaluation tool, developed specifically to assess the impact on work tasks and reduced productivity of migraineurs. The aim of this study was to test the performance of HW on migraine patients treated with MABs.

Methods: We enrolled 69 patients receiving treatment with MABs at the Headache Centres of IRCCS "C. Besta" (Milan) and IRCCS "C. Mondino" (Pavia). They were assessed with the HEADWORK questionnaire at baseline and at the 3rd (M3) and 6th month (M6) of treatment. HW questionnaire consists of two sections: "Work-related difficulties" scale 1 (HW1), 11 items dealing with the degree of difficulty in general skills, problems solving or starting new task; "Factors contributing to work-related difficulties" scale 2 (HW2), 6 items to address the degree to which some factors, such as noise and brightness of the workplace, negatively impact work-related tasks.

Results: Population: 15 M and 54 F, mean age (49.5y±8.6), mean age at onset of disease (18y±7), mean duration of disease (34y±11.6). We observed a marked, consistent and significant reduction in "classical" indicators: monthly migraine days (15±5.7 at baseline, 5±5.8 at M3, 6±6.2 at M6), medications per month (15±8.7 at baseline, 5±12.1 at M3, 6±6.6 at M6), MIDAS (41±43.2 at baseline, 6.5±11.3 at M3, 5±13 at M6), HIT-6 (66±2.8 at baseline, 59±8.7 at M3, 59±8.2 at M6). HW scores paralleled the above parameters: HW1 (20±8.1 at baseline, 11±9 at M3, 7±8.2 at M6), HW2 (9±6 at baseline, 5±4.8 at M3, 3±3.8 at M6).

Conclusion: Our findings confirm the marked effectiveness of MABs on monthly headache frequency and medications intake. HW1 and HW2 also show an extremely positive impact on work related activities. HW appears a suitable tool to assess migraine-related work disability in these patients.

Brain areas involved in pain perception of chronic, disabling migraine pain–functional imaging in a prospective observation

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Background: In 2015 we evidenced abnormal glucose metabolism in thalamic and temporal areas of young chronic cluster headache sufferers.

Aim: Which part of the brain is responsible for refractory chronic migraine pain? As is well-known pain perception originates from a central network of structures processing nociceptive signaling. They include sources integrating nociception with environmental information providing emotional valence of pain and response priority.

Method: Prospective observation started in May 2010, follow-up 20 years.
Procedure: a) (18)F-FDG/ PET-CT during spontaneous attacks; headache exempt group for reference brain areas to derive standardized uptake ratios SUR, CUR, PUR (cut off >1.3); b) evaluation of pain and mood (Hamilton A-D, GAD-7, DMS-V).
Included subjects until May 2022: 106 middle-class, married, caucasian females suffering from chronic migraine refractory to conventional therapies and 50 matched exempts.
Subjects at the end of a 10-year-observation period: Group A: age 25-35 n=32; Group B: age 56-65 n=34; Group C: comparison group n=21 age 35-45 healthy females exempt from headache and psychiatric problems. Confounders: environmental, genetic, epigenetic. Recruiting: Units for Headache Therapy, Internal Medicine and General Neurology.

Results: Group A: 18 patients evidenced hyper-metabolism in the cerebellum no side of prevalence. Group B: 17 sufferers evidenced paramagnetic hyper-metabolism in the Anterior Cingulate Cortex (ACC). The rest of the patients showed metabolic abnormalities of temporal and/or right anterior frontal gyrus (n=14 Group A and B) or no sign n=3 (Group A and B). All mentioned patients showed psychometric tests positive for anxiety. Follow-up: After 10.6$\pm$1.1SD years from baseline observation: Group A: No subject with cerebellum involvement evidenced pain relief higher than 35%. Anxiety worsened >0.001 vs baseline; Group B: In sufferers with ACC abnormal metabolism headache improved 90%, difficulties in cognitive control arose; clinical status did not relate p>0.9 to Stroup test. Both anxiety disorders and motor control difficulties related to PET-CT abnormalities p>0.001.

Conclusion: (18)F-FDG/PET-CT seems to evidence that chronic pain perception seemingly interests cognitive, associative learning. According to data showing cerebellum and ACC activation in response to nociceptive stimulation, results seemingly indicate that pain might scatter away from functional abnormalities not necessarily restricted to sensory areas.

Possible rationale to block CGRP pathway in chronic refractory migraine and medication over-use headache: results from an alliance against central pain sensitization

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Background: In 1990 our group demonstrated increase of tachykinins Substance P and Calcitonin Gene-related Peptide (CGRP) in the cephalic trigeminal area during migraine attacks. Thus, use of CGRP receptor blockade seems to be the rationale in relieving migraine pain.
On the other hand: a) pharmacology rules indicate that in the post-receptor-blocking phase receptor is expected to be hypersensitive to agonists. By repeated dosage a competition is created between receptor-blockade and hypersensitivity, often favouring the latter; b) CGRP seemingly does not act on chronic pain mechanism and central sensitization, except for a co-shared role in maintaining central sensitization evident also for other peripherally acting events/substances.

Aim: To evaluate possible efficacy of CGRP blockers in chronic migraine and medication overuse headache (MOH).

Method: Design: single blind comparison, cohort perspective observation. Observation started in 2018. Exclusion criteria: systemic or organic diseases, psychiatric disorders. Subjects under observation to date 66 males, 196 females.
Data regarding each group: Group A: n=35 females (33.8±3.9SD) with chronic migraine/medication overuse headache were administered specific uncompetitive inhibitory on *N*-methyl-D-aspartate (NMDA); Group B: n=37 female sufferers age 33.4±3.2SD refractory to any prophylactic therapy never testing any NMDA specific antagonist. Measure: whole pain burden (average frequency, severity, duration), number of acute medicines.
Rescue medication: indomethacin 0,06mg/kg.
Pre-Treatment: Group A: 7-day treatment with S-R ketamine. Group B: 7-day wash-out period
Treatment: Erenumab 70 mg sc./month.

Results: Pretreatment: Group A: pain relief p>0.0001 vs baseline. Treatment: Parallel decrease both of pain and acute medicines/painkillers. Group A: month 1-15 98%, month 16-32 95%, month 33-50 81%; Group B: month 1-15 29%, month 16-32 21%, month 33-50 >20%.
Relapse: Group A: month 14 n=1, month 38 n=4, month 45 n=6. Drop-out: Group A: n=0 1, Group B: 3 n=16.
Side-effects and adverse effects: No significant differences between Group A or B.

Conclusion: Since NMDA inhibition is known to manage some withdrawals and might prelude CGRP blockade at the CNS, the shown treatment might be rationally suited to obtain a higher number of responders to anti-CGRP administration in chronic migraine.

Validation of the Italian version of the Cluster Headache Impact Questionnaire (CHIQ): preliminary data from a National multicenter study

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Background: Cluster Headache (CH) is a primary headache disorder with a severe impact on the lives of affected subjects. The first specific questionnaire to assess the current impact of CH, the CH Impact Questionnaire (CHIQ), consists of 8 items on a six-point Likert scale in a score ranging from 0 to 40. Domains assessed by CHIQ include work, household, family, social life, recreational activities, cognition, and emotions. The aim of this study was to validate the Italian version of the CHIQ.

Methods: We considered patients diagnosed with episodic or chronic CH and included in the "Italian Headache Registry" (RICe). The CHIQ was translated from English to Italian by two blinded researchers and then back-translated by a native English speaker to resolve potential discrepancies between the Italian and English version. The questionnaire was then administered to patients through an electronic form. We also administered questionnaires to assess psychological dimensions (Depression Anxiety Stress Scale Short Version, DASS-21) and quality of life (Short Form Health Survey, SF-36). For internal consistency of the CHIQ, Cronbach's alpha was calculated. Convergent validity of the CHIQ with CH characteristics and the results of other questionnaires was assessed using Spearman correlations.

Results: We included 39 patients with CH (82% male) with a median age of 46 years (interquartile range 36-52); 23 patients (59%) reported active CH during the week preceding the questionnaire and 15 (38%) reported current use of preventive medication. The Italian version of the CHIQ had excellent internal validity with Cronbach's alpha value of 0.919 (95% CI:0.834-0.952). CHIQ scores had a positive correlation with the number of CH attacks during the last week (rho=0.445; p=0.005), acute medication frequency during last week (r=0.418, p=0.008), depression (r=0.656, p<0.001), anxiety (r=0.631, p<0.001), and stress (r=0.707, p<0.001). The score was negatively correlated with SF-36 items.

Conclusion: Our preliminary data showed the validity of the Italian version of the CHIQ, which could meet the need for evaluation of the social and psychological impact of CH in clinical practice and research. The questionnaire was brief and easy to administer with an electronic form.

Effectiveness and safety of CGRP monoclonal antibodies in migraine related to mitochondrial diseases: a real-world experience in patients with PEO and NARP syndromes

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Background: Migraine is a contemplated symptom in nearly 55% of patients with mitochondrial disease (MD) showing a significantly higher prevalence respect to the general population. Interestingly, the imbalance between brain demand and energy resources characterizing patients with MD seems to also underpin migraine pathophysiology. However, migraine attacks experienced by patients with MD are more resistant to treatments compared to patients with migraine without MD. Nevertheless, migraine response to monoclonal antibodies acting on the pathway of CGRP (CGRP-mAbs) in patients with MD is unknown to date.

Methods: Monthly subcutaneous galcanezumab 120 mg was administered as preventive treatment in a woman with genetically proven neuropathy, ataxia, and retinitis pigmentosa syndrome (NARP) and in a woman with progressive external ophthalmoplegia (PEO), both experiencing chronic migraine, respectively without and with medication overuse with previous failures of several medication classes. Patients underwent a monthly follow-up for six months in order to assess galcanezumab effectiveness, safety and tolerability. Headache diaries were used for monitoring the number of migraine attacks, attacks duration (hours), headache intensity, number of painkillers intake and painkillers response (hours to pain free). Tolerability and safety were evaluated considering the information reported by the patients.

Results: After the third galcanezumab administration, patients with NARP and PEO reported a significant reduction in monthly migraine headache days from an average of 20 to 2 migraine attacks/month, and from an average of 22 to 14 migraine attacks/month, respectively. Furthermore, headache intensity, number of pain-killers intake and pain killers' response (hours to pain free) showed a significant improvement compared to the baseline. No tolerability or safety concerns emerged in the course of six-month treatment.

Conclusion: Pre-human studies have identified, in the trigeminal ganglion, mitochondrial dynamic regulatory networks as putative therapeutic targets for migraine strategy. We cannot exclude that CGRP-mAbs (besides their peripheral effects on smooth muscular cells of meningeal vasculature and on mast-cell degranulation) may act also on trigeminal ganglion neurons not only, once again, peripherally modulating the CGRP pathway but also indirectly working on dysfunctional neuronal glycolytic metabolism.

Sustained migraine remission during fremanezumab therapy: a case report

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Background: Monoclonal antibodies (mAbs) targeting CGRP or its receptor have demonstrated to be effective, save, and well tolerated in the prevention of episodic or chronic migraine. However, their clinical effect in reducing the migraine frequency is partial, as only about 40-50 percent of patients show meaningful response in randomized controlled trials (RCTs). Nevertheless, a small percentage of super-responders, with a decrease in monthly migraine days of 75 percent or more, has been reported for all four CGRP mAbs. Here, we describe a clinical case with immediate, complete, and sustained response to fremanezumab therapy.

Case report: A 56-year-old female patient was referred to our Headache Centre because of a high frequency episodic migraine since the age of 16. She reported an average migraine frequency of 8 days a month, usually disabling. The pain was strictly localised over the right fronto-temporal region and regularly accompanied by nausea/vomiting, photo/phonophobia, and ipsilateral eyelid ptosis and lacrimation. The headache was partially relieved by zolmitriptan usually associated with a NSAID. A number of prophylactic agents, including amitriptyline, candesartan, flunarizine, propranolol, topiramate, and valproic acid, proved to be inefficacious and/or not tolerated. In April 2021, the patient was started on fremanezumab 225 mg monthly, after that she became completely headache free from the first dose. She remained completely asymptomatic for the subsequent 6 months of fremanezumab administration. After 6 month of therapy, fremanezumab was stopped and, after about one month and a half, the migraine episodes gradually recurred, initially with a low frequency/intensity. By the sixth month from withdrawal of therapy, the migraine frequency and intensity reached again the initial clinical pattern, with 8 days of moderate to severe intensity a month. Fremanezumab was reintroduced with a new complete response.

Discussion: This case is peculiar in that our patient underwent a complete remission from her migraine episodes during fremanezumab therapy. Although a 100 percent response rate has been reported in a small percentage of patients in RCTs, to our knowledge a 100 percent response rate for six consecutive months has never been described. In our patient, the optimal clinical response is in keeping with the hypothesis that migraine symptoms related to peripheral trigeminal sensitization, such as unilateral pain, cranial autonomic symptoms, and allodynia, may predict response and super-response to anti-CGRP mAbs. The migraine recurrence after the withdrawal of therapy might indicate the lack of a disease modifying effect of fremanezumab in this case. However, the pharmacokinetic and pharmacodynamic mechanisms underlying a prolonged super-response remain largely unknown.

Sleep and migraine: the relation between insomnia and headache

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Background: Migraine and sleep show a complex and bidirectional relationship: migraineurs often report insomnia due to attacks, but poor sleep quality is one of the main triggers for a migraine attack. In migraineurs sleep appears to be characterized by a reduction in quality and efficiency. In our study we analyzed the relationship between insomnia and headache days per month.

Methods: Data were collected by a telephone interview of migraine patients, enrolled at the Headache Center of the Policlinico of Palermo. They were asked number of headache days per month, pain intensity ranging from 0 to 10, and were administrated Insomnia Severity Index (ISI). Quantitative variables were analyzed using Pearson coefficient to find any significant correlation.

Results: We interviewed 157 patients with a mean age of 42.7±11.8 years: 104 (67%) had chronic migraine and 53 (33%) episodic migraine, of which 112 (71%) without aura. In our migraine patients, sleep disorder ($p<0.001$), the difficulty in falling asleep score (ISI1a) and in staying asleep (ISI1b) ($p<0.005$), were significantly related with headache days per month. In our sleep profile waking up too early (ISI1c: $p>0.005$), and interference of the sleep problem with their daily functioning (ISI5: $p>0.005$) were not associated with headache days. Insomnia was not significantly correlated with intensity of pain.

Conclusion: Our data confirmed the relation between sleep and migraine in particular, initial and middle insomnia was significantly related with headache days per month. The intensity of headache did not affect insomnia. More studies are necessary to demonstrate this relation between insomnia and migraine.

New model of headache centre organization: first experience to treat migraine with onabotulinumtoxin A or monoclonal antibodies within the territory

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Background: Post-covid 19, territorial specialized activity is implemented with the creation of a new "Case della Salute". Fifty-two percent of the global population is affected by a headache disorder every year, thus it is necessary to increase the number of headache specialized centers. Management of headache within the territory, even with second-level therapies, reduces the burden on hospitals and is easier for patients to access.

Methods: Neurologists of the Headache Centre of the "Casa della salute San Rocco" AUSL Ferrara, are specialized in the diagnosis and treatment of headaches with expertise in the management of monoclonal antibodies and in the treatment with onabotulinumtoxinA. The access to the first visit took place through CUP reservations with a specific diagnostic question: "Headache Clinic" or following a request from another neurologist with code "Access 0" and a reservation in specific slots. The subsequent visit was programmed with a code in the prescription "access 0-12" indicating months of control visit. A neurologist provided an appointment with the Easy CUP Software or the patient personally went or called the reception Points (PDA) distributed in the various health centres.

Results: From April 2021 to July 2022, the number of first visits in our centre was 1792. Presently 30 patients are being treated with monoclonal antibodies (erenumab, galcanezumab, fremanezumab) and 11 patients are being treated with botulinum toxin.

Conclusion: Territory Headache Centres can reduce waiting lists, representing easier access for the patient. Our centre is the first in a "Casa della salute" that treats migraine with II level therapy monoclonal antibodies and OnabotulinumtoxinA, a therapy that is often carried out in headache centres allocated in hospitals. This represents a model for improvement of territorial neurology.

Corticosteroids increase the expression of CGRP within the trigeminal ganglion

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Background: Expression of calcitonin gene-related protein (CGRP) within the trigeminal ganglion (TG) is considered of pathophysiological relevance to migraine. Corticosteroids are key epigenetic regulators of gene expression, and also widely used for the treatment of migraine, medication overused headache, as well as cluster headache. Of note, mechanisms underpinning the therapeutic effects of corticosteroids in headaches wait to be identified. In the present study, we hypothesized that corticosteroids are negative regulators of CGRP expression, an effect that might well explain their therapeutic properties in headache patients.

Methods: CGRP expression was evaluated at the transcript and protein level within the TG and hypothalamus of mice and rats exposed to multiple treatment schedules with betamethasone. The effect of dexamethasone on CGRP expression was also evaluated on human leukocytes and rat CA77 medullary thyroid carcinoma cells. Finally, the impact of dexamethasone on CGRP promoter activity was investigated in SHSY neuroblastoma cells transfected with a luciferase reporter driven by the human CGRP promoter.

Results: Unexpectedly, we found that betamethasone increases the expression of CGRP within the TG of mice and rats exposed to the drug for 7 or 4 days, having no effects on the neuropeptide levels of the hypothalamus. Consistently, dexamethasone induced CGRP expression in cultured human leukocytes and CA77 medullary thyroid carcinoma cells. Induction of CGRP gene expression by corticosteroids was in keeping with the increased CGRP promoter activity in SHSY cells exposed to dexamethasone for 24 and 48 hrs.

Conclusion: Data, are at odds with the working hypothesis that corticosteroids counteract migraine, MOH and cluster headache via epigenetic downregulation of CGRP expression, and also suggest that relevance of CGRP expression within the TG to migraine and other types of headaches might be revisited.

Long-term effects of pandemic of Covid-19 on clinical features and psychological symptoms in adolescents with migraine

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Background: Covid-19 pandemic has changed children/adolescents lifestyle, influencing family organization, social relationship, and school attendance. A previous study showed the role of lifestyle modification, in particular the reduction in school-related stress during the lockdown, in migraine attacks improvement [1]. We aimed to compare the clinical characteristics of migraine, the use of prophylactic treatment and psychological symptoms between patients who referred to our Headache Centre before the Covid-19 pandemic and those who were evaluated during the pandemic.

Methods: We studied 418 adolescents with migraine (m.a. 14 ± 1.7; 110 M and 308 F). Based on the pandemic period, patients were grouped into "Pre Covid" or "Covid". Moreover, the second group was divided into "Covid-1" (March to October 2020, characterised by lockdown) and "Covid-2" (November 2020 to January 2022, characterised by prolonged restrictions). According to migraine clinical characteristics, patients were grouped into: (1) high-frequency (weekly to daily episodes) and low-frequency (≤3 episodes per month); (2) mild and severe pain; (3) need for prophylactic treatment or not. The PHQ-9 and GAD-7 questionnaires were used to assess anxiety and depression symptoms.

Results: We did not find a significant difference in migraine frequency between the "Pre Covid" and "Covid" periods (p=0.295). But in the "Covid-2" period, frequency of the attacks was increased, compared to both the "Pre Covid" period (p=0.038) and the "Covid-1" period (p=0.005). Furthermore, more patients needed prophylactic treatment in the "Covid" period, especially in the "Covid-2" period, than in the "Pre Covid" period (p=<0.001). As for the psychological symptoms, our patients showed higher levels of anxiety and depression during the "Covid" period (GAD-7, p=0.013; PHQ-9, p=<0.001), especially during the "Covid-2" period (p=<0.001). Frontal teaching showed an association with the frequency of attacks and levels of depression in the "Covid" period, compared to the "Pre Covid" period (p=<0.005).

Conclusion: Our results show a long-term negative impact of the Covid-19 pandemic on clinical parameters and psychological symptoms of adolescents with migraine. Considering the relationship between migraine severity and emotional symptomatology, our results suggest that monitoring the emotional status of pediatric patients with migraine is mandatory in the near future of COVID-19 pandemic.

Diagnosis of idiopathic intracranial hypertension with neuroimaging in children: a new challenge

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Background: Headache is the most common neurologic issue in the pediatric population. It can be classified as primary (those not associated with underlying diseases) and secondary (those in which the headache is a symptom of an underlying condition). The conditions that may cause secondary headache in children include idiopathic intracranial hypertension (IHH), defined as an increase in intracranial pressure (ICP) with no clinical, laboratory, or radiographic evidence of associated infection, vascular abnormality and space-occupying lesions.

Methods: A 10-year-old asian boy presented to our Pediatric Emergency Department with a complaint of headache, vomiting and diplopia. Brain TC and MRI were performed to exclude secondary causes of increased intracranial pressure. Personal and family medical history were collected. Blood tests for vitamin deficiency, autoimmune, infectious and thrombotic diseases possibly associated to papilledema were performed.

Results: Family history was unremarkable. Physical examination documented overweight (BMI 87°), decreased visual acuity, right six nerve palsy and bilateral papilledema. Ocular ultrasound excluded optic nerve drusen. Blood tests were normal, and no evidence of recent infection was found. On CT and MRI the brain parenchyma and ventricles appeared normal. Nevertheless, MRI abnormalities suggestive of IHH according to Friedman's criteria were found: distension of perioptic subarachnoid space, empty sella and vertical tortuosity of the orbital optic nerve. In view of the strong clinical suspicion, the specific radiological findings and the exclusion of other possible causes of intracranial hypertension, it was decided not to perform lumbar puncture (LP) to measure ICP and acetazolamide 15 mg/kg/day in three doses was started with resolution of papilledema and diplopia.

Conclusion: IHH should be suspected in children with headache and papilledema if the neuroimaging study reveals no secondary cause of raised ICP. LP is routinely performed in order to document normal cerebrospinal fluid and to measure the opening pressure. Neuroradiological criteria of raised ICP have been established and they may be especially useful in the pediatric population where opening pressure measurement is frequently equivocal. Moreover, ophthalmologic evaluation is required to document the severity of optic nerve involvement and monitor response to treatment.

Ethanol-evoked prolonged periorbital mechanical allodynia is mediated by CGRP and Schwann cells TRPA1 activation

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Background: A large proportion of migraine and cluster headache patients show remarkable sensibility to alcohol, developing headache attacks after ingestion of relatively small amounts of alcoholic beverages. The ICHD-3beta classification of primary headaches describes a delayed alcohol-induced headache (previously defined hangover headache), which develops within 5-12 hours after ingestion of alcohol and resolves within 72 hours of onset. The transient receptor potential vanilloid 1 (TRPV1) that belongs to the TRP family of ion channels, is selectively gated by 1-3% concentrations of ethanol and signals pain and inflammation. Another TRP channel, the ankyrin 1 (TRPA1) subtype is gated by the ethanol metabolite, acetaldehyde. TRPA1 activation leads to calcitonin gene-related peptide (CGRP) release, an endogenous compound related to headache development. The present study explored the role of TRPA1 channels in mediating prolonged responses that may be relevant for the delayed ethanol-evoked headache in patients.

Methods: Ethanol was administered by oral gavage (intragastric) in C57BL/6J, and TRPA1 and TRPV1 wild type and knock out mice. Acetaldehyde was administered by local periorbital injection. Periorbital mechanical allodynia (PMA) was evaluated by applying the von Frey filaments to the periorbital region over the rostral portion of the eye before and after (1-24 h) ethanol. Antagonists were administered by systemic injections.

Results: Intragastric administration of ethanol causes a delayed and prolonged PMA in C57BL/6J mice. TRPV1 deletion did not affect the delayed PMA. Pretreatment with the alcohol dehydrogenase inhibitor, prevented the ethanol-evoked PMA supporting the hypothesis that acetaldehyde, derived from ethanol metabolism, mediates the prolonged allodynic effect of ethanol. TRPA1 genetic deletion prevented ethanol and acetaldehyde-evoked allodynia, underling that the aldehyde plays a major role in the ethanol-evoked PMA. Moreover, the systemic administration of the CGRP receptor antagonist, olcegepant, was also able to reduce ethanol-evoked PMA. Thus, TRPA1 targeted by acetaldehyde, induce the CGRP releases from the terminal neuropeptides which in turn induces PMA.

Conclusion: The present study explored the role of TRP channels in mediating prolonged responses that may be relevant for the delayed ethanol-evoked headaches in patients. Results underline that TRPA1 may be a molecular target for an effective treatment for pain in alcoholics.

Bioelectric changes induced by air microembolism before and after closure of Patent Foramen Ovale in a patient with migraine with aura: a case report

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Background: Patent Foramen Ovale (PFO) is strongly associated with the occurrence of migraine with aura (MA). PFO might cause microemboli to enter the systemic circulation, potentially triggering Cortical Spreading Depression (CSD), a propagating depolarization that underlies migraine aura. This phenomenon was demonstrated in animal models. In humans, air microembolism through a PFO induced bioelectrical abnormalities revealed by EEG [1]. However, whether PFO closure prevents those abnormalities, potentially preventing migraine, is unclear. We present the EEG recordings of a patient with MA before and after PFO closure.

Case report: We evaluated a 30-year-old male, diagnosed with large PFO and MA, who reported about 2 monthly episodes of migraine, all with aura, before PFO closure. The patient was on treatment with acetylsalicylic acid for polycythemia vera. The patient, after consultation with a cardiologist, decided to close PFO. The patient underwent a 19-channel EEG recording before and after PFO closure. During both EEG sessions, we recorded cortical activity before and after the injection of microbubbles, whose passage through the cerebral arteries was monitored with transcranial Doppler. EEG power changes were measured in decibels (ΔP) overall and for each frequency band (theta: 5-7 Hz; alpha: 8-12 Hz; beta: 13-30 Hz; lower gamma: 31-45 Hz). We noticed an increase in EEG power across all the frequency spectrum (theta: +0.43dB, p=0.011; beta: +0.12dB, p<0.001; lower gamma: +0.22dB, p=0.005), except from alpha band (+0.04dB, p=0.180), after microbubble injection before PFO closure. After PFO closure, we noticed a significant increase in EEG power across all the frequency spectrum (theta: +0.57dB, p=0.009; alpha: 0.38dB, p=0.002; beta: +0.22dB, p=0.005), except from lower gamma band (lower gamma: +0.33, p=1.06) even in the absence of microembolism.

Conclusion: Our study suggests that the increase in EEG power found in patients with MA and PFO persists after PFO closure. If confirmed in further subjects, our findings might indicate that EEG power increase is not a consequence of microembolism through a PFO. Notably, the patient, who suffered from polycythemia vera and therefore had a high risk of paradoxical embolism through PFO, had clinical benefit from PFO closure.

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Alexithymia increases muscle tenderness in women with migraine

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Background: Alexithymia is a multidimensional construct, mainly characterized by a deficit in identifying and communicating feelings and in distinguishing between feelings and the bodily sensations. It is highly prevalent in psychosomatic and chronic pain disorders. Emerging evidence suggest a role for alexithymia in migraine, in a complex interplay with psychiatric comorbidity. Muscle tenderness is a remarkable clinical feature in a large proportion of migraine patients. This study is aimed at investigating the relationship between alexithymia and muscle tenderness in female migraineurs.

Methods: Forty-two female patients, fulfilling the diagnostic criteria for migraine (with/without aura, episodic/chronic), were enrolled in this pilot, observational, cross-sectional study. Each patient underwent a structured interview, a psychological assessment to look for alexithymia (by the TAS-20 scale), for and anxiety/mood comorbidity (by the STAI-Y1 STAI-Y2, BDI-II), for migraine-related disability (by the HIT-6) and a specific cranial/cervical musculoskeletal examination. Palpation of pericranial (masseter, lateral-medial pterygoid, temporal) and cervical (sternocleidomastoid, trapetius, nuke) muscles was carried out in a standardized way. For each patient, a Pericranial Muscle Tenderness (PTS) (0-3), a Cervical Muscle Tenderness (CTS) score (0-3) and a Cumulative Muscle Tenderness (CUM) (0-6) were calculated.
A multivariate analysis (by a linear regression model) was performed to study the association among the TAS-20 score (independent variable), the CUM score (dependent variable) and the BDI-II, STAI-Y1, STAI-Y2, HIT-6 scores, age and disease duration (covariates).

Results: The multivariate analysis detected a linear and independent relationship between the TAS-20 and the CUM score, where each one-point increase of the TAS-20 score predicted a 0.0349-point increase of the CUM, with a statistically significant ($p=0.017$) association.

Conclusion: This pilot study suggests a role for alexithymia in increasing muscle tenderness in migraine, independent from psychiatric comorbidity. Hence, alexithymia may affect the complex pain phenotype in migraine. Although further studies are needed to confirm these findings, a novel therapeutical approach targeting alexithymia may be supported by the results of the present study to reduce muscular tenderness in female migraineurs.

Galcanezumab effect on "whole pain burden" and multidimensional outcomes in migraine patients with previous unsuccessful treatments: a real-world experience

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Background: Clinical trials have demonstrated galcanezumab as safe and effective in migraine prevention. However, real-life data are still lacking and overlook the impact of galcanezumab on those different migraine facets strongly contributing to migraine burden. Herein we report the clinical experience from an Italian real-world setting using galcanezumab in patients with migraine experiencing previous unsuccessful preventive treatments.

Methods: Forty-three patients with migraine and failure of at least 3 migraine preventive medication classes received monthly galcanezumab 120 mg s.c. At the first administration and after 3 and 6 months, patients underwent extensive interviews to assess clinical parameters of disease severity. Furthermore, validated questionnaires were administered to explore migraine-related disability, impact, and quality of life as well as symptoms of depression or anxiety, pain catastrophizing, sleep quality and the ictal cutaneous allodynia.

Results: After the third and the sixth administration of monthly galcanezumab 120 mg s.c., headache attacks frequency reduced from 20.56 to 7.44 and 6.37 headache days per month, respectively. Moreover, a significant improvement in headache pain intensity (from 8.95 to 6.84 and 6.21) and duration (from 9.03 to 3.75 and 2.38) as well as in scores assessing migraine related disability and impact, depressive and anxious symptoms, and pain catastrophizing was observed. Furthermore, we demonstrated a significant reduction in the values of "whole pain burden", a composite score derived from the product of the average of headache frequency, intensity, and duration in the last three months.

Conclusion: Real-world data support monthly galcanezumab 120 mg s.c. as a safe and effective preventive treatment in reducing headache frequency, intensity, and duration as well as comorbid depressive or anxious symptoms, pain catastrophizing and quality of life in both episodic and chronic migraine patients with previous unsuccessful preventive treatments. Furthermore, we demonstrated that monthly galcanezumab 120 mg s.c. is able to induce a significant improvement in the scores of "whole pain burden". The latter is a reliable and easy-to-handle tool to be employed in clinical setting to evaluate the effectiveness of preventive drugs (in this case, galcanezumab) or when the decision of continuing the treatment with anti-CGRP mAbs is mandatory.

Influence of the hypothalamus on the duration of migraine attack: a microstructural and functional MRI study

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Background: Neuroimaging studies have shown an involvement of the hypothalamus in the premonitory phase of a migraine attack. Little is known about the role played by the hypothalamus and the brain networks with which it is interconnected during a migraine attack.

Methods: We scanned 15 patients during a spontaneous migraine attack without aura and for comparisons 20 control subjects. We analyzed diffusion tensor imaging (DTI) metrics of the entire hypothalamus and its anterior and posterior regions of interest (ROIs) bilaterally. In addition, we estimated Higuchi fractal dimension (FD) from resting-state functional MRI data as a non-linear measure of neural activity complexity. All MRI data were correlated with clinical disease variables.

Results: In comparison to healthy subjects, patients during the attack had altered diffusivity metrics of the hypothalamus, particularly of the posterior ROIs, and higher FD values in the salience network (SN). Correlation analysis revealed a direct correlation of axial diffusivity of the hypothalamus with disease severity and FD of the SN. Furthermore, the mean duration of the migraine attack correlated positively with the metrics of the anterior hypothalamus bilaterally.

Conclusion: Our results show plastic structural changes in the hypothalamus related to the attacks severity and the complexity of the salience cortical network involved in the multidimensional neurocognitive processing of pain, these suggest that the hypothalamus may play an important role in modulating migraine attack duration.

Angelman Syndrome and cyclic vomiting syndrome: a new potential association - Not all vomiting is only vomiting!

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Background: Angelman Syndrome (AS) includes gastrointestinal issues, such as vomiting, gastroesophageal reflux disease and constipation.
The aim of this case is to show a new possible association between cyclical vomiting syndrome (CVS) and AS (and probably other neurological syndromes), rarely described before.

Methods: We report the case of a patient affected by AS, genetically diagnosed in the postnatal period, who initially was referred to our Neurological Centre for Headache at the age of 8 years. Since one year of age, she had been suffering from repeated episodes of general malaise, during which she touched her head and eyes, she showed photophobia and phonophobia and she had vomiting for hours. The attacks recurred monthly and could rarely occur even during sleep. Her past history included migraine equivalents. Moreover, the familiar history was positive for migraine in the paternal line. Due to her syndromic predisposition to epilepsy, she repeatedly underwent EEG recordings, which showed only the typical abnormalities of the AS.
In order to explain vomiting, we had to exclude organic causes often related to AS and, in general, to neurodevelopmental disorders.
Our patient, as well as many other children with her condition, suffered from severe reflux. In fact, she had been treated with PPI from her first months. However, vomiting episodes kept persisting in spite of all pharmacological treatments for gastrointestinal problems. To note, the patient was completely asymptomatic out of the episodes, which showed a regular periodicity and recurrence. After having excluded the major and acute organic causes, we were able to reach a diagnosis of CVS and its possible progression to migraine without aura, in accordance with the ICHD-3 criteria. The patient received symptomatic therapy for migraine and vomiting (ibuprofen and ondansetron).

Discussion: Many patients with neurodevelopmental disorders suffer from gastrointestinal symptoms, such as nausea and vomiting, as consequences of gastroesophageal reflux and severe constipation.
Our case suggests that in AS, vomiting cannot always be considered as part of a gastrointestinal manifestation of the syndrome. In presence of previous migraine equivalents and a familiar history positive for migraine, CVS should always be considered in the differential diagnosis.

Periorbital Nociception in the Reserpine-Induced Experimental Fibromyalgia

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Background: Fibromyalgia (FM) is a chronic widespread pain condition characterized by complex symptomatology, including anxiety, fatigue, sleep and chronic headache which occurs in 76% of patients with FM. Transient receptor potential ankyrin 1 (TRPA1) can be related to migraine-like behaviour since its activation is mediated by several exogenous and endogenous agonists such as hydrogen peroxide (H_2O_2) and 4-hydroxynonenal (4-HNE) that are increased in periorbital and facial nociception model. Our purpose was to investigate the role of TRPA1 on periorbital mechanical allodynia (PMA) in the reserpine-induced experimental FM model.

Methods: To induce the FM mice model, mice were treated with reserpine 1 mg/kg, subcutaneously (s.c.) daily for 3 consecutive days. Periorbital mechanical allodynia (PMA) was assessed on the 4th day after beginning the treatment. TRPA1 selective antagonist A967079, and antioxidant and TRPA1 knockout mice and macrophages Fas-Induced Apoptosis (MaFIA) mice were used to evaluate the PMA in reserpine-induced experimental FM model.

Results: FM-induced mice presented PMA that was abolished by TRPA1 genetic deletion (*Trpa1*$^{-/-}$ mice) or pharmacological inhibition with the TRPA1 antagonist A967079. We also observed an increase on macrophages in the trigeminal nerve followed by an increase on an oxidative stress marker (4-HNE). The treatment with an antioxidant, N-tert-Butyl-alpha- - phenylnitrone (PBN) reduced PMA. MaFIA mice also showed reduced PMA and the number of macrophages in trigeminal nerve.

Conclusion: The results indicate that macrophages have an influence on oxidative stress generation on the FM model, leading to TRPA1 activation eliciting PMA, since genetic deletion, antagonist and antioxidant treatment was able to reduce PMA. TRPA1 represents a valuable target for headache related symptoms in FM.

Interictal cognitive performance in children and adolescents with primary headache: a narrative review

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Background: Primary headache is a very common and disabling disease. The burden of pain and recurrent attacks may lead to a poor quality of life, anxiety and depression. An increased risk of low functioning and curricular performances in young patients with primary headache has been described. The mechanisms underlying the relationship between migraine and poor school achievement may be various and could be a reflection of weak cognitive skills. Data concerning the cognitive functioning in the free pain interval in pediatric age are under-investigated and results are far from conclusive.

Methods: Suitable studies were identified using MEDLINE and Web of Science. Search terms included “Pediatric migraine” or “Pediatric headache” and “Cognitive performance”, “Cognitive impairment” or “Neuropsychology”, “Intelligence”, “Attention”, “ADHD”, “Memory”, “Language”, “Visuo-spatial”, “Coordination” and “Difficulties” or “Problems”. We considered papers involving subjects with an age ranging from 0 to 18 years. We also included articles that, though focusing on adults, included subjects < 18 years old.

Results: The present review article suggests that, though considered a benign disease, pediatric migraine may be associated to altered neuropsychological functioning in the interictal phase. Although children and adolescents with migraine generally have a normal intelligence, they may show a non-homogeneous cognitive profile, characterized by possible difficulties in verbal skills, in particular comprehension abilities. Pediatric primary headache may present altered neuropsychological functioning involving attentional resources, processing speed and memory, particularly verbal memory.

Conclusion: Given the impact that this disease can have on school performance and the tendency to persist from childhood to adulthood, a cognitive screening in young patients affected by primary headache is pivotal. Additional neuropsychological research using more homogenous methods is needed.

Infodemiology of cluster headache seasonality: a proof of concept by a Google Trends analysis

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Background: Although with conflicting results, CH is reported to follow an annual pattern with a peak in the spring (March–April) and a second peak in autumn (September–October). Patients with headache frequently use search engines, such as Google, to look for terms related to their disease creating trend data which can be analysed with Google Trends. Indeed, Google Trends has been used for surveillance studies and can provide indirect estimates of the burden of diseases and symptoms. The present study investigates the seasonality of Google Trends in the last 10-year search volumes for the search term "cluster headache", in the Northern and Southern hemispheres.

Methods: The search term "cluster headache" was translated into the 10 most spoken languages in the world and searched on Google Trend to obtain the relative search volumes (from 0 to 100), to compare variations of different search terms across periods. Countries were selected according to the following criteria: (1) presence of a relative search volume >50 for CH; (2) presence of at least 20 million inhabitants. For statistical purposes, countries were grouped in relation to the hemisphere (Northern or Southern). Relative search volumes for "cluster headache" were extracted from January 2012 to January 2022. Paired *t*-test was used to compare the mean research volumes in the meteorological seasons sub-groups (i.e. Summer and Winter vs Spring and Autumn).

Results: A seasonal trend for the search of "cluster headache" was found worldwide with higher relative search volumes presenting higher levels in meteorological seasons of spring (March, April and May) and autumn (September, October and November) compared with summer (June, July and August) and winter (December, January and February).

Conclusion: Our data showing higher search volumes for the term "cluster headache" during meteorological seasons of spring and autumn, clearly reflect the circannual pattern of CH occurrence representing new evidence for its seasonality.

Botulinum Toxin Type A in chronic migraine: predictive factors and impact of botulinum toxin dilution

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Background: BoNT/A is an effective preventive treatment for chronic migraine however, there are insufficient data to predict the efficacy of the treatment for individual patients. The objective of the study was to evaluate the predictors of response to BoNT/A in patients with chronic migraine and to assess the efficacy of two different dilutions of BoNT/A.

Methods: We retrospectively collected data from 104 patients (12 M, 92F; mean age 49.24±12.38) with the diagnosis of chronic migraine treated with BoNT/A as a preventive therapy. The patients were treated with 3 rounds of BoNT/A with the initial dose of 155 UI that could be incremented to 195 UI in the second or third round using the PREEMPT paradigm; BoNT/A was reconstituted with saline solution with the dilution of 2 ml (43 patients) or 1 ml (61 patients). The number of migraine days, medication intake, severity, and side effects were reported in the headache diary. At the end of the three rounds of BoNT/A injections, the patients were classified as responders (>50% reduction of migraine days) or non-responders (<50% reduction of migraine days).

Results: Univariate logistic regression showed that BoNT/A response (59 patients) was positively associated with unilateral migraine (OR 5.59, C.I. 2.36-12.27; p<0.001) and negatively associated with the co-occurrence of major depressive disorder (OR 0.21, C.I. 0.08-0.52; p<0.001) or opioids intake as symptomatic medication (OR 0.28, C.I. 0.09-0.81; p<0.0184). On multivariate analysis, these results were preserved however with the exception of opioid intake as symptomatic medication. Dilution of BoNT/A with 2 ml saline was associated with the side effect of eyelid ptosis (OR 6.17, C.I. 1.85-20.59; p 0.003) while the dilution with 1 ml saline did not associate with this side effect; different dilution of BoNT/A did not associate with the response to the treatment.

Conclusion: Unilateral localization of headache pain predicts a good response to the therapy while the presence of a major depressive disorder predicts a bad response. The dilution of Botulinum Toxin Type A does not influence the response to the treatment however, eyelid ptosis is more common when BoNT/A is diluted with 2 ml of saline.

Transient receptor potential ankyrin 1 (TRPA1) contributes to mechanical hypersensitivity in a mouse model of endometriosis

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Background: Endometriosis is caused by the presence of endometrial-like tissue outside the uterus and affects ~10% of reproductive-aged women. Patients may present with a variety of symptoms, including debilitating pelvic or abdominal pain and diffuse pain. Preclinical evidence supports the role of oxidative stress in the pathogenesis of endometriosis and related pain symptoms. However, the pathway that from increased reactive oxygen species results in endometriosis pain symptoms is poorly known. The transient receptor potential ankyrin1 (TRPA1) has been identified as a major oxidative stress sensor, thus contributing to inflammatory, neuropathic, cancer and migraine pain. Here we hypothesize that TRPA1 plays a critical role in pain symptoms associated with endometriosis.

Methods: To induce endometriosis in mice, dissected uterus horns of donor female mice were injected intraperitoneally (i.p.) in recipient female mice. Mechanical hypersensitivity in the abdomen (AMA) in the periorbital areas (PMA) and hindpaw (HMA) was assessed from day 7 to 28 after transplantation. CGRP receptor antagonist (olcegepant), TRPA1 antagonist (A967079), TRPA1, TRPV1, or TRPV4 knockout-mice and the free-radical spin trap, N-tert-alpha-phenlynitrone (PBN) were used. Olcegepant, A967079 and PBN were administered on day 28 after endometrium injection.

Results: Endometrial tissue injection caused a time-dependent (day 7-28) increase in the number of visible endometrial-like lesions in the abdominal cavity in C57BL/6J female mice. The increase in endometrial-like lesions was paralleled by a time-dependent (day 7-28) increase in AMA, HMA and PMA. TRPA1 genetic deletion provided full protection against AMA, PMA and HMA compared to wildtype mice. Deletion of TRPV1 and TRPV4 did not affect the development of AMA, PMA and HMA compared to wildtype mice. Systemic (i.p.) administration of olcegepant, A967079 and PBN transiently and completely reversed the AMA, PMA and HMA at day 28.

Conclusion: Present results confirm that oxidative stress plays a major role in AMA, HMA and PMA. Genetic deletion and pharmacological blockade of TRPA1 indicate that the channel is critically implicated in such allodynia. Thus, TRPA1 seems to have a critical role in sensing oxidative stress to sustain mechanical hypersensitivity in endometriosis.

New-onset headache after COVID-19: an Italian multicenter case series

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Background: SarsCov2 infection leads to several neurological manifestations and headache is a rather frequent symptom. COVID-19 could exacerbate pre-existing headache syndromes but also cause new-onset headache (NoH). Here, we describe patients with NoH after SarsCov2 infection evaluated at three Italian headache centers.

Methods: We collected patients during routine neurologic evaluations at three Italian headache centers. Inclusion criteria were the presence of NoH after SarsCov-2 infection and the consent to participate; the only exclusion criterium was the presence of a previous recurrent headache. We investigated NoH latency after the infection, its location, intensity, quality, duration (hours), frequency (days/month), and concomitant symptoms. Using such information, we tried to attribute a diagnosis following ICHD-3 classification. In addition, data on the effectiveness of acute and preventive medications were collected. Categorical variables were showed in percentages, while quantitative variables were reported as median and interquartile ranges (IQR) and were analyzed with Mann-Whitney U-test and Kruskal-Wallis non-parametric tests for independent samples.

Results: Eleven female patients, 37.0 (10.0 - 60.0) years old, were included. Headache onset was 0.0 (0.0 – 10.0) days from the infection onset. Pain localization was various, and quality was pulsating or tightening. Patients complained of various associated symptoms, such as nausea, photophobia, or phonophobia. Headache was persistent and daily in 8 patients (72.7%), while it occurred in episodes in the remaining subjects. ICHD-3 diagnoses were migraine (18.2%), probable migraine (9.1%), new daily persistent headache (NDPH – 36.4%), probable NDPH (36.4%). Among NDPH, 3 patients showed a tension-type headache phenotype and 1 presented a migraine-like one, while among probable NDPH patients there was the opposite trend (3 migraine-like and 1 tension-type headache phenotype). Ten patients received one or more preventive treatments and six of them showed an improvement in headache days/month.

Conclusion: Post COVID-19 NoH is a heterogenous condition with an uncertain pathogenesis (central nervous system inflammation persisting after the infection?). Such type of headache may become persistent and severe, with a broad spectrum of manifestations. Response to treatment is variable, so more studies are needed to better identify this recent disease.

Heart rate variability in episodic migraine

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Background: Migraineurs show several symptoms suggesting an involvement of the autonomic nervous system (ANS) both during attacks and interictally. Heart rate variability (HRV) study is a simple tool able to identify ANS alterations. We aim to study HRV in migraineurs, comparing data with healthy subjects.

Methods: We included episodic migraineurs (EM) and healthy subjects (HS) of the same age. Electrocardiographic (EKG) signal was collected using Polar-H10 thoracic band; data were analyzed using Kubios-HRV software. EM were included during the interictal phase. All measurements were acquired in standardized conditions. EKG signal was recorded during the following conditions: i) basal (resting respiratory rate at 12-16 bpm, 15 min recording); ii) deep breath test (DBT, 6 deep breaths in 1 min). HRV was studied in the frequency domain, analyzing high frequencies (HF, influenced by parasympathetic system) power, low frequencies (LF, influenced by sympathetic system) power, total power and LF/HF ratio. Moreover, we calculated HRV in basal and DBT conditions with the formula: $((Fc_{max}–Fc_{min})/Fc_{mean})*100$. Statistical analyses were performed using Kruskal-Wallis test.

Results: We included 14 EM (34.7±8.8 years old, 11 females) and 14 HS (30.3±2.8 years old, 6 females). We found a significant difference in basal HRV between the two groups (EM 20.2±6.6%; HS 27.0±7.3%, p=0.024). About frequency domain analysis, we found a significant difference in total power (EM 1268.1±1073.3ms^2; HS 1767.5±780.6ms^2 p=0.048) and LF one (EM 460.6±356.6 ms^2; HS 891.1±429.3 ms^2; p=0.012). Conversely, HF power, LF/HF ratio and DBT HRV did not show any significant difference.

Conclusion: We observed a reduction of basal HRV in EM compared to HS; basal HRV depends mainly on parasympathetic tone, but a similar reduction in HF power was not appreciated. Differently, the reduction of LF power in migraineurs may suggest a reduced sympathetic tone. Our data confirm that migraineurs show differences in ANS compared to healthy subjects, but more studies and wider samples are needed to better understand such aspects of the disease.

Use of anti-CGRP monoclonal antibodies in pediatric migraine: first evaluations of a phase 3, randomized, double-blind, placebo-controlled study

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Background: To date, prophylactic therapies for migraine include the use of antiepileptic drugs, calcium antagonists or antidepressants. In recent years, studies have been conducted on adults with the monoclonal antibody that binds the receptor of the peptide related to the calcitonin gene (GCRP), which competes specifically with the binding of CGRP to its receptor by inhibiting its function. CGRP modulates the nociceptive signal and is associated with the pathophysiology of migraine. Therapies currently available in children have limited efficacy. There is therefore a need for additional drugs.

Methods: Eight patients with chronic migraine and 1 patient with episodic migraine were enrolled in the study according to the criteria of the International Classification of Headaches (ICHD-III). Patients with chronic migraine are in the following phases: 1 finished the study, 1 dropped out, 2 in the double-blind phase, 3 in the open-label and dose-blind phase, and 1 moved from the episodic migraine study to chronic.

Results: Among the 8 patients with chronic migraine, it can be stated that 4 patients reported a reduction in the frequency and intensity of monthly migraine attacks, 2 patients reported the ineffectiveness of the therapy and 2 patients, in whom the double-blind phase was not yet started, are being evaluated. In three of the four patients with chronic migraine, who had a good response to therapy, a reduction in the frequency and intensity of monthly attacks was observed starting from the double-blind phase.

Conclusion: To date our preliminary data on the efficacy of anti-CGRP antibodies in the pediatric age, even if under evaluation, confirm what has been found in double-blind studies in the adult population, or the possibility of having a prophylactic drug specific and efficacy for migraine. However, more pediatric studies will be needed to confirm these preliminary results.

To detox or not to detox? Proposal of a bridging detoxification before starting prevention with anti CGRP-mAbs based on a real-life experience

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Background: Medication overuse headache (MOH) is a secondary headache disorder attributed to acute headache medications overuse by a person with an underlying headache disorder, usually chronic migraine (CM). The generally accepted approach to MOH comorbid with CM is withdrawal/detoxification from the overused medication(s) plus preventive treatment. Antibodies targeting the CGRP pathway (mAbs) have however proved effective also in CM patients with MOH. The aim of this study was to evaluate whether a proper detoxification protocol may add benefit in patients with CM and MOH starting mAbs treatment.

Methods: We conducted a retrospective study on 153 patients with CM and MOH who completed one-year treatment with mAbs (erenumab, galcanezumab or fremanezumab) monthly administered. Fifty-eight percent of patients underwent in-patient detoxification immediately before starting mAbs (DETOX group), while 41.8% did not (NO-DETOX group). The absolute difference between the last month of treatment (12th month) in monthly migraine days (MMDs), and monthly days and doses of drug intake represented the outcome measures of interest. These were derived from the *ad hoc* headache diaries that the patients filled in prospectively.

Results: Population characteristics: 76.3% F, mean age 52.3±13.6 years and history of chronicity 13.7±10.4 years. At baseline, the DETOX group had significantly more MMDs and monthly days of drug intake as compared to the NO-DETOX group (p=0.001 and p=0.006, respectively). After one-year treatment the DETOX group showed a more pronounced reduction in the endpoints considered, when compared to the NO-DETOX group. Specifically: absolute reduction in MMDs (DETOX -15.1±SD8.3, NO-DETOX -10.3±11.8, p=0.006), monthly drug doses (DETOX -33.8±36.4, NO-DETOX -21.5±31.0, p=0.04) and days of drug intake (DETOX -16.4±8.2, NO-DETOX -12.2±8.6, p=0.004).

Conclusion: The present findings confirm the effectiveness of CGRP-targeting mAbs in CM+MOH in the real-life setting. In addition they suggest that a proper in-patient detoxification protocol put in place before the initiation of mABs treatment may heighten the benefit of the latter. The baseline differences in the two groups and the retrospective design of the study suggest caution in the interpretation of the results and call for data confirmation in prospective comparative trials.

MIDAS reduction after 3 months of erenumab administration: does it predict treatment outcome in the real-life setting?

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Background: In Italy, monoclonal antibodies targeting CGRP pathway are subsidized for preventive treatment of high frequency and chronic migraine (CM) in patients with a baseline Migraine Disability Assessment (MIDAS) score ≥11. Treatment continuation requires a reduction in MIDAS score ≥50% after three months (T3). Our aim was to evaluate whether: i) ≥50% MIDAS score reduction at T3 is a reliable predictor of one-year erenumab response; ii) ≥50% reduction in monthly migraine days (MMDs) at T3 could act as an alternative indicator.

Methods: We conducted a prospective, real-world, study on 77 CM patients treated with erenumab 70-140 mg s.c. every 28 days for one year (T13). We collected: changes in MMDs and MIDAS score. Erenumab response was evaluated based on average reduction of MMDs during 1-year treatment and ≥50% reduction in MMDs during the last 4 weeks after the 13th injection (Responders-T13).

Results: At the end of the one-year treatment with erenumab 64.9% of patients qualified as Responders-T13. At T3, 55.8% of patients showed a reduction ≥50% in MIDAS score (MIDAS^{Res}) and 55.4% of patients reported a ≥50% reduction in MMDs (MMD^{Res}). Both responders exhibited a more pronounced reduction in MMDs during 1-year treatment as compared to NON-MIDAS^{Res} (MIDAS^{Res} 23.5±4.9 at T0 vs 7.7±6.2 at T13, NON- MIDAS^{Res} 21.6±5.4 at T0 vs 11.3±8.8 at T13, p=0.045) and NON-MMD^{Res} (MMD^{Res} 23.0±4.5 at T0 vs 6.6±4.8 at T13, NON-MMD^{Res} 22.3±6.0 at T0 vs 12.7±9.2 at T13, p<0.001) groups. Only MMD^{Res} predicted long-term outcome according to a multivariate analysis (Exp(B)=7.128; p=0.001), while MIDAS^{Res} did not. Up to 36% of Responders-T13 would have been discontinued early based on MIDAS^{Res} criteria. By contrast, discontinuation based on either MIDAS^{Res} or MMD^{Res} would have only excluded 16% of future Responders-T13.

Conclusion: MIDAS^{Res} partly reflects long-term response of erenumab treatment in CM, but it excludes more than one third of late responders too soon. The alternative consideration of ≥50% reduction in MIDAS score or MMDs in the first three months of treatment may represent a more accurate and inclusive option to select patients who can continue treatment.

Association between migraine severity and diet: a collection of data from a cohort of Southern Italy patients

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Background: Migraine is a primary headache whose pathogenesis is yet not completely understood; it is however well known that many factors have a role in triggering or relieving migraine attacks. Our study aimed to explore the impact of diet in migraine severity by examining a cohort of patients from Southern Italy, considering their peculiar dietary intake.

Methods: Patients with a diagnosis of migraine with or without aura participated in a structured telephone interview and answered a list of questions about migraine severity, estimated using both the number of headache days per month and the pain intensity ranging from 0 to 10, and their monthly intake of specific Italian dietary products. Moreover, we recorded weight and height to calculate BMI. Quantitative variables were analyzed using Pearson coefficient to find any significant correlation.

Results: We interviewed 157 patients with a mean age of 42.7±11.8 years. Twenty-one patients (13.3%) already recognized the role of diet in triggering their migraine attacks. We found out that the intake of pizza, a primary food in Mediterranean diet, has a slight positive correlation with migraine frequency ($r=0.254$, $p=0.001$), such as the intake of fruit ($r=0.212$, $p=0.008$), vegetables ($r=0.228$, $p=0.004$) and tomato ($r=0.236$, $p=0.003$). The same mild correlation ($r=0.2$, $p<0.05$) was found between headache days per month and the intake of non-alcoholic beverage (eg. coke), melon, broccoli, peas and fish. Instead, a few dietary products show a slight negative correlation with headache intensity ($r=-0.2$, $p<0.05$), such as ice cream, tea and vegetables or with headache days per month (only apples with a significance of $r=-0.17$, $p=0,034$). Besides, even if the correlation was barely non-significant ($r=0.156$, $p=0,052$), data about BMI are worthy of attention, showing an increase of this value together with the days of headache per month.

Conclusion: Our data confirmed the important role of dietary factors on migraine frequency and intensity, with a particular eye on food belonging to the Mediterranean diet. It is, therefore, necessary that we further investigate this aspect of migraine, considering the slight significant correlation we found, to help patients embrace a lifestyle suitable to their needs and well-being.