ABSTRACTS

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RATIONAL

The health, social and economic impact of brain diseases is increasing, and the World Health Organization has launched the Brain Health program to improve knowledge and treatment of brain diseases worldwide. Headache pathology, in particular migraine, is responsible for a significant share of disability related to diseases of the nervous system, especially in women. In recent years, scientific research has been responsible for a genuine revolution in the knowledge and treatment methods of headaches. The growth of knowledge regarding the pathophysiological mechanisms of headache pathology has enabled the development of new drugs, with specific mechanisms, for attack therapy and migraine prophylaxis. New national and international guidelines have been published to guide the physician in choosing the most effective treatments.

However, there remains a proportion of patients who are unresponsive to available therapies, and more importantly, the need for new diagnostic strategies is becoming increasingly clear for headache medicine to reach the standards of personalized medicine. The goal of the 38th SISC National Congress, held in the city of Turin, is precisely to bring this “revolution” in headache knowledge up to date by providing researchers and clinicians with an adequate update on current knowledge.

ORAL COMMUNICATIONS

Effects of anti-CGRP antibodies on tumor growth

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Background: CGRP activates canonical and amylin receptors coupled to adenylate cyclase and cAMP accumulation. The latter triggers a signaling cascade via PKA and ERK kinases that profoundly affects cellular homeostasis including growth and proliferation. Several studies also highlight a key role of CGRP in promoting angiogenesis and endothelial cell growth under physiological or pathological conditions. Lastly, CGRP released from intratumoral nerve endings emerges as an unexpected inhibitor of antitumor cytotoxic T cells, as well as a booster of cytoprotective autophagy of cancer cells. This information prompted us to evaluate the antitumoral effects of anti-CGRP antibodies in neoplasms releasing or non-releasing the neuropeptide.

Methods: The effect of fremanezumab and galcanezumab on PKA and ERK signaling pathways as well as proliferation of different cancer cell lines in culture was evaluated over time. The antibodies have also been tested on tumor growth *in vivo* (100 mg/kg) adopting the xenograft model in nude mice.

Results: We found that fremanezumab and galcanezumab inhibited both PKA and ERK pathways in cancer cell lines including C26, CA77, HTT and SHSY. The antibodies also counteracted cell proliferation *in vitro* in a concentration-dependent manner. When tested *in vivo*, we found that fremanezumab significantly reduced xenograft growth of two CGRP-releasing tumor cells such as C26 colorectal cancer cell and C77 medullary thyroid carcinoma cells. Remarkably, the anti-CGRP antibody also reduced expression of pro-angiogenic factors such as VEGF and cadherins in xenograft cells. Of note, fremanezumab showed no effects on xenograft growth when the CGRP non-expressing HTT medullary thyroid carcinoma cell line was used.

Conclusion: In addition to the proneoplastic effects of CGRP released from terminal nerve endings infiltrating tumors, our data disclose the ability of anti-CGRP antibodies to counteract the proneoplastic, autocrine/paracrine effects of CGRP directly released from tumor cells.

Calcitonin gene-related peptide levels are elevated in tear fluid of migraine patients

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Background: Calcitonin gene-related peptide (CGRP) has emerged as a key player in migraine pathophysiology, but challenges remain in its utilization as a biomarker. This study aimed to compare CGRP in tear fluid of migraine patients and healthy controls (HCs).

Methods: In this cross-sectional study, consecutive patients with a diagnosis of migraine with or without aura, according to the International Classification of Headache Disorders, third edition, were enrolled in the study. Tear fluid was collected from migraine patients in the interictal phase and from HCs through blotting strips of the Schirmer test (35 mm Flo™ Tear Measurement strips); CGRP concentration in tear fluid was assessed using ELISA. Clinical characteristics of migraine patients were collected, including monthly headache days (MHDs), monthly days with acute medication use (AMDs), number of analgesics (AMNs), Headache Impact Test-6 (HIT-6) and The Migraine Disability Assessment (MIDAS).

Results: Thirty patients with migraine (26 [87%] episodic, 4 [13%] chronic, 9 with aura [30%]) and 8 HCs were included with mean MHDs of 6.7± 6.2 and AMNs of 4.6± 4.7. Tear fluid CGRP concentrations were significantly elevated in interictal migraine patients (5.85± 4.54 pg/ml) compared to HCs (2.32± 1.98 pg/ml) (p=0.03). We evaluated the ability of CGRP tear levels to distinguish between migraine and HC groups, achieving an AUC of 0.731 ($P < 0.01$). The optimal threshold identified was 6.28, yielding a sensitivity of 44.83% and a specificity of 100%. We did not find a significant correlation between tear fluid CGRP levels with MHD, AMDs, HIT-6, and MIDAS scores. No significant differences emerged between patients with and without aura. As a proof-of-concept, tear fluid CGRP concentration in one patient was measured before starting galcanezumab treatment and after six months of therapy. The concentration decreased from 9.08 pg/ml to 0.72 pg/ml, indicating an absolute reduction of 8.36 pg/ml and a percentage reduction of 92.07%.

Conclusion: CGRP in tear fluid is significantly elevated compared to HCs. Detection of CGRP in tear fluid is non-invasive and likely allows more direct access to CGRP released from first-division trigeminal nerve fibers in migraine patients.

Exploring PACAP-38 levels in migraine patients receiving treatment with anti-CGRP monoclonal antibodies

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Background: Pituitary adenylate cyclase activating peptide-38 (PACAP-38) is considered a potential biomarker for migraine and may play a role in migraine pathophysiology alongside (Calcitonin Gene-Related Peptide) (CGRP), making it a promising target for biological treatment. Monoclonal antibodies targeting anti-CGRP (and the anti-CGRP receptor have shown high efficacy in preventing migraines. Despite their effectiveness, a subset of patients remains non-responsive to these therapies. Our study aims to investigate two hypotheses: first, PACAP-38 levels are elevated in migraine patients compared to control subjects, and second, PACAP-38 serves as a marker for low response to anti-CGRP therapy.

Methods: We recruited 40 patients (33 females, 7 males; mean age 52.05 ± 12.60 years; 22 chronic migraine, 18 episodic migraine) who initiated monoclonal antibody therapy (7 received Erenumab, 16 Galcanezumab, and 17 Fremanezumab). At the initial visit (T0), plasma PACAP-38 levels were measured. Patients were reassessed at 3 and 6 months (T3 and T6) based on monthly migraine days (MMD) and MIDAS scores. Responses at T3 and T6 were categorized as follows: LR (low responders, MMD or MIDAS decrease < 50%), GR (good responders, MMD or MIDAS decrease ≥ 50% and < 75%), and VGR (very good responders, MMD or MIDAS decrease ≥ 75%). A control group of 16 subjects (13 females, 3 males; mean age 51.31 ± 12.48 years) was also included.

Results: At baseline, patients exhibited significantly higher PACAP-38 levels compared to controls (229.91 ± 57.43 pg/ml vs 126.83 ± 43.95 pg/ml; p< 0.001). By T3, clinical outcomes based on monthly migraine days (MMD) showed 11 low responders (LR), 18 good responders (GR), and 11 very good responders (VGR), while MIDAS scores indicated 0 LR, 21 GR, and 19 VGR. By T6, we observed 10 LR, 11 GR, and 19 VGR based on MMD, and 2 LR, 6 GR, and 32 VGR based on MIDAS scores. However, no significant differences were found in PACAP-38 plasma concentrations among LR, GR, and VGR groups at T3 and T6. Furthermore, baseline PACAP-38 levels did not correlate significantly with clinical parameters at any time point (T0, T3, and T6).

Conclusion: While monoclonal antibodies (mAbs) targeting CGRP signaling effectively prevent migraines, their mechanism appears independent of PACAP-38 plasma levels. Despite the potential role of PACAP-38 in migraine pathophysiology alongside CGRP, our findings suggest that the therapeutic efficacy of mAbs in migraine prevention does not correlate with PACAP-38 plasma levels.

Psychological and biological markers of refractory migraine: data from a 6-month follow-up

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Background: Refractory migraine is a particularly aggressive form of the disease in which the patient does not benefit from any of the preventive therapies, including monoclonal antibodies (mABs). The understanding of factors involved in the prognosis of complicated forms of migraine is becoming a topic of interest in the current debate. Compelling evidence has suggested a negative prognostic value for psychopathological disorders. A possible role may also be played by a dysfunction of the endocannabinoid system. In this frame, the present study aims to identify psychological and potential biochemical/molecular factors associated with refractoriness to treatment with mABs.

Methods: Eighty subjects (mean age = 46.7 ± 12.5) with chronic (CM) or episodic (EM) migraine (according to ICHD-III) with at least three failures with preventive therapies received mABs treatment and were followed up at 6 months for their clinical condition. At enrolment, the patients underwent a comprehensive psychological evaluation according to the DSM-V criteria for mood, anxiety, and personality disorders. Gene expression of enzymes involved in the synthesis and degradation of endocannabinoids and their receptors were assessed in peripheral blood mononuclear cells, while levels of endocannabinoids and related lipids were evaluated in plasma.

Results: At the 6-month follow-up, 45 subjects reported a reduction of at least 50% in monthly migraine days (Responders - age: 46.8±11.8); whereas 28 did not (Refractories - age: 47.7±13.6). When compared to Responders, Refractories were characterized by a higher prevalence of anxiety disorders (67% vs 40%, p=.019), personality disorders belonging to Cluster C (avoidant, dependent, and obsessive-compulsive) (64% vs 33%, p=.009), more alexithymic traits (45.3±10.8 vs 39.8±8.4, p=.016), and a higher prevalence of childhood trauma (57% vs 29%, p=.016). Refractories had higher levels of gene expression of the enzymes NAPE-PLD (1.7±0.5 vs 1.4±0.5, p=.006) and MAGL (1.7±0.7 vs 1.4±0.5, p =.049) compared to Responders. By contrast, we found no significant difference in endocannabinoid, PEA, or OEA plasma levels between groups.

Conclusion: These findings suggest that psychological vulnerability associated with a peripheral alteration in the metabolism of N-acyl ethanolamines (NAEs) and 2-AG is indicative of a negative outcome of mAB treatment in people with migraine. Due to the complexity of NAE action and bioactive lipids with signaling cascades linked to NAPE-PLD activity, more research is necessary to understand the role of their lipid bioproducts in migraine refractoriness.

Molecular-enriched functional connectivity changes after mindfulness practice in serotonin and dopamine systems of Medication Overuse Headache patients

Davide Fedeli[1], Giuseppe Ciullo[1], Greta Demichelis[1], Jean Paul Medina Carrion[1], Maria Grazia Bruzzone[1], Emilio Ciusani[2], Alessandra Erbetta[1], Marina Grisoli[1], Erika Guastafierro[3], Danilo Antonio Montisano[4], Domenico D'Amico[4], Alberto Raggi[3], Anna Nigri[1], Licia Grazzi[4]

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Background: Mindfulness has gained significant interest in managing Chronic Migraine associated with Medication Overuse Headache (CM-MOH), with relevant clinical improvements associated with changes in brain functional connectivity (FC). However, the relationship between these findings and the underlying neurotransmitter systems remains still unexplored. In this study we capitalized on the recently-developed molecular-enriched connectivity framework to investigate one-year longitudinal FC changes associated with serotonin, dopamine, and noradrenaline receptors and transporters distribution in CM-MOH patients treated with mindfulness practice alongside treatment as usual.

Methods: Thirty-four adult CM-MOH patients obtained from a previous RCT study were divided into two groups: Treatment as Usual (TaU, n=17) and mindfulness-added-to-TaU (TaU+MIND, n=17). Participants underwent rs-fMRI scans before (T0) and after one year (T1). Longitudinal group differences in serotonin, dopamine, and noradrenaline molecular-enriched FC were investigated with REACT toolbox.

Results: TaU+MIND group compared with TaU group showed increased dopamine-enriched FC (D_1 receptor and DAT transporter) in the right anterior insular cortex and increased serotonin-enriched FC ($5HT_{1b}$ receptor, 5HTT transporter) in the caudate nuclei. No noradrenaline-related FC changes were found.

Conclusion: Dopamine-enriched increased insular connectivity may reflect a mindfulness-related remodulation of the emotional processing of nociceptive information, as dopamine regulates motivation, mood, reward, and addictive behaviour. Insular FC alterations have been recently observed in CM-MOH patients and associated with depression and sensory input integration through the Salience Network. Additionally, increased serotonin-enriched FC with caudate nuclei may indicate a normalization of the serotonergic system, which is often dysregulated in chronic pain conditions and in mood disorders. The caudate nucleus plays an important role in the emotional, cognitive, and sensory modulation of pain experience. By reporting significant changes in serotonin and dopamine molecular-enriched FC, our study provides a deeper understanding of how mindfulness practice impacts on the brain, highlighting its beneficial clinical effects for CM-MOH treatment.

Accelerated repetitive transcranial magnetic stimulation over left dorsolateral prefrontal cortex could improve migraine in CGRP antagonists resistance

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Background: Drug-resistant headaches, especially those that do not respond to calcitonin gene-related peptide (CGRP) antagonists, represent a major therapeutic challenge. Cognitive and emotional dysfunction could lead to treatment failure, which could be addressed by stimulating the left dorsolateral prefrontal cortex (lDPF) with an accelerated intermittent burst theta stimulation (aiTBS) protocol.

Methods: Participants underwent an initial EEG examination that included a computerized cognitive and emotional Stroop task, as well as clinical, psychological, and cognitive examinations to measure pain, quality of life, psychological symptoms, and cognitive function. The assessments were conducted at baseline (T0), after which sham stimulation was administered. One month after the first assessment (T1), participants underwent the actual stimulation, which consisted of five sessions per day on four consecutive days. Each session consisted of 1,620 pulses divided into 54 triple bursts, with a train duration of 2 seconds and an interval of 8 seconds between trains. Pulses were delivered at 110% of motor threshold with a 15-minute break between sessions. A third study was conducted one month after T1 (T2) to evaluate the efficacy of the actual stimulation.

Results: Twelve patients completed the protocol. The results showed no statistically significant differences in the EEG tasks (Stroop and emotional Stroop), probably due to the well-preserved cognitive and emotional status of the participants. Pain perception (NRS) showed a significant improvement after sham stimulation (T1) compared to baseline (T0) ($p = 0.039$), suggesting a placebo effect, but the improvement was further significant after actual stimulation (T2) ($p = 0.004$). The aiTBS caused a significant improvement in the number of days with headache ($p = 0.039$) and in the use of acute medication ($p = 0.013$).

Conclusion: Stimulation of the lDPF cortex could act on the basal mechanisms of migraine and represents a reliable option for patients who do not respond to CGRP antagonists. Further prospective studies could confirm aiTBS as an effective non-pharmacological approach for drug-resistant migraine.

Predictors of recurrence and outcome of idiopathic intracranial hypertension in children and adolescents: an Italian single-center retrospective study

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Background: Idiopathic intracranial hypertension (IIH) is a syndrome of increased intracranial pressure (PIC) without structural lesions of the central nervous system. In the pediatric population, this condition usually has a good prognosis but rarely may lead to irreversible outcomes (i.e. visual loss). In children with IIH, data on the prognostic factors and the risk of recurrence are limited and many studies are based on small series. The aim of this study is to identify factors related to relapses and functional outcome, clarifying the eventual relation with clinical severity at onset of symptoms.

Methods: Retrospective cohort study on pediatric patients (under 18 years at presentation) diagnosed with IIH, hospitalized in the Pediatric Neurology Unit of Padua's University Hospital, between 2010 and 2023. The following clinical data were collected: demographic, anthropometric, neurological, ophthalmic, laboratory, intracranial pressure value at lumbar puncture and neuroimaging data at clinical onset and data regarding recurrence and functional outcome at last follow-up. Patients with incomplete data or lost at follow-up were excluded.

Results: Thirty-four out of fifty-eight patients were enrolled in the study (18, 53% male). The median age at onset was 10 years. At presentation all the patients were symptomatic, with headache as the most common symptom (82.4%). At follow-up, 11/34 (32%) patients had a long (more than 3 months) symptomatic course and this was significantly associated to a late IIH diagnosis and a normal neurological examination; 12/34 (35%) patients had one or more IIH recurrences; the only significant risk factor for recurrence was a higher Body Mass Index (BMI).

Conclusion: Our retrospective study provides insights into predictive factors for recurrence and symptoms persistence in pediatric IIH. Based on our data, a late diagnosis and a normal neurological examination are the main factors related to a prolonged symptomatic course, therefore a timely diagnosis through an accurate anamnesis is fundamental. When faced with a first diagnosis of IIH, due to the risk of recurrence caused by a high BMI, reduction in body weight is a treatment goal. Finally, the clinical severity at onset does not appear to be related to a more unfavorable prognosis or course.

HeaRT-Headache, Resilience and Trauma in Adolescence: a multicentre Italian project

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Background: The research conducted represents a contribution within a large multicentre project focused on analysing the relationship between headache and resilience. This project involves several juvenile headache centres in Italy, and aims to explore levels of resilience in adolescent subjects between 14 and 18 years of age, with and without primary headache, in relation to levels of psychopathology and trauma.

Methods: A total of 1008 adolescents (14-18 years old) were involved in this study. The sample was divided into (a) Experimental Group (EG) consisting of 293 subjects with a diagnosis of primary headache according to the International Classification of Headache Disorders (ICHD-3) and (b) Control Group (CG) including 715 subjects without a diagnosis of headache. All participants completed the Youth Self Report for Ages 11-18 (YSR, Achenbach, 2001) to assess behavioral competency and behavioral problems, Connor Davidson Resilience Scale (CD-RISC, Connor, Davidson 2003) to assess the resilience and ITEM-Revised to assess traumatic events.

Results: Higher rates of emotional and behavioral problems were found in the adolescents of the CG (M: 65.3; sd: 10.4) in comparison to the adolescents of the EG (M: 57.7; sd: 17.5) ($p<0.01$). The differences between the two groups in the CD-RISC total score were not significant.
In the total group, 95.2% report at least one stressful event; in particular CG reported a higher percentage of stressful events (96.2%) than the EG (92.8%), showing a statistically significant difference ($p=0.03$). The inverse/negative correlation between the total YSR and CD-RISC and the positive correlation between YSR and ITEM were significant for both groups.

Conclusion: The results indicated that although there were no statistically significant differences in resilience levels between the two groups, the controls had higher levels of psychopathology than the headache patients and reported a higher number of traumatic events. This suggests that the presence of headache may be a protective factor for the onset of psychopathology and helps shed light on the high psychic distress of adolescents that goes unnoticed and remains unseen.

Post-ictal headache: clinical characteristics in consecutive patients with epilepsy

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Background: Post-ictal headache (PIH) represents a frequent and interesting association between headache and epilepsy, although poorly investigated and treated by epileptologists. Its duration and severity can have a significant impact on the quality of life of affected patients. The pathophysiology of this condition is still under debate, and its comprehension would be of paramount importance to improve therapeutic strategies.
The objective of our study is to investigate the prevalence and characteristics of post-ictal headache (PIH) in a cohort of 173 consecutive patients attending the first and second level Epilepsy outpatient Clinic in the University Hospital of Padua.

Methods: We collected data about type and aetiology of epilepsy, type and frequency of epileptic seizures, antiseizure medications, drug resistance and presence of PIH; if PIH was present a questionnaire was administered evaluating frequency of PIH respect to the global amount of seizures, severity and duration of pain, type of pain, localisation, associated symptoms, pain medication use and their efficacy. Patients with epileptic encephalopathies were excluded from the study.

Results: A total of 209 patients were studied, of which 36 were excluded. Among 173 patients included, 81 were males and 92 females, mean age was 43 years; 18,5% (32) reported PIH. PIH affected around one third of patients with active epilepsy or drug resistance. 77.4% of patients with PIH were on polytherapy and 55.9% reported tonic-clonic epileptic seizures. Pain of PIH was of moderate or severe intensity (87.5%), gravative (75%), had a bifrontal or diffuse localisation (60%), mean duration of 3-6 hours (37.5%); most frequently associated symptoms were nausea (34.4%) and confusion (25%). Almost half of the patients (46.9%) treated pain with over-the-counter medications, with significant benefit only in 60% of cases.

Conclusion: PIH is significantly associated with active epilepsy, polytherapy, drug resistance, generalized tonic-clonic seizures and focal-onset seizures with subsequent tonic-clonic evolution; it is also associated with a higher frequency of epileptic seizures.
PIH is not correlated with the type and aetiology of epilepsy disorder, nor with the type of anti-seizure medications. Further studies are needed to elucidate the best therapeutic options for pain management in these patients.

OnaBotulinumtoxin-A effectiveness evaluation in chronic migraine patients with short or long disease history: an Italian multicentric study (the BACH Study)

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Background: The aim of this ongoing observational prospective multicentric study is to investigate whether the history of Chronic Migraine (CM), i.e. its duration for more than or less than 10 years, can predict Onabotulinumtoxin-A (OBT-A) treatment effectiveness. Moreover, since psychiatric symptoms often may impact migraine treatment effectiveness, the present study will also aim at evaluating if the psychopathological profile of the enrolled CM patients may influence the outcome.

Methods: Consecutive CM patients, undergoing OBT-A treatment in 8 Italian headache centers, have been enrolled since January 2024. Evaluation times were at baseline (T0) and after the other 3 times of treatment (T1-3). We collected Monthly Headache Days (MHDs) and Monthly Acute Medication Intake (MAMI). Disability was assessed by means of HIT-6 and MIDAS. The intensity and quality of perceived pain was evaluated by means of VAS, BS-11, PPI, BRS-6 and SF-MPQ scales. The psychopathological profile was evaluated by means of BDI-II, BIS-11, STAI-Y, DERS, TAS-20 questionnaires.

Results: We have currently enrolled 99 patients (aged 46.7 SD 1.5 yrs, F 87.9%), undergoing OBT-A for the first time; 66 patients (66.7%) had a CM history longer than 10 years. At baseline, TAS-20 scores did not show alexithymia (48.1 SD 13.5); STAY scores revealed moderate level of anxiety (42.9 SD 6.5) and BDI moderate depression (15.5 SD 10.6). At T0 MHDs resulted 22.4 SD 7.4 and MAMI 19.5 SD 11.2, MIDAS was 78.7 SD 58.4, HIT-6 63.7 SD 10.7 and VAS 8.5 SD 1.3. Of the entire cohort, 68 patients completed T1 evaluation. At T1 patients experienced a significant reduction ($p<.001$) for all explored variables: MHDs (13.9 SD 7.4;), MAMI (10.7 SD 11.1), MIDAS (44.4 SD 41.1), HIT-6 (59.2 SD 10.8) and VAS (7.6 SD 1.5). A 50%RR was achieved in 25 out of 68 patients (36.8%) at T1. CM history did not influence the improvement after T1 in MHDs ($p=.109$), MAMI ($p=.380$), HIT-6 ($p=.402$); MIDAS ($p=.675$) and VAS ($p=.636$). However, patients achieving a 50RR% more frequently presented a CM history less than 10 years ($p=.037$).

Conclusion: In this preliminary report OBT-A was more effective in terms of 50%RR in patients with shorter CM duration.

Do European Headache Federation criteria reflect response to acute treatments in resistant and refractory migraine? Results from the REFINE study

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Background: The European Headache Federation (EHF) provided definitions for resistant and refractory migraine. Both definitions include the presence of debilitating headache for ≥8 days/month for at least 3 months (resistant migraine) or 6 months (refractory). The term "debilitating" headache implies that in individuals with resistant and refractory migraine, the treatment of acute attack is also unsuccessful. We aimed to evaluate if the EHF criteria, based on previous preventative failures, also reflect the acute treatment response rate.

Methods: We performed a multicenter, prospective, international study (REFINE study) to test in a real-life setting the proposed EHF definitions of resistant and refractory migraine. We calculated the acute treatment response rates investigating the patients' perception about the effectiveness of intervention against headache through the Headache Under-Response to Treatment (HURT) questionnaire [Westergaard, 2013]. We compared the effectiveness of acute treatment in the three groups of patients with non-resistant and non-refractory, resistant, and refractory migraine.

Results: We included 689 patients from 18 European headache Centers: 354 patients (51.4%) with non-resistant and non-refractory, 262 (38.0%) with resistant and 73 (10.6%) with refractory migraine. HURT questionnaire question 5 “Does one dose of your acute headache medication get rid of your headache and keep it away?” patients with non-resistant and non-refractory migraine were more likely to answer “always” or “often”, compared to those with resistant and refractory (52.0%; vs 26.7%; vs 6.9%, respectively; $p<0.001$). On the other hand, patients with refractory migraine were more likely to answer that one dose of acute medication “never” got rid of their headache compared to those with resistant and non-resistant non-refractory migraine (40.3% vs 10.9% vs 7.2%, respectively; $p<0.001$).

Conclusion: According to our results, patients with resistant and especially refractory migraine exhibit worse rates of acute treatment response compared to those with non-resistant and non-refractory migraine. Beyond selecting appropriate preventative drugs, managing resistant and refractory migraine should also focus on optimizing acute treatment, including switching medications if necessary and addressing potential medication overuse.


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POSTERS

Insights into the involvement of TRPA1 channels in the neuroinflammatory machinery of trigeminal neuralgia

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Background: Antagonism of transient receptor potential ankyrin type-1 (TRPA1) channels counteracts the experimentally-induced trigeminal neuralgia pain. TRPA1 channels activated/sensitized by inflammatory stimuli can modulate glial cells activity, a driving force for pathological pain. Additionally, a functional interaction between the inflammatory-related toll-like receptor-7 (TLR7), activated by miR-let-7b, and TRPA1 was reported *in vitro*. However, the precise mechanisms and players involved are unknown. Here, we aimed at investigating the potential mechanisms involving TRPA1 channels in the inflammatory pathways following the development of trigeminal neuralgia.

Methods: Adult male rats undergoing chronic constriction injury of the infraorbital nerve (IoN-CCI)/sham surgery were treated with a single administration of the TRPA1 antagonist ADM_12/vehicle after the development of allodynia. Trigeminal system-related areas (trigeminal ganglion and areas containing the trigeminal nucleus caudalis) and plasma samples were used to evaluate central and peripheral inflammatory mediators (by rt-PCR and ELISA) and immunofluorescence staining of glial activation in the trigeminal nucleus caudalis.

Results: IoN-CCI rats showed a significantly more marked activation of microglia and astroglia in the trigeminal nucleus caudalis compared to sham-operated rats. Additionally, in the trigeminal-related areas, IoN-CCI animals showed significantly higher gene expression levels of pro-inflammatory cytokines, associated to lower gene expression levels of anti-inflammatory cytokines, together with consistent altered changes in the respective protein plasma levels. ADM_12 in IoN-CCI rats prevented the observed alterations regarding cytokines, but did not affect glial activation in the trigeminal nucleus caudalis. It also counteracted the IoN-CCI-induced increase in miR-let-7b and TLR7 mRNA gene expression in all the considered areas, supporting a possible interplay with TRPA1 channels.

Conclusion: The findings suggest that, in addition to their known involvement in the nociceptive pathway, TRPA1 channels may also play a direct or indirect role in pain-related inflammation, through the activation of the miR-let-7b/TLR7/TRPA1 axis at neuronal and glial level.

Intestinal dysbiosis and chronic migraine: preliminary assessment in an animal model

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Background: Gut microbiota, the community of symbiotic microorganisms that colonise the gastrointestinal tract, influences numerous physiological and pathological processes and modulates the bidirectional communication network between the gut and the brain. Mounting evidence suggests that microbiota-mediated gut-brain crosstalk may contribute to migraine pathogenesis. Alteration of the gut microbiota profile can lead to impaired intestinal barrier function with consequent release of the bacterial endotoxin lipopolysaccharide (LPS), which may stimulate pro-inflammatory pathways. Here, we investigated changes in the gut microbiota composition in the chronic migraine-like animal model based on chronic nitroglycerin (NTG) administration. We also assessed the circulating levels of LPS binding protein (LBP) and the protein expression of occludin - tight junction protein - in the small intestine.

Methods: Adult male Sprague-Dawley rats were treated with NTG (5 mg/kg i.p.) or vehicle every two days over nine days (5 total injections). On day nine, four hours after the last administration of NTG or vehicle, rats underwent the orofacial formalin test to validate the correct development of migraine-like hyperalgesia. Rats were sacrificed after undergoing behavioural testing. Serum and small intestine samples were collected to assess LBP by ELISA and occludin protein levels by Western blot. Fecal 16S ribosomal RNA gene sequencing was conducted to analyse changes in the gut microbiota.

Results: NTG administration increased nocifensive behavior in phase II of the orofacial formalin test, confirming the development of migraine-like hyperalgesia at the trigeminal level. The gut microbiota analyses revealed significant differences in beta diversity and gut microbial composition between the NTG-treated and vehicle groups. Among the differentially abundant taxa identified between the two groups, several bacteria belonging to the Lachnospiraceae family and Gastranaerophilales order were more represented in NTG-treated animals. NTG-treated animals also had significantly higher serum levels of LBP. Conversely, no substantial alterations were found in the levels of occludin, which is responsible for the intestinal barrier integrity.

Conclusion: These findings confirm a link between the gut microbiota and migraine-like pain. In support of this relationship, it seems conceivable that dysbiosis may influence trigeminal pain, probably via the release of gut LPS into the systemic circulation, which is probably unrelated to intestinal tight junction changes.

Effects of dual inhibition of fatty acid amide hydrolase and TRPV1 in an animal model of migraine

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Background: Fatty acid amide hydrolase (FAAH) inhibition is a potential target for treating pain, including migraine. Dual-acting drugs that simultaneously inhibit FAAH and antagonize transient receptor potential vanilloid 1 (TRPV1) represent a promising and more effective therapeutic approach for pain management, minimizing side effects associated with single-target agents. N-arachidonoylserotonin (AA-5-HT) is an attractive dual-acting compound that exerts analgesic actions in acute and chronic pain animal models. Here, we assessed the effect of AA-5-HT on trigeminal hyperalgesia and anxiety-like behavior in the migraine animal model induced by acute nitroglycerin (NTG) administration. We also evaluated the action of this dual inhibitor on calcitonin gene-related peptide (CGRP) and inflammatory cytokines mRNA levels in specific cranial areas.

Methods: The study was performed in male Sprague-Dawley rats pre-treated with NTG (10 mg/kg, i.p.) or vehicle (4 hours before) and treated with the AA-5-HT (5 mg/kg, i.p.) or vehicle 15 minutes before behavioral testing. Gene expression of CGRP and inflammatory cytokines were assessed in the cranial regions of rats that underwent the orofacial formalin test by rt-PCR. We also investigated the modulation of NTG-induced anxiety-like behavior in elevated plus maze (EPM) test.

Results: The findings show that AA-5-HT did not affect NTG-induced changes in open arms entries in EPM, while it inhibited NTG-induced hyperalgesia in the orofacial formalin test. Furthermore, AA-5-HT significantly decreased the gene expression of CGRP, tumor necrosis factor alpha (TNF-alpha) and interleukin 6 (IL-6) in the trigeminal ganglia and central areas. On the contrary, treatment with AA-5-HT did not reverse the anxiogenic effect in the group treated with NTG. In basal conditions (without NTG), it induced an anxiogenic effect without modifying nocifensive behavior.

Conclusions: The study confirms that anandamide has therapeutic potential in treating migraine pain. It also suggests that increasing endogenous endocannabinoid levels and blocking the TRPV1 receptor in specific areas reduces the inflammatory pathway associated with trigeminal hyperalgesia, but it does not affect anxiogenic behavior.
Further studies are needed to assess anandamide levels in brain areas involved in the trigeminal system and those involved in emotional regulation, both in the absence and presence of NTG.

Altered functional connectivity of the thalamus and medulla-pons in a rat model of migraine based on nitroglycerin administration

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Background: Migraine is a burdensome neurological disease that manifests with recurrent attacks of pain associated to other symptoms. The complex mechanisms underlying the disorder are only partly known. Resting-state functional magnetic resonance imaging (rs-fMRI) has provided important information in brain functional connectivity (FC) changes during migraine attacks, showing a reduction in FC between sensorimotor brain regions and other areas in migraine sufferers, impacting various processes such as visual processing, sensory integration, pain signal processing, attention, and cognitive assessment. In this pilot study, we used a validated animal model of migraine induced by a single administration of nitroglycerin (NTG) to explore the alterations in brain FC in a well-controlled experimental setting.

Methods: Male Sprague-Dawley rats (N= 5 per group) were injected with NTG (10mg/kg, i.p.) or vehicle (control group) 3 hours before undergoing rs-fMRI. Each acquired rs-fMRI series was preprocessed with the RABIES tool for removing noise and then parcellated using the rat brain anatomical SIGMA atlas to obtain a functional connectome. Parcellated rs-fMRIs were then analysed with the Brain Connectivity Toolbox in Matlab to calculate graph theoretical metrics for each atlas area.

Results: A Statistical comparison (t-test) of graph metrics' values between NTG-treated rats and controls revealed a significant reduction in betweenness centrality (0.03±0.02 vs 0.007± 0.002) in the thalamus and increased Clustering Coefficient (0.05±0.032 vs 0.004 ±0.008) and Local Efficiency (0.085±0.05vs 0.004±0.008; 1.115±0.73 vs 0.048±0.108) in the pons.

Conclusion: These findings suggest the enhanced functional influence of these brain regions on the networks of NTG-stimulated rats, shedding light on potential mechanisms underlying migraine-related alterations in brain connectivity.

Vascular Compression in Trigeminal Neuralgia discloses Trigeminal Root Somatotopic Organization

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Background: In Trigeminal Neuralgia (TN) pain is localized in the distribution of one or more branches of the trigeminal nerve. A hallmark of TN is the presence of discrete skin areas able to trigger pain attacks when touched. In classical TN trigeminal reflexes are normal but dedicated MRI studies can recognize a vascular compression with morphological changes of trigeminal root. In this combined clinical, neuroimaging and neurophysiological study we aim to disclose trigeminal root somatotopic organization.

Methods: We enrolled 53 patients with a definite diagnosis of classical TN. From MRI images we measured the polar coordinates of the impacting vessel on the trigeminal root circumference and then correlate it with pain distribution, trigger zones and latencies of the early components of the trigeminal reflexes.

Results: Pain in V1, V2 and V3 is associated, respectively, with vascular compression in the medial, superior and lateral aspect of the nerve ($p<0.05$). Cutaneous trigger zones are associated with corresponding region of the circumference ($p<0.05$). Side asymmetry in the latency of the R1 component of the blink reflex is associated with superomedial compression, while side asymmetry in the latency of the SP1 component of the masseter inhibitory reflex is associated with superior compression when the reflex is evoked from the infraorbital nerve, and with lateral compression when it is evoked from the mental nerve ($p<0.05$).

Conclusion: In TN, pain distribution, trigger zones and increased latencies of trigeminal reflexes are correlated with specific sites of neurovascular compression along trigeminal root circumference, disclosing its somatotopic organization.

Role of specific microRNAs in cluster headache: correlation with disease phenotype and neuropeptide levels

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Background: The role of microRNAs has been studied in episodic and chronic migraine, but their involvement in cluster headache pathophysiology is yet to be demonstrated. We aim to evaluate the role of specific microRNAs in subjects with episodic cluster headache during active (AeCH) and remission (ReCH) phases, in subjects with chronic cluster headache (cCH), and in healthy controls (HCs).

Methods: In this cross-sectional controlled study, we assessed the gene expression of miR-382-5p, miR-34a-5p, and miR-155 in peripheral blood mononuclear cells (rtPCR - Relative Quantification to Ubiquitin C). Participants with AeCH and cCH were assessed in an intercritical phase, i.e. outside of an acute cluster headache attack.

Results: We enrolled 18 AeCH (45.7±12.8 years of age, 14 males, 16.3±9.6 attacks/week), 7 ReCH (48.6±19.8 years, 5 males), 10 cCH (50.1±16.2 years of age, 9 males, 21.4±18.8 attacks/week), and 14 HCs (45.4±15.2 years of age, 2 males). miR-382-5p, mir-34a, and miR-155 levels were higher in all CH subgroups when compared to HCs ($p<0.001$ for all comparisons). miR-382-5p expression was higher in AeCH (1.7±0.8) when compared to ReCH (0.8±0.2, $p<0.005$). miR-34a-5p expression was higher in AeCH (1.7±0.4) when compared with ReCH (1.0±0.3), and cCH (1.2±0.3) ($p<0.001$ for all comparisons). miR-155 expression did not differ among AeCH (1.7±0.5), ReCH (1.3±0.3) and cCH (1.3±0.5).

Conclusion: The expression of miR-382-5p, miR-34a-5p and miR-155 is higher in CH when compared to HCs. miR-382-5p and miR-34a-5p were associated with disease activity status, being higher during the active bouts when compared to remission. Our data pave the way to further studies to assess a possible role of these microRNAs in the pathophysiology of CH.

miR-382-5p and miR-34a in migraine: gene expression in monocytes and post-hoc comparison with peripheral blood mononuclear cells levels

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Background: We previously demonstrated altered gene expression of miR-382-5p and miR-34a in peripheral blood mononuclear cells (PBMCs) of subjects with migraine. PBMCs include a variety of cells with immune function. In the present study we aim to: i) define the specific monocytic expression of miR-382-5p and miR-34a; and ii) compare microRNAs expression between PBMCs and monocytes.

Methods: i) microRNAs monocyte gene expression. Monocytic gene expression (rtPCR - Relative Quantification) of miR-382-5p and miR-34a was performed as a secondary analysis of a larger study (NCT05891808). We enrolled 50 subjects with episodic migraine (EM, 41.2±10.5 years of age, 74.0% female), 35 subjects with chronic migraine and medication overuse (CM-MO, 46.6±10.7 years of age, 82.9% female), and 30 healthy controls (HC, 43.3±11.9 years of age, 66.7% female).
ii) comparison between PBMCs and monocytes. We conducted a post-hoc analysis comparing expression in monocytes and PBMCs. Data of PBMCs gene expression were derived from a previously published dataset (see https://doi.org/10.1186/s10194-020-01189-0 for details) based on a study with comparable design, inclusion/exclusion criteria and laboratory procedures.

Results: i) microRNAs monocyte gene expression. miR-382-5p monocytic gene expression was higher in EM (1.2±0.5 RQ) and CM-MO (1.7±0.6 RQ) when compared to HCs (0.4±0.1 RQ, p=0.001). miR-34a monocytic gene expression was higher in EM (1.1±0.4 RQ) and CM-MO (2.2±0.9 RQ) when compared to HCs (0.6±0.2 RQ, p=0.001). Expression of both microRNAs was higher in CM-MO when compared to EM (p=0.001).
ii) comparison between PBMCs and monocytes. The two study populations were comparable in terms of clinical/demographic features. mir-382-5p and mir-34a gene expressions were higher in PBMCs when compared to monocytes (p=0.001), and in CM-MO when compared to EM (p=0.001). For both microRNAs, the higher expression in PBMCs was mainly explained by the higher levels in CM-MO patients (interaction: p=0.001).

Conclusions: miR-382-5p and miR-34a expression is increased in monocytes of subjects with migraine, being higher in CM-MO when compared to EM. Bearing in mind the limits of a post-hoc analysis with a historical cohort, miR-382-5p and miR-34a expressions were higher in PBMCs when compared to monocyte, with this difference being driven by the higher values observed in the CM-MO group.

A human provocation model with capsaicin (TRPV1) and cinnamaldehyde (TRPA1) to evaluate CGRP-mediated neurogenic responses in patients with endometriosis and comorbid endometriosis and migraine

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Background: Endometriosis and migraine are two chronic diseases that share some similarities in clinical symptoms and in the pathophysiological mechanisms underlying. Transient receptor potential (TRP) channels, particularly TRPV1 and TRPA1, are primarily expressed by sensory neurons, but also in the endometrium. Main nerve fibers in endometriotic lesions are CGRP-, TRPA1-, and TRPV1-positive. No studies have evaluated TRP sensitization in patients with endometriosis or in those with both endometriosis and migraine. Herein, we evaluate differences in the CGRP-mediated neurogenic responses through TRPV1 and TRPA1 activation in patients with endometriosis and comorbid endometriosis and migraine using a human provocation model.

Methods: The study included two cohorts: i) patients affected by both endometriosis and migraine, and ii) patients affected by endometriosis-only. Two additional cohorts are ongoing (i.e., patients with migraine-only and healthy controls). An established provocation test was used to evaluate cutaneous neurogenic responses (i.e., vasodilation [DBF, dermal blood flow] and evoked pain/tingling sensation) to the topical application of capsaicin (TRPV1), cinnamaldehyde (TRPA1), and placebo solutions at the forearm. Enrolled subjects underwent a single experimental session with measurements at baseline and 30, 45, 60, and 90 minutes (tn) post solutions application. DBF were assessed using Laser Doppler perfusion imaging and reported as a percentage of change compared to baseline (DBF%). The primary outcome was the DBF difference (overall and at single time points) after capsaicin or cinnamaldehyde stimulation between patients with endometriosis or endometriosis and migraine. DBF% were normally distributed; therefore, multiple unpaired and Welch's t-tests were performed.

Results: Thirty-five patients (21 with endometriosis and 14 with comorbid endometriosis/migraine) were recruited. All patients were free from other severe diseases or taking any regular drug. No overall significant changes were reported between patients with endometriosis and those with endometriosis/migraine after application with capsaicin (DBF% mean difference ± SEM, -25.74±44.03, p=0.58) or cinnamaldehyde (-13.51±61.33, p=0.83). No vasodilation was reported in any group or time point with placebo solutions. Interestingly, the endometriosis-only group had a not significative higher DBF% in response to capsaicin at t30 (32.51 ± 27.9, p=0.25) and t45 (39.23 ±

26.5, p = 0.14) compared to endometriosis/migraine patients. A similar, but lower, trend was observed for cinnamaldehyde at t30 (25.7 ± 31.5, p=0.42) and t45 (25.06±27.2, p=0.36). The peak of DBF% for both groups was reported at t45 for capsaicin (endometriosis-only: mean 283.87, range 321.6-246.13; endometriosis/migraine: mean 244.63, range 283.3-205.88) and at t30 for cinnamaldehyde (209.22, range 255.10-163.2 vs183.5, range 226.0-140.9). A sustained effect of capsaicin (defined as at least 100 DBF%) was still observed at t90, whereas DBF% in response to cinnamaldehyde returned to baseline at t60.

Conclusion: No vasodilation differences after both TRPV1 and TRPA1 cutaneous stimulations have been reported between patients with migraine and comorbid endometriosis and migraine, although the endometriosis-only group seems to be more sensitized by both capsaicin and cinnamaldehyde. Further analysis, including other ongoing groups and stratification of patients are needed to validate these findings.

Plasma levels of glial fibrillary acidic protein and neurofilament light chain in patients with chronic migraine: a monocentric case-control study

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Background: Plasma neurofilament light chain (pNFL) and plasma glial fibrillary acidic protein (pGFAP) levels reflect neuronal damage and astrocyte activation, respectively. Whether these phenomena play a role in migraine is still unknown. This study aimed to compare pGFAP and pNFL levels between patients with chronic migraine (CM) and healthy controls (HC), to analyze their relation with clinical features and to evaluate their utility as possible biomarkers of CM.

Methods: We studied 40 CM patients and 28 HC. pGFAP and pNFL were quantified with single molecule array (Simoa) technology. We collected for each subject demographic and clinical data.

Results: In our cohort, pGFAP and pNFL correlated with age. We did not find a statistically significant difference in pGFAP or pNFL levels between CM patients and HC, nor did we observe a correlation of pGFAP and pNFL with migraine characteristics (such as presence of migraine aura, attack frequency, migraine intensity, years of disease, etc).

Conclusion: Our results strongly support the assumption that migraine represents a benign condition, characterized by transient functional brain alterations only and not by the accumulation over time of neuronal damage and/or astrocyte activation.

Migraine-like pain in patients treated with Immune Checkpoint Inhibitors: the role of PD-1 and PD L1 in migraine development

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Background: Studies in animal models show that the pharmacological blockade of PD-1 increases acute nitroglycerin-induced hyperalgesia, in association with a significant increase in CGRP levels. Moving from this evidence, we hypothesize that a pharmacological blockade of PD-L1 and PD-1 with Immune Check Point Inhibitors (ICIs) may cause migraine pain even in humans.

Methods: This was an observational retrospective study. All patients consecutively admitted to the Medical Oncology Department of the San Salvatore Hospital of L'Aquila, in a two-year period were screened for the inclusion. Inclusion criteria were age ≥ 18 years, start of a treatment with ICIs for a cancer diagnosis and a follow-up period of a at least 6 months to monitor neurological side effects through a structured chart reviews process. ICI were classified according to their mechanism of action: anti-PD-1 monoclonal antibodies (cemiplimab, nivolumab, pembrolizumab), anti PD-L1 monoclonal antibodies (avelumab, atezolizumab), and anti-CTLA-4 monoclonal antibodies (iplimumab).

Results: A total of 157 patients (103 men mean age±SD 69.7±11.7 and 54 females mean age±SD 64.0±16.3) received a treatment with ICIs. ICIs were the first-line treatment in most of the patients (n=125: 80%). Anti PD1 monoclonal antibodies (n=128; 82%) were the most frequently used drugs, followed by anti-PD-L1 monoclonal antibodies (n=17; 11%). A minority of patients was treated with an anti-CTLA-4 monoclonal antibody singly (iplimumab n=2; 1%) or in combination with an antiPD1 monoclonal antibody (n=10; 6%). Central Nervous System side effects included headache with migraine features (n=17;11%) and focal neurological symptoms caused by stroke (n=1). Peripheral nervous system manifestations included acute inflammatory demyelinating polyneuropathy (n=1), myasthenic syndrome (n=1) and non-specific peripheral symptoms like neuropathic pain, dysgeusia, myalgias (n=25). All patients showing headache had been treated with anti-PD-1 monoclonal antibodies (pembrolizumab, nivolumab and cemiplimab), although differences among groups receiving different ICIs were not statistically significant (p= 0.6677).

Conclusion: Our data provides the first human evidence of the role of PD-1 and PD-L1 in migraine-like pain development. Future prospective studies are necessary to validate these preliminary findings.

Usage of real-world data to quantify people who might benefit from new therapeutic approaches to treat migraine in Italy

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Background: Once diagnosed, migraine pharmacotherapy can be either acute or preventive. Triptans were specifically developed for acute treatment however, sometimes, they might not be effective and/or poorly tolerated, and are contraindicated in subjects with certain cardiovascular (CV) diseases. Conventional preventive treatments are not migraine-specific and are frequently associated with side effects and low adherence. A range of migraine-specific novel therapies have recently emerged, both for acute and prophylactic regimens. This analysis aimed to quantify Italian adults who might benefit from different therapeutic approaches for the treatment of migraine acute episodes or because eligible to prophylaxis for episodic migraine (EM) using electronic medical records.

Methods: Retrospective analysis using data from Italian IQVIA Longitudinal Patient Database. Four cohorts were identified during 2019 and extrapolated to get yearly national-level estimates: 1) subjects with prescriptions of triptans before and no triptans prescriptions after a health encounter for migraine, i.e., triptan withdrawers; 2) subjects without triptans prescriptions neither before nor after a health encounter for migraine; 3) subjects experiencing 4≤ migraine attacks/month<8; 4) subjects experiencing 8≤ migraine attacks/month<15. Demographic and clinical characteristics of all cohorts were separately provided.

Results: Triptan withdrawers numbered 605 leading to an estimate of ~ 30,000 subjects interrupting treatment with triptans in Italy; subjects without triptans prescriptions were 3,270: of them, 621 (19%) had a registration for a CV diagnosis, leading to ~ 31,000 subjects with triptans contraindications in Italy; people with 4≤ migraine attacks/month<8 were 2,531, translating into a national-level estimate of 126,000 subjects; subjects with 8≤ migraine attacks/month<15 were 1,540 and translated to 75,000 people in Italy. The vast majority of patients in all cohorts were female (77-83%), and mean age ranged from 47 (±14) to 52 (±11) years among groups. Hypertension and thyroid diseases were the most common comorbidities among triptans withdrawers (22 and 19%) and no triptans patients (28 and 21%), while headache was more frequently observed for the remaining cohorts (34-37%).

Conclusion: Italian adults who might benefit from new therapeutic approaches for the treatment of migraine acute episodes are no less than 60,000, while those who are eligible to prophylaxis treatments for EM are around 200,000.

Artificial Neural Network applied to neurophysiology may assist in migraine classification

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Background: Finding a biomarker to diagnose migraine is one of the long-standing challenges in the headache field. Individuals with migraine have dynamic and recurrent alterations in the brainstem-thalamus-cortex loop, with reduced thalamocortical activity and abnormal habituation in the interictal phase. Although these alterations were helpful in understanding migraine pathogenesis, they are not currently used in clinical settings. This study aims to investigate the potential of Artificial Neural Network (ANN) in discriminating migraine patients from healthy subjects using neurophysiology recordings.

Methods: We recorded somatosensory evoked potentials (SSEPs) to collect electrophysiological data from low- and high-frequency signal's bands in 177 individuals, including 91 individuals with migraine during their interictal period (MO) and 86 healthy subjects (HS). Eleven neurophysiological variables were analyzed, and a priori Principal Component Analysis (PCA) and Forward Feature Selection (FFS) techniques were applied to select relevant variables, refine the feature space, and bolster model interpretability. We trained the ANN as a data-driven model to delineate the relationship between the electrophysiological input variables and the desired output, testing its accuracy in discriminating between MO and HS.

Results: The achieved results underscored a robust performance of the neural network, yielding a final accuracy in identifying individuals with migraine exceeding 70%, along with sensitivity, specificity, and F1 scores surpassing the value of 0.7.

Conclusion: Our ANN trained with variables from SSEP recordings revealed good accuracy in distinguishing between migraine patients and healthy individuals. The ANN could potentially serve as a powerful tool for implementing noninvasive neurophysiology techniques and gaining new insights into migraine classification.

The impact of the virtual "Enfacement Illusion" on pain perception in persons with chronic migraine: 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 are gaining attention. In this frame, body ownership illusions have been proposed as a non-pharmacological strategy for pain relief. This study reports data from a randomized controlled trial (RCT) evaluating the efficacy of reducing pain perception through the enfacement illusion of a happy face observed via an immersive virtual reality (VR) system in people with CM.

Methods: Persons with CM were randomly assigned to either the experimental or the control intervention. The experimental group experienced the enfacement illusion, while the control group was exposed to a pleasant immersive VR environment. Both groups underwent three VR sessions (approximately 20 minutes each) over one week. At baseline (T0) and at the end of the intervention (T1), patients completed behavioral measures related to their emotional and psychological state, and body image perception. Before and after each VR session, we assessed pain levels using the Visual Analogue Scale (VAS), body image perception, and the affective state of the patients.

Results: We enrolled 85 subjects with CM. Forty-four subjects (43.81±10.08 years old) received the experimental treatment and forty-one (44.31±11 years old) were exposed to the control condition. Subjects were comparable in terms of clinical and psychological variables. The data showed a decrease in pain perception on the VAS score in the experimental group from session one to session three (z=-2.75, p=0.02) and from session two to session three (z=-3-04, p=0.01). Further, a decrease in pain perception was observed in the control group but only from session one to session three (z=-2.93, p=0.014).

Discussion: The results of this study showed the effectiveness of immersive virtual reality, as an effective strategy for distraction of pain perception. Further, inducing body ownership illusions through the enfacement illusion may enhance the analgesic effect of virtual reality interventions.

Difference in sensitization mechanism across low-frequency episodic, high-frequency episodic, and chronic migraine

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Aim: This observational study assessed differences in sensitization mechanisms across chronic migraine (CM), low-frequency (LFEM), high-frequency episodic migraine (HFEM), and healthy controls.

Methods: Signs of sensitization were assessed with Quantitative sensory tests (QST) (Wind-up ratio (WUR), pressure pain threshold (PPT) from the trigeminal area, and PPT from the upper-cervical spine). CM were assessed ictally and interictally and compared vs controls. LFEM and HFEM were assessed interictally, preictally, ictally, and postictally and compared vs. 1) each other's, matched for the phase; 2) CM (ictal LFEM and HEM were compared vs. ictal CM; postictal, interictal, preictal LFEM and HFEM were compared vs interictal CM); 3) control. Symptoms related to central sensitization were assessed with the Central Sensitization Inventory (CSI) questionnaire and CSI results of CM, HFEM, and LFEM were compared.

Results: A total of 56 controls, 32 CM, 105 LFEM, and 74 HFEM were included. Regarding QST results, compared to controls: **1)** ictal CM had lower trigeminal and upper cervical PPTs ($p<0.001$), and higher trigeminal WUR ($p=0.020$); no differences were observed with interictal CM; **2)** preictal HFEM had lower upper-cervical PPT ($p=0.014$); ictal HFEM had lower trigeminal ($p=0.002$) and upper-cervical ($p=0.009$) PPTs, and higher trigeminal WUR ($p=0.002$); postictal HFEM had lower trigeminal ($p=0.004$) and upper-cervical ($p=0.010$) PPT. No differences were observed with interictal HFEM. **3)** interictal LFEM had lower trigeminal ($p=0.002$) and upper-cervical ($p=0.016$) PPTs; preictal LFEM had lower upper-cervical PPT ($p=0.014$); postictal LFEM had lower upper cervical PPT ($p=0.006$). No differences were observed with ictal LFEM. Ictal LFEM had higher trigeminal ($p=0.013$) and upper cervical ($p=0.012$) PPTs compared to CM. No other differences were observed between HFEM and LFEM or HFEM and CM.
Regarding CSI, patients with HFEM and CM had increased symptoms related to sensitization (HFEM, $p=0.003$; CM, $p<0.001$) compared to LFEM with no differences between HFEM and CM ($p> 0.05$).

Conclusion: This study suggested that HFEM patients have a sensory profile matching CM better than LFEM.

The second exteroceptive suppression period of the temporalis muscle in migraine patients with allodynia differs from controls

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Background: The study of the second exteroceptive suppression period (ES2) of the masseter or temporalis muscle could provide information as to the neural circuits involved in migraine pathophysiology. Indeed, the interneurons responsible for ES2 are close to the trigeminal nucleus caudalis and receive afferents from the anti-nociceptive system. Allodynia is known to be related to the sensitization of second and third order neurons in the trigeminal nucleus caudalis and sensory thalamus, respectively.
This observational, retrospective study is aimed at investigating the ES2 of the temporalis muscle in female migraineurs, with and without allodynia, in the interictal period, compared to controls.

Methods: Thirty female patients, fulfilling the diagnostic criteria for migraine (13 with aura, 17 without aura, 20 episodic, 10 chronic), naïve from any pharmacological prophylactic treatment, without relevant psychiatric comorbidities and 20 healthy controls were enrolled.
The exteroceptive suppression of the temporalis muscle activity was registered, according to the standards recommended by the European Headache Federation, in the interictal period (at least 72 hours after the last migraine attack).

Results: Twenty-two migraineurs had allodynia, which was assessed by the Allodynia Symptom Checklist. Their average migraine day frequency was 17 per month.
The ES2 latency and duration between the groups were compared by Student's t-test. There were no differences in the ES2 latency or its duration between the migraine patients or controls, allodynic versus non-allodynic migraineurs. Conversely, the ES2 latency was statistically significantly shorter in allodynic migraineurs than in controls ($p=0.07$).

Conclusion: This study suggests that the reduced latency of ES2 observed in allodynic migraineurs, compared to controls, may reflect an impaired activity of brainstem circuits (second-order neurons in the trigeminal cervical complex and/or inhibitory control from superior antinociceptive systems). Indeed, we suppose that this alteration in ES2 may be a neurophysiological correlate of central sensitization in migraine patients with allodynia.
Further studies are required to confirm these preliminary findings on larger patient samples and such an intriguing hypothesis.

Different responses to dynamic noxious heat stimuli throughout the migraine cycle and in chronic migraine with and without medication overuse

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Background: Assessment of changes in visual analogue scale (VAS) values during the application of tonic or dynamic heat pain stimuli can provide insight into the mechanisms underlying sensitization, adaptation, and offset analgesia (OA) phenomena. OA refers to the disproportionately large decrease in perceived pain following a slight decrease in the intensity of a noxious heat stimulus and is considered an expression of the activation of the endogenous pain-modulation system, whose dysfunction is believed to be involved in the pathophysiology of chronic pain syndromes, including migraine.

Methods: We enrolled 34 patients with chronic migraine (CM) with (n=23) or without (n=11) medication overuse (MO), along with 68 subjects with episodic migraine (EM) evaluated in different phases of the migraine cycle, and 30 healthy controls. All subjects underwent an experimental paradigm consisting of 3 stimulus offset trials (OT) and 3 constant temperature trials (CT) at the trigeminal supraorbital region. Visual analogue scale (VAS) values were recorded during the OT and CT using a computerized VAS (CoVAS).

Results: Interictal EM patients and CM patients with MO did not show the physiological OA phenomenon observed in the healthy subjects. A paradoxical pronociceptive facilitation during the offset trial was observed in the CM without MO patient subgroup, similar to that observed in EM patients evaluated during the preictal and ictal periods. The OA phenomenon was observed only in EM patients in the postictal phase. The magnitude of VAS changes during the offset trial negatively correlated with scores on the 12-item Allodynia Symptom Checklist and mean severity of migraine pain.

Conclusion: Dysfunction in the endogenous pain-modulation system may contribute to the recurrence of migraine attacks in patients with episodic migraine, as well as to the transformation of migraine from an episodic to a chronic pattern. Various pathophysiological mechanisms may be involved in chronic migraine patients, with sensitization phenomena prevailing in patients with medication overuse (MO), and a shift from endogenous anti-nociceptive to pro-nociceptive mechanisms predominantly seen in patients without MO.

Habituation patterns of high-frequency oscillations: insights into somatosensory processing in episodic migraine

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Background: Episodic migraine patients are characterized by reduced thalamocortical drive during the interictal period, which normalizes during the attacks. Contrary to the typical lack of habituation observed in low-frequency somatosensory evoked potentials, the HFOs don't undergo habituation during the interictal period. However, it is unclear what is the pattern of habituation of HFOs during migraine attacks.

Methods: We recorded low-frequency somatosensory evoked potentials (LS-SSEP) in 27 episodic migraine patients, 13 between attacks (MO) and 14 during the ictal period (MI), and 22 healthy volunteers (HV). The HFOs were obtained using digital zero-phase shift band-pass filtering between 450 and 750 Hz on the parietal N20 LS-SSEP. Three consecutive series of 500 sweeps each were collected, and the amplitude and habituation of pre-synaptic (pre-HFO) and post-synaptic-HFO (post-HFO) were calculated for each block and were correlated with clinical variables.

Results: We observed a decrease in the amplitude of the pre-HFO interictally (1° block pre-HFO: MO= 0.04±0.01, MI= 0.07±0.03; MO vs. MI: p= 0.014), which returned to normal levels during the attacks (MI vs HV: p= 0.995). Increase in the post-HFO during attacks (1° block post-HFO MO= 0.04±0.02; MI= 0.072±0.03: MO vs. MI: p= 0.036) and a positive correlation between the amplitude of the pre-HFO and the ASC-12 (r= 0.455, p= 0.022) were observed. Additionally, migraine patients with moderate or severe allodynia on the ASC-12 (score>5) had higher amplitude of the pre-HFO than patients with none or mild allodynia (score<5) (p= 0.023). The pre-HFO and post-HFO didn't undergo habituation either between (p= 0.200) or during the attacks (p= 0.217).

Conclusion: Our findings confirmed that episodic migraine patients are characterized by a reduced level of thalamocortical activation between attacks, which normalizes during the attacks when the cortical activation increases and the sensitization develops. Additionally, higher thalamocortical activation was associated with increased levels of allodynia. However, the HFO activity remains stable during repetitive stimulation and maintains its arousal somatosensory system activity throughout the migraine cycle.

The 4-D migraine scale: a composite score evaluating migraine severity and treatment efficacy

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Background: A composite measure, including a weighted approach and the most relevant parameters of frequency and disability, would better evaluate the migraine burden and treatment efficacy.

Methods: We chose 4 of the most used endpoints: monthly migraine days (MMDs), acute medications intake (MAMI), pain intensity (by Numerical Rating Score, NRS) and Migraine Disability Assessment (MIDAS), to create the composite 4-D migraine scale. According to ISPOR guidelines for the selection of levels, for each parameter four levels were chosen, representing mild (MMD 7, MAMI 7, NRS 3, MIDAS 3), moderate (MMD 14, MAMI 14, NRS 5, MIDAS 8), severe (MMD 21, MAMI 21, NRS 7, MIDAS 16), very severe condition (MMD 28, MAMI 28, NRS 9, MIDAS 25). First, the relative weight of each level per parameter was rated by 100 patients and 100 headache experts according to the Conjoint Analysis, which is based on how respondents choose among specific, hypothetical, but plausible options. Secondly, we applied the 4-D migraine score to a sample of 205 episodic and chronic migraine patients treated with galcanezumab. We assessed its concurrent validity with respect to HIT-6.

Results: There was strong agreement between clinicians and patients about the weight of each parameter: MIDAS was the most important attribute (weight 33%), followed by MMDs and MAMI which resulted equally important (weight 23%), while NRS was slightly less relevant (weight 21%). A definite score was attributed to each level of the 4 parameters and, finally, the total 4-D score was calculated summing up each of the 4 parameters score for each patient. Since MAMI and MIDAS were log-normally distributed, a log transformation was applied before obtaining z-score for each of the 4 measures. Then, the Conjoint Analysis based 4-D migraine score was computed according to the formula (0.23* Z-MMDs+0.23* Z-MAMI+0.33* Z-MIDAS+0.21* Z-NRS). In our sample, the correlation with HIT-6 resulted higher (Spearman rho=0.31) for 4-D score than for each single measure (MMD: rho=0.18; NRS: rho=0.25; MAMI: rho=0.16; MIDAS: rho=0.22).

Conclusion: Such composite score based on the preference weights of clinicians and patients could be useful as a Clinician- and Patient-Reported Outcome in clinical trials and real-world studies.

Clinical impact of Rimegepant in acute migraine management for triptan non-responders

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Background: The acute treatment of migraine is crucial for patients' quality of life. Despite the availability of numerous therapies, they are not always effective and free of adverse events. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most used classes of drugs, but they are often associated with gastrointestinal disturbances and contraindications in older age. Triptans are currently the treatment of choice for acute management. However, their use is partially limited by contraindications in older age, cardiovascular comorbidities, and the presence of non-responders. In this context, it is crucial to introduce new medications such as Rimegepant into the real-world clinical setting and to delineate their potential role in patients who are non-responders or have contraindications to current acute therapies.

Methods: This prospective observational study included a cohort of patients with episodic or chronic migraine, who had an unsatisfactory or absent response to triptans, and were referred to the Headache Center at the IRCCS ISNB. All patients were provided with two doses of Rimegepant to treat two migraine attacks, using Rimegepant as the primary drug for acute treatment.

Results: In this study, 22 patients were recruited, including 18 women (81.8%) and 4 men (18.2%), with a mean age of 49 years and an average of 8.45 monthly migraine days (MMD). Rimegepant was used for 35 migraine attacks, and in 57% of cases, it was preferred over the usual therapy, especially among those using NSAIDs or triptans. 63% of patients rated Rimegepant positively, with 80% expressing overall satisfaction. Pain relief was achieved within two hours in 74.3% of attacks. Rimegepant effectively alleviated nausea (81.26%), photophobia (88.23%), phonophobia (88.88%), and osmophobia (100%). Mild side effects, primarily nausea, were reported in six attacks (17.14%). A slight correlation was observed between the time of drug administration and its effectiveness, while a weak negative correlation was noted between the time of administration and the frequency of migraine attacks.

Conclusion: Rimegepant demonstrated effectiveness and patient satisfaction in acute migraine treatment, particularly for those unresponsive to triptans. It provided rapid pain relief and alleviated associated symptoms with minimal side effects, highlighting its potential as a valuable therapeutic option.

Rimegepant effectiveness and tolerability in the acute migraine treatment (GAINER): a real-world multicentric Italian study

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Background: Rimegepant is a novel calcitonin gene-related peptide receptor antagonist. It has been recently approved in Italy for the acute treatment of migraine attacks. We designed a prospective multicentric study to evaluate its effectiveness and tolerability in the real-world setting (NCT05903027).

Methods: We enrolled 103 subjects with migraine (74.8% females, 44.4±11.9 years of age, mean baseline monthly migraine days 9.6±6.9). One fourth of the population had chronic migraine (CM, 24.3%, 25/103). Participants were instructed to treat up to four migraine attacks with rimegepant 75 mg, as needed. We prospectively collected migraine-attack features at baseline and every 30 minutes up to 2 hours (2h) post-dosing using an ad hoc diary.

Results: We analysed 103 first-treated attacks. At rimegepant intake, 40.8% of participants rated migraine intensity as severe (3 on a 0-3 rating scale). Two-hour pain freedom was reported in 44.7% (46/103) of participants and was not influenced by baseline pain severity (p=0.064), while it was influenced by timing of rimegepant intake (p=0.032), with higher chances of achieving the response if rimegepant was taken within 1 hour from migraine onset. Pain relief 2h post-dose, defined as a reduction of at least one point at the headache intensity scale, was reported in 82.5% and was not

influenced by baseline pain severity (p=0.293) or timing of intake >60 min (p=0.576). Mild adverse events were reported in 18.4% of total attacks (19/103), mainly as gastrointestinal discomforts (n=5) and fatigue (n=7).

Conclusion: Our real-world data supports rimegepant effectiveness, safety, and tolerability in the acute treatment of migraine attacks. While rimegepant effectiveness was not influenced by baseline pain severity, an early intake was associated with higher chances of achieving 2h pain freedom.

Influence of triptans use on anti-CGRP mAbs response: a prospective cohort study

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Background: Real-world studies have attempted to identify response predictors to monoclonal antibodies (mAbs) that target and inhibit calcitonin gene-related peptide (CGRP) with conflicting results. This study aimed to compare the differences in clinical characteristics and response to anti-CGRP mAbs at baseline and during treatment between patients who habitually used triptans (TRIPTANS group) and patients who never used triptans (NO TRIPTANS group).

Methods: In this observational study with prospective cohort design, all consecutive patients treated with anti-CGRP mAbs over a period of 12 months at two tertiary headache centers were included. Demographic and clinical data were collected at baseline, and the following data were collected monthly: number of monthly headache days (MHDs), the absolute number of analgesics (AMNs) and the number of days with at least one analgesic (AMDs) per month. Additionally, patients completed the Migraine Disability Assessment (MIDAS) questionnaire quarterly. Response rates were assessed based on reductions in MHDs (≤25%, ≥50% ≥75% at months 1, 3, 6, 9 and 12).

Results: Three hundred thirty-six consecutive patients treated with mAbs were included in the study. Comparative analysis showed significant and sustained lower MHDs during treatment in the TRIPTANS group. The MIDAS score was also significantly lower in the TRIPTANS group compared to the NO TRIPTANS group for each time point assessed (months 3, 6, 9 and 12). The TRIPTANS group had lower AMDs and AMNs compared to the NO TRIPTANS group. Regarding the responding status, the number of patients with ≥50% reduction of MHDs was higher in the TRIPTANS group. The number of patients with ≤25% reduction of MHDs (*i.e.*, non-responders) was lower in the TRIPTANS group at almost all time points.

Conclusion: Head-to-head prospective comparison between triptans users and triptans non-users, each month of treatment over a 12-month treatment cycle, confirmed and expanded the evidence of the greater effectiveness of anti-CGRP mAb in triptans habitual users. It is possible to hypothesize that this is the consequence of a common and/or synergistic action of triptans and mAbs on the trigeminovascular system. A good response to triptans is a predictor of a better response to anti-CGRP mAbs, suggesting a possible synergistic effect.

Analysis of factors influencing the monoclonal antibodies against CGRP prescription in a cohort of very young adults with migraine

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Background: Anti Calcitonin Gene Related Peptide monoclonal antibodies (anti CGRP-Mabs) have revolutionized the treatment of migraine, therefore the factors that determine therapeutic choices have changed, especially in young patients.

Methods: We have considered 179 adult patients < 25 years old who have undergone a first visit for migraine at the Fondazione Campus Bio-Medico Headache Center. We collected baseline demographical data, comorbidities, monthly migraine days (MMD), monthly acute medication intake (MAMI), migraine history, and possible referral from a Pediatric Headache Center. We also assessed previous treatments and prescriptions at the first visit and at the one-year follow-up.

Results: At the first visit, 9 (5.1%) were prescribed MAbs, while at the end of 1-year observation in 37 patients (20.6%). The onset of the disease is 9.7 years for patients who received a MAbs at the first visit and 13.7 in the remaining patients. Those receiving mABs at baseline have an average clinical history of 10.3 years versus 6.61 years for the other patients and they present a higher frequency of migraine at baseline (22.11 days vs 10.53). Patients in transition from a Pediatric Center did not receive MAbs more frequently at the first visit p=0.479, and comorbidities do not influence the prescription of MAbs (p=1) at the first visit and follow-up (p=.446), as well as the familiar history of headache (p=0.724) at the first and follow-up (p=0.453). 115 patients were lost to follow-up before completing 1 year of observation (63.5%). Lost patients had a higher age at migraine onset (14.28 vs. 12.2), fewer years of disease (6.25 vs. 7.8), and less MMD at baseline (10.4 vs 13.3). Chronic migraine patients and people with comorbidities are less lost to follow-up (p=0.049 and p=0.012 respectively), while familiar history has no influence on follow-up discontinuation.

Conclusion: The prescription of MAbs in young migraine patients seems to be influenced only by the frequency of migraine days, which also mainly influences adherence to follow-up visits. Although more than half of the patients stopped follow-up within 1 year from the first visit, more than half of the patients who are still being followed receive a MAb prescription within 1 year.

Predicting response to OnabotulinumtoxinA treatment in chronic migraine patients: a cluster analysis approach

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Background: OnabotulinumtoxinA (BoNTA) is considered a safe and effective treatment for chronic migraine (CM). However limited information available in the literature on predictors of response and characteristics of non-responders. To identify possible subgroups of CM patients in order to predict their responses to BoNTA treatment using K-means cluster analysis.

Methods: We prospectively analysed 50 adult CM patients undergoing their first treatment with three cycles of BoNTA (175 UI) according to the PREEMPT protocol. A positive response was defined as a reduction in headache days per month of at least 50%, assessed nine months after treatment initiation, compared to baseline. Logistic regression was employed to identify significant predictors of response, which were then used as inputs for K-means cluster analysis.

Results: Cluster analysis revealed two distinct subgroups. Cluster 1 (n = 13) exhibited a poorer response rate to BoNTA treatment at nine months compared to Cluster 2 (n = 37) (7.7% vs. 62.2%, p = 0.0007). Cluster 1 was characterized by a higher number of previous preventive treatments (5.3 ± 1.7 vs. 1.8 ± 0.8, p < 0.0001) and a greater prevalence of triptan overuse (84.6% vs. 45.9%, p = 0.01). Logistic regression analysis further indicated that higher numbers of previous preventive treatments or triptan overuse were associated with lower response rates to BoNTA at nine months, with odds ratios of 0.4 (95% CI 0.2-0.7, p = 0.004) and 0.3 (95% CI 0.1-0.9, p = 0.03), respectively. No significant differences were observed between the cluster subgroups in terms of sex, age at disease onset, comorbidities, family history of headache, and MIDAS pre-treatment score. Additionally, no adverse events were reported in either subgroup.

Conclusion: Our study provides novel evidence indicating that patients with a higher number of previous preventive treatments and triptan overuse are less likely to respond to BoNTA treatment. In clinical practice, these factors should be considered to personalize the selection of candidates for BoNTA treatment. Recognizing these predictors can help tailor therapeutic strategies, potentially enhancing treatment outcomes by selecting patients who are more likely to benefit from BoNTA therapy.

The influence of migraine oral preventives on clinical outcome of patients co-treated with monoclonal antibodies anti-CGRP

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Background: The role of oral preventive treatments (OPT) in patients co-treated with monoclonal antibodies anti-CGRP is still uncertain, and it has been investigated only in two studies [1, 2].

Method: In 5 Italian Headache centres we consecutively enrolled patients affected by episodic and chronic migraine, who started a new therapy with monoclonal antibodies anti-CGRP, in presence or absence of an OPT at the baseline. The start of a new OPT during the therapy with monoclonal antibodies was also checked. OPT withdrawal or its reduction was evaluated after 6 and 12 months compared to baseline in relation to the clinical outcome.

Results: We have enrolled 555 patients (aged 49.3 SD 12.4 ys, F 83.6%; 416 affected by CM (75%). Of these, 261 subjects received galcanezumab (47.0%), 168 erenumab (29.9%) and 128 fremanezumab (23.1%). At baseline, MHDs resulted 19.7 SD 7.4, MIDAS was 91.6 SD 53 and NRS 8.2 SD 1.3. From baseline to T12 the use of ADD-ON OPT therapy gradually decreased (from 35.1%, T6 28.8% and T12 19.6%). At T6 only 7 subjects introduced or augmented ADD-ON OPT therapy (in 4 cases, amitriptyline, in 2 anti-epileptic and in 1 beta-blocker). At T12, only 5 patients introduced or augmented ADD-ON OPT therapy (in 2 cases, amitriptyline, in 1 anti-epileptic and in 2 beta-blockers). After 1 year of therapy MMDs (8.0 SD 6.6) and MIDAS (20.4 SD 20.3) significantly reduced ($p<.001$) as well as NRS (5.9 SD 1.7). The presence of ADD-ON OPT therapy at T12 was not associated with the degree of decrease in MMDs (p=5669 and NRS (p=-835) but was associated with a less pronounced decrease in MIDAS (p=.015).

Conclusion: The positive effect of monoclonal antibodies permitted a gradual decrease of the ADD-ON OPT. The presence of ADD-ON OPT does not seem to influence the clinical outcome, its maintenance at T12 was observed in those with a less pronounced decrease in MIDAS.

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Impact of Erenumab treatment duration on cutaneous allodynia in patient with episodic and chronic migraine

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Background: Previous studies showed progressive migraine deterioration after anti-calcitonin gene-related peptide (CCRP) monoclonal antibodies (mAbs) discontinuation. This real-life study aims to evaluate the efficacy of erenumab, an anti-CGRP receptor mAb, over a one-year period in comparison to treatments lasting beyond one year, among patients suffering from either episodic or chronic migraine.

Methods: In the episodic patient cohort, 25 received treatment over a one-year period (GroupA), while 16 beyond one year, up to a maximum of 21 months (GroupB). Among chronic patients, 71 and 68 were allocated to GroupA and GroupB, respectively. Clinical data were collected at baseline (T0), end of treatment (T1), after an average of 3.5 months of treatment suspension (T2), and 3-month after resuming therapy (T3). Variables included monthly headache and migraine days, acute medication usage, patients' disability, migraine impact, pain intensity and intra-ictal allodynia, quantified using the ASC-12 score. Intra-group variations were assessed using Wilcoxon-tests whereas between-group differences of clinical variables modification among timepoints were explored through linear and cumulative effect statistical models

Results: Both chronic and episodic migraine patients exhibited significant reductions in most clinical variables between T0 and T1, with no differences between the two treatment groups. Notably, in chronic patients, GroupB demonstrated a reduction in ASC12 scores during treatment, maintaining the post-discontinuation effect. Conversely, GroupA showed no reduction during treatment, but a delayed effect during suspension. After resuming therapy all patients showed significant improvement with no differences between groups.

Conclusion: These findings suggest that erenumab could modulate nociceptive networks, contributing to allodynia symptom. However, to achieve and maintain this effect an extended treatment duration is required.

Response to fremanezumab is swift, sustained, and substantial over one year: results from the Italian cohort of the real-world PEARL study

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Background: PEARL is a 24-month, prospective, observational pan-European real-world study, evaluating the effectiveness and safety of fremanezumab in migraine prevention in adults with episodic or chronic migraine. Here we present the results of the Italian cohort to show the effectiveness and safety of fremanezumab over 12 months.

Methods: The full analysis set (FAS) included all participants with available follow-up data (n=343) and the safety analysis set (SAS) included all participants receiving ≥1 administration of fremanezumab (n=354). The primary outcome was the proportion of participants with a ≥50% reduction from baseline in average monthly migraine days (MMD) over 6 months of treatment. Secondary outcomes included change in MMD from baseline to Month 6, the proportion of ≥50% responders at Month 1, the proportion of sustained responders (participants maintaining a ≥50% response from Month 3 to Month 12), and the proportion of ≥75% and 100% responders at Month 6. Adverse events (AEs) were recorded.

Results: The primary endpoint was achieved by 61.2% of participants (207/338); the mean difference from baseline in MMD was –8.2 ± 7.3 at Month 1, –8.3 ± 6.6 at Month 3, –9.3 ± 6.8 at Month 6, and –8.9 ± 6.9 at Month 12. At Month 1, 59.2% of participants (203/343) achieved a ≥50% response, while 60.1% of participants (184/303) achieved a ≥50% response at Month 12. Notably, 42.9% of participants (130/303) achieved a sustained response status at both Month 3 and Month 12. At Month 6, a ≥75% response was achieved by 38.2% of participants (128/335) and a 100% response was achieved by 14% of participants (47/335). In the SAS, treatment-related AEs were reported in 14.4% of participants (51/354). Overall, 25 participants (7.3%) permanently discontinued fremanezumab treatment due to lack of efficacy (4.7%), lack of tolerability (1.7%), or other reasons (0.9%).

Conclusion: This real-world Italian cohort study demonstrated that fremanezumab is rapid-acting, well-tolerated, and effective in the long term, confirming it as an ideal candidate for long-term migraine prevention.

Eptinezumab prophylaxis after therapy with others anti-CGRP R monoclonal antibodies (mAbs): a real-world clinical evidence of efficacy and safety

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Background: Eptinezumab is a humanized recombinant antibody with high affinity for CGRP, rapid onset and long half-life, and binds and inhibits CGRP twice as fast as other mAbs. For these reasons, the aim of the following study is to demonstrate the efficacy of eptinezumab in migraineurs non-responsive to other mAbs.

Methods: We included all patients eligible for eptinezumab therapy. The first dose of eptinezumab was 100 mg for all patients; thereafter, if well tolerated, the dosage was increased to 300 mg. We therefore divided the population into: Group 1, the migraineurs who had never undergone therapy with mAbs, and Group 2, the migraineurs who had already undergone prophylaxis therapy with mAbs with no benefit (< 50% headache reduction) or side effects. Clinical variables were collected at T0 every three months thereafter for one year.

Results: Both groups achieved a great headache improvement; the number of responders in G1 was 14 out of 17 patients (82%), and in G2 the number was 10 out of 12 patients (83%); therefore, no statistically significant difference in response to eptinezumab was found between patients who had already failed with other mAbs and those who had never tried this therapy (chi-square 0.0047. p-value 0.94).

Conclusion: Eptinezumab show a high efficacy and safety also in migraineurs who failed other anti-CGRP(R) mAbs, making this drugs the most effective therapeutic alternative at the present.

Multi-parametric efficacy assessment of Eptinezumab in patients with chronic migraine and medication overuse headache

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Background: Migraine is a very common and disabling condition especially in its chronic form and when complicated by medication overuse. Among the new anti-CGRP preventive treatments, recently a new intravenous monoclonal antibody Eptinezumab has been approved in Italy. Objective of this study is to define efficacy and sustainability of new intravenous monoclonal antibody Eptinezumab.

Methods: We collected 20 patients followed at Besta Institute in Milan, eligible according to AIFA criteria for mAbs anti-CGRP treatment, between December 2023 and May 2024. We started treatment with Eptinezumab 100mg, and moved to Eptinezumab 300mg, according to the patient's response. We investigated clinical history, days of headache and medication per month, MIDAS, HIT-6, ASC-12, PIGC, MIBS4, PCS, at baseline, 3 and 6 months of treatment.

Results: In our sample: 11 patients out of 20, underwent one or more withdrawal treatment in their history, they failed at least 3 preventive classes, at baseline MHD 17 ± 5.5, MAM 20±6, NRS 9±0,75, MIDAS 47±31,2, HIT-6 66±3.23, ASC-12 6±5,71, PCS 20±7,8, MIBS 9±3,2; at 3 months MHD 10±6,7, MAM 11±7,7, NRS 8±1,1, MIDAS 27,5±28, HIT-6 64±7,45, ASC 1,5±5,5, PCS 19,5±7, MIBS 7,5±3,4, PGIC 4±1,56: at 6 months 7 patients moved to 300mg dose, MHD 6±2,31, MAM 10±3,46, NRS 8±2,89, MIDAS 13±25, HIT-6 63±4,16, ASC 1±7,8, PCS 24±11, MIBS 2±1,73, PGIC 3±2.

Conclusion: We observed a ≥ 50% rate response at 6 months in terms of MHD, MAM, MIDAS and HIT-6. Also, the interictal burden decreased in our patients. The patient's impression of change was good, and a slightly catastrophizing trait improvement was observed. Eptinezumab showed a good outcome even in such a complicated migraine population.

Real-world effectiveness and tolerability of Eptinezumab in migraine: The multicenter prospective cohort TACHIS study

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Background: Eptinezumab, the only intravenous calcitonin gene-related peptide (CGRP) monoclonal antibody (mAb), has been approved in Europe for the preventive treatment of migraine. We designed a prospective multicentric study to evaluate the effectiveness and tolerability of eptinezumab in the real-world setting (TACHIS study, NCT06409845). Herein, we report the preliminary results from the first three months of treatment in the TACHIS study.

Methods: TACHIS is a multicentre real-world study that involves 33 Italian headache centers and will follow-up people with migraine treated with eptinezumab for a period of 2 years. Baseline demographic and clinical data were collected at the initial visit, and migraine-related variables are being recorded every three months. Participants fill in a headache diary to track monthly headache days (MHDs), migraine days (MMDs), migraine severity, associated symptoms and analgesics use (both number of doses [AMNs] and days of use [AMDs]). Questionnaire on quality of life, allodynia, interictal burden and disability were completed by patients on an eCRF. Primary outcomes were

changes in MMDs after three months of treatment and percentage of 50% responders (namely patients who presented a reduction of MMDs ≥50% compared to baseline). Several secondary outcomes at different follow-ups, including tolerability, quality of life improvement, use of analgesics, and disability burden, have been preregistered.

Results: We included 30 patients (83.3% females, 50.7±9.7 years, 70% with chronic migraine [CM], baseline MMDs 18.9±8.2) with a potential three-month follow-up. The 83.3% of patients had medication overuse, with a mean AMD of 19.1±7.9 and AMN 21.9±18.0. The mean number of prior preventive ineffectiveness treatment was 4.7+1.9, including 11 (36.7%) and 14 (46.7%) patients that were unresponsive to other anti-CGRP mAb and/or BTX-A, respectively. All patients except one started with a 100 mg dose. The main reasons (cumulative) for eptinezumab prescription were: prior preventive drugs ineffective (86.7%) or partially ineffective (33.3%).
After the first infusion (three months follow-up), two patients (6.6%) did not continue treatment, one each for ineffectiveness or adverse events (i.e., constipation). The number of patients with CM decreased to 42.9% and with MO to 46.4% (13/28 both). Significant differences were reported from baseline to month-3 in MMDs (median [IQR], -6.0 [19.7], p=0.01) and AMDs (-5.5 [18.2], p=0.002), but not in AMNs (-2.5 [23.0], p=0.224).
A response rate ≥50% (in MMDs) was achieved by 39.3%, with 17.9% reaching a ≥75% response. Overall, 53.6% of patients reported at least a 30% response. The dose from 100 to 300 mg was increased in 42.9% of patients for the second infusion. Only one AE was reported (the above reported constipation) that lead to discontinuation.

Conclusion: In these preliminary results, eptinezumab confirmed its effectiveness and tolerability in real-world settings, including patients who switched from other anti-CGRP mAbs. Almost half of the patients had their dose increased from 100 mg to 300 mg. Just after the first administration, several patients reverted from MO to EM. Long-term effectiveness data are highly anticipated.

Eptinezumab for the prevention of chronic migraine: The initial experience of the Calabrian Regional Headache Centre

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Background: Eptinezumab is a monoclonal antibody that targets calcitonin gene-related peptide (CGRP). Although there is robust clinical evidence from pivotal Phase 3 placebo-controlled trials of the efficacy of eptinezumab for migraine prevention, there are limited data on the real-world effectiveness of eptinezumab. This study aims to describe the preliminary outcomes of a small series of chronic migraine (CM) subjects treated with eptinezumab in a real-life setting.

Methods: We consecutively enrolled adult subjects with CM. All patients were treated with eptinezumab infusion into a vein over 30 minutes once every 12 weeks. Changes from baseline in headache days and migraine-related disability were measured using headache diaries and the Migraine Disability Assessment (MIDAS) questionnaire, respectively. Adverse events were recorded. Patients with medication overuse (MO) were included.

Results: Twenty patients (16 women, 4 men; mean age±SD: 44±13.9 years) with an average of 3.1 (SD 2.5) previous preventive treatments failed, received at least one eptinezumab infusion. At the three-month follow-up after the first eptinezumab infusion, 18/20 (90%) patients reported at least a 30-49% reduction in headache days; 6/20 (30%) reported a 50-74% reduction in headache days; and 1/20 (5%) reported a ≥75% reduction. The proportion of patients with MO at baseline (31%) was reduced to 15% after the second infusion. The average MIDAS score was reduced from 69.4 at baseline to 54.8 at the last follow-up in all patients. A single patient reported asthenia for a few hours, which then resolved spontaneously.

Conclusion: Our real-life preliminary results confirm the safety and efficacy of eptinezumab in CM patients, including those with MO.

Effectiveness of transcranial direct current stimulation and monoclonal antibodies acting on the CGRP as a combined treatment for migraine (TACTIC)

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Background: Migraine is a recurring headache disorder with an unclear pathophysiology involving the central and peripheral nervous systems. Monoclonal antibodies targeting the calcitonin gene-related pathway (CGRP-MAbs) are designed specifically for migraine, acting peripherally on the trigeminal ganglion. In contrast, neuromodulation techniques like transcranial direct current stimulation (tDCS) act centrally by influencing cortical neuronal firing rates. This study aims to assess whether tDCS, when combined with CGRP-MAbs, effectively reduces migraine frequency, intensity, and medication use.

Methods: Our study is a randomized, double-blind, multicenter, sham-controlled trial including patients with migraine in CGRP-Mabs treatment with residual monthly migraine days (MMDs) ≥8. After 5-day of tDCS bilateral occipital cathodal and frontal anodal stimulation (sham/active sessions lasting 20 minutes), we closely monitored patients for 28 days, assessing changes in monthly migraine days and clinical scales such as MIDAS, HIT6, HADS. We analyzed the change in migraine days and clinical scales using two-way mixed-design ANCOVAs, with Session (baseline vs. follow-up) as the within-subjects factor and Treatment (Sham vs. Active) as the between-subjects factor. The sample size calculation was performed using GPower 3.1. Based on previous literature, a between-groups mean difference of 3 ± 2 migraine days per month was deemed significant. The minimum suggested sample size was 9 patients per group. To account for possible dropouts, we set the population size to 30 patients, 15 per group.

Results: We included 29 patients (mean age 46±11.5 years, 82.8% female), with 15 in the active session and 14 in the sham group. At baseline, the active group reported a mean of 13.20±6.16 MMDs, while the sham group reported 17.38±7.71 MMDs. tDCS led to a significant reduction in MMDs in the active group (mean 10.10±1.25) compared to the sham group (mean 15.38±1.29; p=0.008). Additionally, a significant improvement was observed in the HIT-6 scale for both the active (p=0.005) and sham (p=0.003) groups.

Conclusion: tDCS, as add-on therapy to CGRP-Mabs, exerts a significant effectiveness to MMDs reduction. The observed benefits suggest that integrating tDCS with CGRP-MAbs could offer a more comprehensive and effective management strategy for individuals suffering from chronic migraines. Further research is warranted to fully understand the underlying mechanisms and long-term effects of this combined therapy.

From pain to awareness of malaise: the benefits of anti-CGRP mAbs

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Background: Calcitonin Gene-Related Peptide (CGRP) is implicated in various affective behaviours, including anxiety, fear, and aversive responses, which frequently overlap with pain perception. Therapeutic strategies targeting the dysregulation of interoceptive processing and related emotional valence are essential to alleviate the burden on patients affected by multiple disorders. Anti-CGRP monoclonal antibodies (mAbs) have been approved for migraine prophylaxis due to their effectiveness in counteracting pain originating from peripheral trigeminovascular neurons. Nevertheless, the genuine preventative effects of anti-CGRP mAbs, along with the understanding that migraine originates within the brain, suggest that these antibodies may also exert central actions. Given this background, our study aimed at evaluating the potential of anti-CGRP mAbs to affect interoception and improve emotional dysregulation in humans.

Methods: A cross-sectional, self-reported questionnaire study was conducted at the Headache Center of the Careggi University Hospital, Florence, Italy. Consecutive outpatients treated with an anti-CGRP mAbs for at least three months and up to 24 months, in accordance with local regulatory guidelines, were enrolled in the study. All patients, who provided written informed consent, completed an ad hoc questionnaire developed to assess the potential treatment effects on emotional symptoms. The primary aim of the study was to assess the perceived effects of treatment on emotional symptoms, such as emotional self-control, stress, anxiety, mood, and panic. Patients were also asked whether they perceived such changes as dependent or independent of monthly headache day (MHD) reduction. An improvement greater than 25% for each questionnaire item was considered significant. Due to the exploratory and descriptive nature of the study, the sample size was not based on any statistical considerations.

Results: A total of 217 patients completed the questionnaire and were included in the analysis. Patients were categorized according to the mean reduction of MHD into responders (>50% MHD reduction, 142/217, 65.5%) and non-responders (<50% MHD reduction, 75/217, 34.5%). Remarkably, substantial fractions of both responders and non-responders reported treatment-dependent amelioration of emotional distress. Both non-responders (36%) and responders (38.7%) perceived that treatment improved well-being independently of migraine reduction. Consistently, amelioration of each emotional symptom was associated with perception of independence from migraine improvement in both responders and non-responders.

Conclusion: Data suggest that anti-CGRP mAbs have beneficial effects on emotional dysregulation and interoception in migraine patients, independent from their effects on headache frequency. This study highlights the potential of anti-CGRP mAbs to improve mental disorders and counteract malaise sensations.

Early gains don't last: exploring the long-term response of switching anti-CGRP mAbs in migraine

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Background: A pharmacological class effect was initially assumed for monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway (anti-CGRP mAbs). However, emerging evidence suggests that switching non-responder patients from a receptor-targeted mAb (anti-CGRP/R mAb) to a ligand-targeted mAb (anti-CGRP/L mAb), and *vice versa*, can benefit approximately 30% of patients (refractory to a previous anti-CGRP monoclonal therapy) after 3 and 6 months of treatment. Herein, we assess the long-term response (12-months) in a group of patients who switched between anti-CGRP antibodies.

Methods: We performed a retrospective analysis of outpatients treated consecutively with two anti-CGRP mAb who discontinued the first treatment due to lack of efficacy. Ineffectiveness of the first anti-CGRP mAb was defined using three different variables assessed after three months of treatment: migraine disability assessment (MIDAS), monthly headache days (MHDs), and days with at least one analgesic (AMDs). All patients had a minimum 12-month follow-up after receiving the second anti-CGRP mAb.

Results: A total of 540 patients received at least one subcutaneous injection of anti-CGRP/R mAbs. Among them, 31 patients were subsequently treated with two different mAbs. Nine were excluded based on inclusion criteria related to the initial response on the three variables used for patient selection. Out of the 22 selected patients, only 10 (45.4%) achieved at least a 30% reduction of MHDs after 3 months of treatment. However, only 4 of them continued anti-CGRP mAb treatment at 12 months, only 3 (13.6%) maintained a response rate greater than 30%, and only 2 (9.09%) showed a response rate greater than 50%.

Conclusion: Switching anti-CGRP mAbs may be a viable strategy for some patients experiencing inadequate response to the first treatment. Our findings suggest that upon the switch the response rates achieved at 3 months is not sustained throughout the course of treatment, reducing the percentage of patients who benefit from this therapeutic option. In particular, given that 40-70% of naïve patients show a >50% migraine improvement after anti-CGRP treatment, our data showing that only 9% of switched patients reach the same target suggest that either CGRP-independent or pharmacokinetic mechanisms are operating in non-responders. Future studies are needed to explore the long-term effectiveness and underlying mechanisms of this phenomenon.

Switching anti-CGRP (R) monoclonal antibodies in resistant migraine: real life experience at the Pisa University Headache Center

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Background: Managing patients with resistant migraine is still one of the main challenges for clinicians, also in the era of anti-CGRP and anti CGRP receptor (R) monoclonal antibodies (mAb). Several studies have shown that these drugs also have a failure rate of about 20-30%. Initially, a class effect was proposed; however, recent limited evidence suggests that in selected patients (those who do not respond to conventional treatments and a first monoclonal antibody), switching the class of antibody could be an option to consider.

Methods: We studied a population of 140 patients referred to the Headache Center (Neurology Unit) at the Pisa University (between June 2020 and June 2023) with drug resistant high-frequency episodic or chronic migraine. These patients were treated with anti CGRP (Fremanezumab or Galcanezumab) or anti CGRP receptor (Erenumab) mAb. Eighteen patients with an unsatisfactory response (less than a 50% reduction in monthly migraine days -MMD- at 6 months were switched to a different class of mAb (i.e patients first treated with antibodies against CGRP ligand were switched to anti-CGRP receptor and vice versa).

Results: Just after 3 months from switching, 10 of the 18 patients showed a favorable outcome with at least a 30% reduction in MMD compared to their baseline, resulting mild responders (response rate between 30% and 50%) or responders (response rate greater than 50% in comparison with their baseline). In these patients migraine related disability improvement also resulted greater with the second treatment. In 2 patients, there was a slight decrease in the number of headache days, but it was less than 30%, with both the first and the second antibody. Finally, 6 patients did not show any change in MMD with both drugs.

Conclusion: There are currently no clinical variables or biomarkers that can predict treatment response to anti-migraine prophylaxis. The lack of response to CGRP pathway inhibition may depend on the implication of other neuropeptides, such as PACAP and amylin, that may play a predominant role in migraine pathogenesis at least in some patients. Even with this limitation, CGRP antibodies switching may represent a relevant opportunity in difficult to treat migraineurs but further studies on larger populations and extended follow-up are necessary to confirm and validate these observations.

Restarting migraine preventive treatment with CGRP antibodies after drug holiday: Insights from Pavia real-world experience

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Background: Monoclonal antibodies against the CGRP pathway (mAbs) are widely used as preventive therapies for migraine. Resuming migraine preventive treatment with mAbs after a drug holiday has shown to be effective in real-world settings. In this study, we evaluated the course of migraine after treatment resumption at the tertiary headache centre of the Mondino Foundation.

Methods: This is a retrospective, monocentric, open-label, real-life study. Headache trend over time was assessed through the variation of monthly migraine days (MMD), monthly doses of symptomatic drugs and migraine disability assessment score questionnaire (MIDAS).

Results: We enrolled 337 outpatients referring to the Mondino Foundation from 2019 to 2023. Erenumab was used by 175 subjects, galcanezumab in 93 subjects and fremanezumab in 69. At baseline, subjects presented 21±7.2 MMD, they presented a median consumption of 20 doses of symptomatic drugs per month and a median of 15 days of use. Subjects reported a median MIDAS score of 60 points. Overall, 267 subjects completed at least 1 year-cycle of treatment obtaining a median reduction of 11 MMD compared to baseline (-62.5%), a decrease in symptomatic consumption (using 12 abortive medications less than before) and a median decrease in MIDAS score of 46 points. MMD reduction of least a 50% was obtained by 76% of subjects who completed the first-year cycle and by 57.6% of the entire population. After a median of 4 months of drug holiday, patients presented a significant increase of 6 MMD (+62,5%) and 20 MIDAS points, compared to the last trimester of treatment. After 3 months of the second cycle, the 210 subjects who restarted treatment obtained a reduction of 5 MMD compared to the suspension period (-40%) and a reduction of 18 points in the MIDAS score. Only 4 patients stopped mAbs after the first trimester of restart due to inefficacy.

Conclusion: Treatment restart with CGRP mAbs after a drug holiday leads to a significant reduction of migraine frequency and medication use, as well as, an improvement in quality of life

Impact of monoclonal antibody discontinuation on migraine prevention: a prospective cohort study

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Background: The monoclonal antibodies (mAbs) targeting the CGRP pathway have revolutionized migraine prophylaxis. The Italian Medicines Agency's prescription policy requires treatment discontinuation after 1 year for a follow-up period of 1 month; after that, if the prescription criteria are met again, treatment can be reinitiated. Limited data are reported by clinical trials on the persistence of mAbs efficacy, and predictors of prolonged response are lacking. In this study, we evaluate the patients' clinical course after discontinuation and try to identify predictive factors for clinical progression.

Methods: In this monocentric prospective cohort study, we enrolled 55 migraine patients (41 female, 75%; 17 with chronic migraine, 31%) who started therapy with mAbs. We collected demographic and clinical data, along with the results of 6 questionnaires, at the beginning of therapy (T0), 2 months (T1), and 5 months (T2) after the last mAbs administration. The questionnaires were: Migraine Disability Assessment Score (MIDAS), Headache Impact Test (HIT-6), State-Trait Anxiety Inventory (STAI), Beck's Depression Inventory (BDI-II), Pittsburgh Sleep Quality Index (PSQI), and Allodynia Symptom Checklist (ASC-12).

Results: Overall, during the discontinuation period, patients reported a progressive clinical worsening. At T1, patients who met the criteria for restarting mAbs presented significantly higher values of monthly migraine days (MMD; p=0.008), monthly medication intake (MMI; p=0.035), and MIDAS (p=0.002). They were also older (p=0.008) and had a longer history of the disease (p=0.02). At T2, MMD, MMI, and MIDAS were significantly decreased in the mAbs group compared to patients who did not restart treatment, while STAI and ASC-12 scores were higher in the latter group. We also found that the presence of depressive symptoms and sleep disturbances were correlated with a higher HIT-6 at T2. Finally, through multivariable analysis, we identified the presence of mAbs treatment as the main predictor of MMD, MIDAS, and HIT-6 T1-T2 decrease.

Conclusion: Our study suggests that early restart of mAbs treatment is the main factor associated with overall improvement in migraine, in terms of MIDAS, MMD, and HIT-6. This response could be influenced by the presence of comorbidities, which therefore need to be properly investigated.

Adverse events reporting of anti-calcitonin gene related peptide monoclonal antibodies in migraine prevention: real-world experience in the Veneto region

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Background: Anti-calcitonin gene related peptide monoclonal antibodies (anti-CGRP mAbs) have shown significant efficacy preventing migraine. Despite growing evidence, knowledge of post-marketing adverse events is still limited. This study aimed to collect and analyze adverse events reported related to anti-CGRP mAbs use in a population of migrainous patients.

Methods: We collected self-reported adverse events with three anti-CGRP mAbs (Erenumab, Galcanezumab and Fremanezumab) retrieved from the National Pharmacovigilance Network and coming from 30 patients residing in the Veneto region, from 2018 up until January 23rd 2024.

Results: Patients' mean age was 44 years old (22 – 78) and 86% were female; a total of 30 patients provided their reports: 14 (46.7%) were receiving treatment with Galcanezumab, 10 (33.3%) were treated with Fremanezumab and 6 (20%) with Erenumab. A number of 57 adverse reactions were described: 30 (52.6%) of them regarded Galcanezumab, 16 (28%) were attributed to Fremanezumab and 11 (36.7%) to Erenumab. Adverse reactions were classified as follows (in order of frequency): administration site conditions (21/36.8%), minor infections (5/8.8%), dizziness (4/7.0%), other minor and unrelated reactions (4/7.0%), nausea and vomiting (3/5.3%), malaise (3/5.3%), flu-like symptoms (3/5.3%), constipation (3/5.3%), vascular events (3/5.3%), intestinal bloating and flatulence (2/3.5%), hypersensitivity reactions (2/3.5%), tachyphylaxis (2/3.5%), alopecia (1/1.8%) and, finally, subjective dyspnoea (1/1.8%). Among these, only vascular events were considered severe and comprised acute ischemic stroke, transient ischemic attack and Raynaud's phenomenon; the first 2 were attributed to Fremanezumab while the third one was attributed to Galcanezumab. In our study, according to the existing literature, mild and self-limiting administration site conditions such as swelling, urticaria, pruritus, rash and bruising, were most commonly reported, while severe adverse reactions, such as cerebrovascular events and Raynaud's phenomenon, were reported in only 3 cases (not certainly related).

Conclusion: Our real-world post-marketing data confirm the safety profile of anti-CGRP mAbs in migraine treatment. However, since self-reporting is prone to bias, continuous monitoring is needed to determine the causal relationship between exposure and outcome.

Cerebral hemodynamic features associated to monoclonal antibodies efficacy in migraine patients

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Background: Monoclonal antibodies (mAbs) represent nowadays the most effective treatment as migraine prophylaxis, and their utilization dramatically changed the migraine natural history of most patients. However, a variable percentage of patients are non-responsive to mAbs. Transcranial Color-Coded Sonography (TCCS) is highly valuable for studying cerebral hemodynamics and has been recently applied to migraine patients to identify specific characteristics of this condition. The aim of the study was to assess the haemodynamic profiles associated with response or non-response to mAbs treatment.

Methods: Patients consecutively admitted to the Perugia Headache Centre and treated with mAbs underwent a full TCCS exam at months 3, 6, and 12. Velocity data, as well as pulsatility index (PI) and resistivity index (RI) on proximal tracts of Willis circle were collected. Patients with anatomical features of pathological conditions potentially affecting cerebral hemodynamics were excluded. Demographic and clinical data were also collected. TCCS data were compared between responders (defined as a reduction of headache days per month by ≥50%) and non-responders at each timepoint of the study.

Results: Thirty-three consecutive patients were enrolled (2 M, 31 F), aged between 22 and 59 years, with an average frequency of attacks per month of 16.5: 26 responders and 7 non-responders to mAbs treatment. Responders showed higher mean flow velocity (MFV) and lower PI on middle cerebral arteries and basilar artery compared to non responders at baseline as well as 3, 6 and 12 months of treatment. While the higher MFV could indirectly represent a greater intrinsic vasoreactivity, the lower PI can be explained as a sign of more efficient hemodynamic capability, with particular regards to microcirculation.

Conclusion: Responders to monoclonal antibodies (mAbs) exhibited distinct cerebral hemodynamic characteristics compared to non-responders. Specifically, the Pulsatility Index (PI) may serve as a predictor of balanced microcirculatory function. Transcranial Color-Coded Sonography (TCCS) can aid in a better understanding of migraine pathophysiology and patient management. Further research is necessary to confirm and expand these findings.

SAFHYPER: A clinical study about blood pressure changes in episodic migraine patients without hypertension treated with anti-CGRP monoclonal antibodies

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Background: Development of hypertension (HTN) and worsening of pre-existing HTN have been reported following the use of erenumab in the post-marketing setting. According to the Food and Drug Administration (FDA) database, in the majority of the cases, the onset or worsening of HTN was reported after the first dose of erenumab [1]. The objective of this study is to describe systolic (SBP) and diastolic blood pressure (DBP) changes, using a 24-hour blood pressure monitoring (BPM), in patients (pts) without HTN treated with anti-CGRP antibodies (anti-CGRP-AB).

Methods: We enrolled pts with episodic migraine. HTN was ruled out at baseline visit, a baseline BPM was performed (V1) and anti-CGRP-AB treatment was started (V2 - time 0). After 30 to 45 days from the first BPM, they performed the follow-up BPM (V3). The end-of-study visit (V4) was performed within 15 days from V3.

Results: We enrolled 18 pts with episodic migraine (76.5% female, with a median age of 49 y.o.). One patient had a diagnosed psychiatric comorbidity, 29.4% was affected by chronic pain syndromes and 17.6% by gastrointestinal disorders. As acute therapy, pts used FANS and triptans, and 10 pts had a concomitant prophylaxis with tricyclics or calcium antagonists or beta-blockers. Comparing the two BPM values, the median, daytime and nightime SBP and DBP showed no difference from baseline to follow-up even if a trend towards reduction was observed, except for a single significant reduction in mean nightime DBP. Consequentially, the patients' dipper profile was more represented at the second BPM (p=0.008). Heart rates were similar between the two BPM.

Conclusion: Among patients without HTN, after a month of anti-CGRP-AB therapy, there was no difference in blood pressure and heart rate values, with a trend towards reduction in blood pressure parameters and an increase in patients' dipper profile.

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Influence of withdrawal from overused drug on central sensitization mechanisms in chronic migraine with medication overuse headache

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Background: Chronic migraine with medication overuse headache (CM-MOH) is neurophysiologically characterized by increased cortical excitability with sensitization at both thalamocortical and cortical levels. It is unclear whether the increased cortical excitability is due to a brain state (due to the medication overuse) or a brain trait. In this study, we aim to investigate if the withdrawal from the overused drugs can influence these neurophysiological variables.

Methods: Somatosensory evoked potentials (SSEPs) were performed by electrical stimulation of the median nerve (M), ulnar nerve (U) and simultaneous stimulation of both nerves (MU) in 14 patients with MOH before (T_0) and after (T_1) a three-week withdrawal protocol.
We measured the level of thalamocortical (pre-HFO) and cortical activation (post-HFO) by analyzing the high-frequency oscillations (HFOs) embedded in parietal N20 median SSEPs and calculated the habituation and the degree of cortical lateral inhibition (dLI) of N20-P25 low-frequency SSEPs.

Results: After the three-week withdrawal protocol (T_1), we observed a normalization of the baseline (T_0) habituation deficit (T_0: +0.096 ± 0.538; T_1: -0.532 ± 0.803; p= 0.040) and a reduction in the amplitude for both pre-HFO (p< 0.009) and post-HFO (p= 0.042), while no effects were observed on the dLI at T_1 (p= 0.141). These changes were not influenced by the reduction in headache days as no differences emerged between responders (RR ≥50%) and non-responders.

Conclusion: Our findings showed that withdrawal from overused drugs can influence and restore the increased excitability at both thalamocortical and cortical levels in patients with CM-MOH independently from the reduction of headache days. It could be hypothesized that the increased excitability is a brain state due to medication overuse rather than the headache frequency.

Head-to-head observational cohort study on the effectiveness and tolerability of subcutaneous monoclonal antibodies acting on CGRP pathway in patients with high frequency episodic migraine and chronic migraine

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Background: Monoclonal antibodies antibody acting of CGRP pathway have been demonstrated to be effective, safe and well-tolerated as preventive treatment in migraine patients. Among subcutaneous antibodies, erenumab antagonizes CGRP receptor while galcanezumab and fremanezumab antagonize CGRP ligand. We aimed to compare the effectiveness and safety of galcanezumab, fremanezumab, and erenumab for the treatment of chronic and episodic migraine, through real-world data.

Methods: This is a 6-months real world, monocentric, prospective, cohort study enrolling 186 migraine patients (19.8% high frequency episodic migraine and 80.2% chronic migraine) treated with erenumab (29.9%), galcanezumab (36.2%), or fremanezumab (33.9%). During the run-in period and after the first, the third and the sixth month of treatment, the patients underwent an extensive interview in order to assess clinical parameters of disease severity (headache days per month, monthly symptomatic medication intake, average headache pain intensity, and headache attack duration) and putative tolerability issues.

Results: No significant differences were observed at baseline between the three group under examination in demographic data as well as in the parameters of disease severity. After the sixth administration, a statistically significant reduction in monthly headache days compared to baseline was observed for both erenumab (12.77 ± 7.9, $p<0.001$), galcanezumab (11.67 ± 8.61, $p<0.001$) and fremanezumab (12.76 ± 6.64, $p<0.001$). Similarly, a statistically significant reduction compared with baseline was observed in monthly symptomatic medication intake, average headache pain intensity, and headache attack duration. We found no significant differences between mAbs in the reduction of mean monthly headache days after 6 months between the three groups under examination ($p=0.119$). Contrariwise, a significant higher percentage of patients reported constipation among erenumab group (14% vs 7% vs 4% $p=0.02$). Although it has been demonstrated that therapeutic effects of antibodies targeting the CGRP ligand versus receptor for migraine prevention may involve distinct mechanisms of action, these differing mechanisms seem not to affect their effectiveness in migraine prevention. Contrariwise, galcanezumab and fremanezumab, have a lower incidence of constipation probably due to the ability of inhibiting the effects of CGRP at both the CGRP and AMY1 receptors, physiologically characterized by opposing impact on gastrointestinal transit.

Conclusion: The present results confirm the effectiveness of CGRP-mAbs. There is no evidence that suggests that one antibody may be superior to the others in terms of effectiveness, both in chronic and episodic patients.

Anti-CGRP monoclonal antibodies and day hospital withdrawal treatment for medication overuse headache: a prospective cohort study of effectiveness and potential clinical and plasmatic biomarkers

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Background: Medication Overuse Headache (MOH) is a debilitating form of chronic headache resulting from the excessive use of symptomatic medications. MOH affects individuals with primary headaches, which progresses towards chronic forms due to medication overuse. This study focuses on comparing different treatment approaches and identifying prognostic clinical and plasmatic biomarkers in MOH patients. Considering the burden of comorbidities, we investigated sleep quality and depressive and anxiety symptoms and their impact on MOH prognosis.

Methods: We enrolled 59 patients (48 females and 11 males) diagnosed with chronic migraine and MOH. Patients were divided into three groups based on treatment: day hospital withdrawal treatment (DhW, 15 patients), start of anti-CGRP (16 with Fremanezumab and 16 with Galcanezumab) or anti-CGRP receptor (12 with Erenumab) monoclonal antibody (moAb) therapy or both of them (moAb + DhW, 20 patients). Clinical evaluation was performed at the start of treatment (T0) and at three-months follow-up (T1) including monthly migraine days (MMD), monthly medication intake (MMI) and migraine disability assessment (MIDAS). We included also evaluation of sleep quality (PSQI), anxiety (STAI) and depressive symptoms (BDI). Patients eligible for moAb therapy, underwent baseline blood sampling to measure plasmatic concentrations of CGRP and Pituitary adenilate cyclase activating peptide-38 (PACAP-38).

Results: We found that treatment with moAb, either alone or in combination with DhW, was associated with a greater probability of MIDAS decrease > 50% at T1 compared to untreated patients ($p < 0.001$) The combination of moAb and DhW did not show additional benefits, compared to moAb treatment alone. We found a direct correlation between baseline MIDAS and sleep disorder and depressive symptoms (Pearson $r = 0.47$; $p = 0.044$ and $r = 0.48$; $p = 0.049$ respectively). The multivariate analysis, including potential confounders, did not display significant prognostic predictors.

Conclusion: Anti-CGRP moAb, not even combined with hospital-based withdrawal therapy, are an effective treatment strategy for patients with MOH. Despite limitations such as a relatively small sample size and a three-month follow-up, these findings represent a basis for further research and clinical practice suggestions for managing MOH. Future studies with larger samples and longer observation periods are required to support these findings.

The effect of three anti-CGRPs on sleep quality fatigue

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Background: Anti-CGRPs improved the management of chronic migraineurs. Migraineurs tend to have low sleep quality and tend to lament fatigue; this study aims to determine whether the treatment with anti-CGRPs might improve this symptom.

Methods: We collected data on 100 chronic migraineurs from January 2020 to May 2023 who were treated with three anti-CGRP drugs for 12 months (31 Erenumab, 34 Galcanezumab, and 35 Fremanezumab). Basal migraine days and migraine intensity were collected through a headache diary. FSS, ESS, and PSQI scales were collected at the baseline and after the 12 months of therapy; these data were compared.

Results: The FSS (5.2±1.7 vs 3.8±1.7; p<0.001), ESS (7.4±5.1 vs 6.1±4.5; p 0.005), and PSQI (11.5±4.9 vs 8.7±6.4; p<0.001) scales improved after the 12 months of therapy. There was a mild correlation between the mean migraine days per month reduction and the mean PSQI reduction during these 12 months (r 0.249; p 0.13); there was no significant correlation involving the mean ESS and FSS reduction. There were no differences between the three groups at the baseline regarding the FSS (p 0.261), ESS (p 0.633), and PSQI (p 0.315). There was a significant reduction in the three groups regarding FSS (mean reduction: 1.3±2.3 p 0.002 for Erenumab, 1.1±1.9 p 0.002 for Galcanezumab, and 1.7±2.2 p<0.001 for Fremanezumab) and PSQI (mean reduction: 2.8±10.1 p<0.001 for Erenumab, 1.3±4.7 p 0.026 for Galcanezumab, and 3.8±6.3 p 0.002 for Fremanezumab) scales; only the Erenumab group significantly improved in ESS (mean reduction 2.1±5.7; p 0.017). there were no differences in the magnitude of improvement between the three groups regarding the FSS (p 0.603), ESS (p 0.292), and PSQI (p 0.057).

Conclusion: The administration of anti-CGRP in chronic migraineurs might ameliorate sleep quality and fatigue symptoms. There were no significant differences between the three anti-CGRPs, although only the Erenumab group had a significant reduction in ESS. The reduction of migraine days per month correlates with the improvement of sleep quality.

Effectiveness of anti-CGRP monoclonal antibodies in patients under 25 years: do younger patients make it better?

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Background: Since their introduction**,** monoclonal antibodies against CGRP or its receptor (CGRP MABs) have been principally offered to middle-aged patients with a long history of disease. More recently, their use has more frequently extended to younger populations. This analysis aims to define whether CGRP MABs are more effective in the younger population.

Method: In 5 Italian Headache Centers, we consecutively enrolled patients who started CGRP MABs for migraine prevention and were followed up for 1 year. We collected from headache diaries monthly migraine days (MMDs), pain intensity (NRS), and disability (MIDAS) at baseline, after 6 and 9 months, previous preventive medications, and comorbidities.

Results: We have enrolled 555 patients (aged 49.3 SD 12.4 ys, F 83.6%; 416 affected by CM (75%). Of these, 261 subjects received galcanezumab (47.0%), 168 erenumab (29.9%) and 128 fremanezumab (23.1%). In this cohort, 29 patients were under 25 years old (YOUNG). YOUNG patients had experienced fewer previous ineffective preventives (3 IQR 2 vs. 4 IQR 2); specifically, less often had received Beta-blockers (58.6% vs 86.7%: p<.001). Besides, they less frequently presented with comorbidity (6.9% vs. 23.6%; p=.039). At baseline, MMDs resulted in 19.7 SD 7.4, MIDAS was 91.6 SD 53, and NRS 8.2 SD 1.3 in the whole cohort with no difference between YOUNG and non-YOUNG (consistently p>.500). However, YOUNG tended to be less frequently affected by CM (65.5% vs 75.5%; p=.270). From baseline to T6 and T12, MMDs (8.0 SD 6.3; 8.9 SD 6.6), MIDAS (21.6 SD 20.2; 20.3 SD 20.3), and NRS (5.9 SD 1.8; 5.9 SD 1.7) significantly decreased (consistently p<001). The decrease in MMDs (p=0-202) and NRS (p=0.536) was not different in the younger population compared to the entire cohort, while MIDAS variation tended to differ in the YOUNG population (p=.054). More specifically, MIDAS scores increased from T6 to T12 in the YOUNG compared to the non-YOUNG population (p=.037).

Conclusion: CGRP MABs seem not to display higher effectiveness in the younger population.

Shall we treat children with migraine?

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Background: In 2017, the prophylaxis of pediatric migraine was revolutionized by the results of the Childhood and Adolescent Migraine Prevention (CHAMP) study which, in a large population of children and adolescents with migraine, showed that placebo was not inferior to both topiramate and amitriptyline (Powers et al, 2017). This raised several doubts about the use of medications in young migraineurs, leading some authors to maintain that in children and adolescents only psychotherapy should have been prescribed. In the present study, we aimed at investigating whether pharmacological prophylaxis of pediatric migraine could: 1) improve the efficacy of the medications for the acute migraine attack, and 2) counteract the progression of an episodic migraine toward a chronic form.

Methods: We conducted two retrospective different studies. In the first, we recruited 70 patients (mean age: 14.2 ± 2.4 years) with chronic migraine who had undergone pharmacological prophylaxis. Paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), and triptans were considered as acute medication in their own category. A patient was defined as not responding to acute therapy when he did not respond to paracetamol, an NSAID, and a triptan. We compared the percentage of non-responders before and after migraine prophylaxis. In the second study, 165 patients (mean age: 13.1 ± 2.8 years) with episodic migraine (more than 4 attacks/month) at T0 they were divided into two groups: the first underwent prophylactic treatment (PT), and the second without prophylaxis (noPT). At T1, we compared the percentage of patients with chronic migraine between PT and noPT groups.

Results: In the first study, we showed that after prophylaxis, the prevalence of patients responding to the analgesic drugs increased from 27% to 71.4%, while non-responder patients decreased from 73% to 28.6%. The bivariate analysis identified only prophylactic therapy as a factor associated with response to acute therapy (R 0.9; C.I. 0.7–0.95; $p<0.05$). In the second study, among PT patients only 14% evolved into chronic migraine, while migraine chronicization was observed in 89% of noPT patients (Chi-squared test, $p<0.001$).

Conclusion: We showed that, in children and adolescents with migraine, prophylactic treatment is able to: 1) improve the efficacy of the medications for the acute attack, and 2) reduce the risk of migraine chronification. In addition to the CHAMP study results, the present findings should also be considered when we need to decide whether to prescribe a pharmacological prophylaxis for pediatric migraine.

Diagnosing migraine in children and adolescence using ID-Migraine: results of an Italian multicenter validation

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Background: Migraine is the most frequent neurological condition, and an early diagnosis is important to limit the impact of the disease on the quality of life. Migraine diagnosis is clinical applying ICHD3 criteria. For adulthood ID-Migraine, is a screening tool that allows migraine diagnosis. For pediatric age no validated tools are available. The aim of this study is to validate ID-Migraine for diagnose migraine in developmental age.

Methods: All patients consecutively attending the Headache Center of the Bambino Gesù Children's Hospital in Rome, San Paolo Hospital in Bari and Civico Hospital in Palermo (Italy), in the period January 2022 - February 2024 aged 6-17 years were included in the study.
The administered questionnaire had been validated in Italian for adult migraineurs by Brighina et al. The diagnosis according with the ICHD3 criteria, formulated at the end of visit, was matched with the answers provided to the ID-migraine.
Specificity, sensitivity, negative and positive predictive factor were statistically evaluated. They were considered reliable for values >80%.

Results: Two hundred eighty-nine pediatric patients (mean of 12.14 years ± 3.15, range 6-17), attending our third level headache centers, were enrolled and filled-in the Italian version of the ID-migraine for adulthood. Clinical and neurological examination were performed, and headache diagnosis was postulated according to the ICHD3 criteria. Two hundred thirty patients received migraine diagnosis and were included in the migraine group, while 59 received other headache diagnosis and were included in the control group.
Considering the response to the ID-Migraine, specificity, sensitivity, negative and positive predictive values were statistically evaluated. Considering the positive response to the ID-Migraine, i.e the presence of 2 positive responses, the sensitivity was 0.86 (86%), the specificity 0.95 (95%), the PPV 0.98 (98%) and NPV 0.64 (64%).

Conclusion: From our results ID-Migraine can be considered a valid tool to diagnose migraine also in pediatric age starting from 6 years.

Pediatric migraine severity: understanding the association with cognitive and psychological dimensions

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Background: Research suggests that young migraine patients, often exhibiting perfectionist tendencies, face increased risks of low functioning, poor academic performance, and heightened anxiety. Their headaches typically follow a seasonal pattern, exacerbating their school experience. However, research on the link between migraine severity, neuropsychological difficulties, and psychological symptoms is limited. This study explores the prevalence of neuropsychological difficulties and learning disabilities in pediatric migraine patients and examines the association between cognitive performance, psychological symptoms, and migraine severity.

Methods: We included 34 children/adolescents with migraine (m.a=12.6, SD=2.47; F=21, M=13). We assessed the following variables: verbal memory (forward and backward span, BVN 5-18 battery), verbal fluency (BVN 5-18), attention and executive functions (the visual attention, the naming, inhibition and switching subtest, NEPSY-II), processing speed (SDMT), anxiety and depression symptoms (SAFA-A and D). Migraine episodes were categorized as: 1) high frequency (weekly to daily) and 2) low frequency (≤3 per month). Since the frequency of attacks at evaluation may not accurately represent migraine severity, subjects were divided into those who were taking prophylactic drugs (or needed prophylactic treatment within the past year) and those who did not require medications.

Results: We identified borderline and clinical scores in 51.85% of our sample for naming, and in 62.96% for inhibition and switching tasks. A substantial proportion of patients (more than 40%) scored below the normal range in the speed performance of these tasks. We found that 64.70% of the patients tested positive for learning disabilities. Patients with high migraine frequency exhibited significantly lower scores in backward digit span ($p=0.030$); on the other hand, they had higher scores in school anxiety ($p=0.022$) and irritable mood ($p=0.036$). The use of prophylactic treatment was not associated with neuropsychological fragilities or the presence of learning disabilities ($p>0.05$), but it was associated with school-anxiety ($p=0.007$), anhedonia ($p=0.034$) and irritable mood ($p=0.015$).

Conclusions: Our study suggests that pediatric migraines may be associated with difficulties in speed performance tasks, involving executive functions, and learning difficulties. Since no association was found between the need for prophylactic treatments and neuropsychological performance, we hypothesize that anxiety may be the most relevant factor associated with migraine severity.

Morphometric Similarity Networks in pediatric migraine without aura: unravelling the role of gender

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Background: Pediatric migraine without aura is the most common form of headache in children, carrying a significant social and economic burden. Literature proved that migraine causes structural and functional alterations on brain cortex and connectome, yet the underlying mechanism is still unclear. To our knowledge, morphometric similarity mapping (MSM) for studying cerebral connectivity and cortical pattern have never been applied to the study of pediatric migraine without aura. Our study aims to: a) identify differences in morphometric similarity networks (MSNs) in pediatric patients affected by migraine without aura compared to healthy controls and in subgroups of patients; and b) correlate these differences in MSNs with patients' demographic and clinical characteristics.

Methods: Eighty-three patients affected by migraine without aura aged between 6 and 18 years, and eighty-one age- and sex-matched controls were retrospectively recruited from the archive of our Institution with the following inclusion criteria: high-quality MRI exams without any morphological and signal abnormality, no abnormal neurological examination, no comorbidities. 3D T1 MPRAGE and DWI/ADC were pre-processed to obtain eleven cortical parameters for the MSN analysis.
Subsequently, both the global mean morphometric similarity (MS) and the regional mean MS were calculated. The statistical analysis was performed between patients and controls and within subgroups of patients divided by demographic and clinical characteristics.

Results: MSM identified significant differences in MSNs in pediatric patients affected by migraine without aura in relation to demographic and clinical parameters. In particular, gender appeared to be the most significant parameter affecting MSNs. The cerebral pathways that showed the most significant alterations encompassed the executive function pathway, the nociceptive pathway and the default mode network.

Conclusion: Differences in MSNs between controls and patients and within subgroups of patients suggest that migraine shapes cerebral connectome and favours neuronal plasticity. The resulting abnormalities in the executive function pathway, the nociceptive pathway and the default mode network may lead to chronicization of migraine symptoms. Gender is confirmed as a paramount parameter in migraine, supporting the hypothesis of a sex specific phenotype.

The identification of *in-vivo* migraine biomarkers linked to anomalies of brain cortex and cerebral connectivity in pediatric patients affected by migraine without aura is crucial to offer a tailored therapy to pediatric migraine patients and improve their quality of life.

Gut microbiota ecosystem in pediatric migraine. How are dysbiosis, inflammation and intestinal metabolites involved?

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Background: Migraine is a debilitating condition that is not fully understood. There has been a recent increase in interest in the possibility that the gut microbiota (GM) plays a role in the onset of migraine. Our aim was to verify whether populations of bacteria associated with dysbiosis are found in pediatric patients suffering from migraine. We looked for the metabolic pathways where the bacteria were more active and whether they could be associated with gut inflammation and increased intestinal permeability.

Methods: Patients aged between 6 and 18 years were recruited. The GM profiling was obtained by the 16S rRNA region sequencing from faecal samples of migraine patients (n = 98, MIMIC) and of healthy subjects (n = 98, CTRL). Alpha and beta diversity analyses and multivariate (unsupervised Principal Component Analysis [PCA] and the supervised Partial Least Square Discriminant Analysis [PLS-DA]) and univariate (Linear Discriminant analysis [LDA] effect size [LEfSe]) tests were applied to compare the gut microbiota profiles between migraine and CTRL groups by R v4.0.2. The level of indican in urine was analysed to confirm the presence of dysbiosis. To predict functional metabolic pathways, we used phylogenetic analysis of communities using unobserved states software. To assess gut inflammation and increased intestinal permeability, we measured the levels of lipopolysaccharide and occludin respectively in plasma.

Results: We assigned Gemmiger, Phocaeicola, Roseburia, Escherichia, ER4, Acetatifactor, Alistipes_A_871400, Dorea_A and Rombustia for MIMIC subjects, while Eggerthella, Alistipes_A_871404, Clostridium, Collinsella, Parabacteroides, Erysipelatoclostridium, Akkermansia and Faecalibacillus for CTRL. Thirty-seven metabolic pathways play a role in the MIMIC profile, which includes changes in tryptophan and phenylalanine metabolism. The presence of dysbiosis was confirmed by the increased level of indican in urine. Plasmatic occluding levels were found to be higher, which means there is an increase in gut permeability. The absence of a high level of lipopolyxacharide in plasma indicates that MIMIC do not have significant intestinal inflammation.

Conclusion: MIMIC patients present different GM profiles than CTRLs and which are connected to metabolic pathways important for migraine. The low levels of intestinal inflammation associated with increased intestinal permeability suggest that the products of these metabolic pathways may play a role in the onset of migraine more than intestinal inflammatory mediators.

Sphenopalatine Ganglion Block in the management of pharmacoresistant chronic headache in children and adolescents: the experience of the Juvenile Headache Center of Padova

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Background: Chronic headache (CH) is frequent in both the pediatric and adult population, carrying a high impact on the quality of life (QoL) and often not responding to prophylaxis therapy. Because of its central role in the pathogenesis of facial pain and headache, the sphenopalatine ganglion (SPG) block by intranasal injection of anaesthetics has been used as treatment with good efficacy on adults with CH. Less studies are available for the pediatric population. The objective of this study is to describe the efficacy and safety of SPG block in pediatric/adolescent patients with pharmacoresistant CH.

Methods: We included patients younger than 18 years of age with a diagnosis of CH who already received at least two lines of treatment. For each patient who underwent SPG block we investigated: pain at each headache episode through the Visual Analog Scale; number of days per month with headache, and QoL (sleep, absences from school or other recreational activities, PedMIDAS). Each parameter was monitored before the procedure, and after 1 and 3 months. Pain was measured every 2 hours for the first 6 hours after the procedure, and then every day for 7 days. Secondary effects were evaluated for 24 hours after the procedure. The procedure was considered effective if a reduction of pain intensity and/or frequency of at least 50% from baseline was observed.

Results: Out of 6 patients enrolled in the study (age range 12-17), SPG block was not effective in 2 at both baseline and after 3 months; effective in 1 acutely and chronically in 3 out of 4 procedures performed; in 1 patient it reduced the intensity of the acute headache attack; and in the last 2 it reduced the frequency of headache episodes, with positive effects in the QoL in both. Only one patient reported transient dysgeusia as minor secondary effect.

Conclusion: The procedure was well tolerated and we observed an overall benefit in both terms of prevention and treatment. Further studies are needed in order to confirm these data and to better understand the role of SPG block in pediatric patients with CH, especially as treatment for acute severe, prolonged and pharmacoresistant attacks.

Psychiatric and neurodevelopmental disorders in patients with acute headache referred to the Emergency Department: data from a tertiary pediatric hospital

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Background: Headache is the most prevalent neurological disorder in children and a frequent cause of emergency department (ED) visits. It is often associated with several comorbidities, primarily psychiatric and neurodevelopmental disorders. Evidence indicates a bidirectional relationship between these conditions, although the underlying biological mechanisms remain unclear. Psychiatric comorbidities can significantly diminish quality of life and complicate headache management. Identifying these comorbidities allows for more targeted interventions, enhancing effectiveness through pharmacological and rehabilitative approaches.

Methods: We retrospectively evaluated patients referred for headache to our pediatric ED from January 2021 to December 2023 and we analysed the association between headache and the diagnosis of a neuropsychiatric disorder in the following 6 months after the visit. Secondly, we analysed the group with neuropsychiatric disorders in order to identify peculiar features, which can help the ED pediatrician to refer them promptly to the neuropsychiatric division.

Results: 921 patients with headache (49.4% male; median age 10.9, CI 2.16 – 35.74) were admitted to our ED: 555 (60.3%) patients underwent a neuropsychiatric evaluation in ED or in the following 6 months, and among these the following psychiatric diagnosis and/or neurodevelopmental disorders were identified in 201 patients (36.2%): 118 (21.3%) anxiety disorders, 21 (3.8%) mood disorders with predominance of depressive disorders (17 = 3.06%); 17 (3.06%) eating disorders; 30 (5.4%) somatic symptoms (and related) disorders; 99 (17.8%) neurodevelopment disorders with predominance of specific learning disorders (42 = 7.6%). Comparing the characteristics of headache in the population of psychiatric patients to non-psychiatric patients, it emerged that the first group complains more frequently of visual disturbances (23.4% vs 14.4%, p = 0.01), and presents a greater number of headache episodes per month (11.14±11,12 vs 7.76±10.33, p = 0.05).

Conclusion: Headache in children is often associated with psychiatric and/or neurodevelopmental disorders, especially anxiety disorders. Patients with neuropsychiatric comorbidity who referred to ED with headache present more frequently visual disturbances in association and have an increased frequency of headache episodes per month compared to the population without neuropsychiatric comorbidity.

Pediatric onset multiple sclerosis and primary headaches: is there a link?

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Background: The objective of our study is to study what impact primary headaches have on the clinical, neuroradiological and therapeutic course in our patients with pediatric mulitple sclerosis (MSp).

Methods: We conducted a retrospective analysis from January to April 2024 on a PMS population to verify whether there are differences between the two populations of PMS patients with headache and without headache. The definition of headache and its respective categories is based on the ICHD-3 criteria. For each cephalalgic patient, the frequency of headaches and any chronicity, aura, location, side, and quality of the pain were evaluated in the analysis, together with associated symptoms (photo-phonophobia, nausea and vomiting), and then the response to painkillers and prophylactic therapies. We used the chi-test for the categorical variables [type of therapy, sex and lesion load, defined as low with lesions 10] and Anova test for the continuous variables (age at onset of the disease) and placed significance at $p < 0.05$.

Results: Our sample consists of 64 patients with PMS (average onset: 13.6 years - 5.4 and 17.8), of which 50 with headache and 14 without headache. From our analysis no significant relationships emerged between age at onset, type of therapy or lesion load. However, a relationship with sex emerged (F-SMp 37/50; M-SMp 13/50 - $p < 0.05$), with prevalences of primary headaches similar to those of the general population. Similarly, patients with migraine are those who most frequently may present a high frequency of attacks compared to tension headaches and the need to resort to prophylactic therapies ($p < 0.05$).

Conclusion: Our data support the hypothesis that in pediatric age there is no relationship between primary headache and some parameters related to MS such as age at onset, type of drug and extent of lesion load. The progress of the two diseases therefore seems independent. The study should be conducted on a larger number of patients (polycentric), prospectively and with longer follow-up.
A further study should evaluate the influence of headache on neuropsychological variables (e.g. cognitive, adaptive, executive functions) as well as the impact on the quality of life of patients with PMS and highlight any changes in CSF or humoral inflammatory markers.

Clinical characteristics of headache in children and adolescents: A cross-sectional school study

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Background: While there is ample evidence of the burden of headaches among adults, there is limited data on the burden of headaches in children and adolescents. The aim of this study was to investigate the clinical characteristics of headache disorders among children (aged 6–11 years) and adolescents (aged 12–17 years).

Methods: This study was a cross-sectional survey conducted using self-completed structured questionnaires administered in five primary and secondary schools from the L'Aquila district. After obtaining a signed informed consent from parents, the child or adolescent versions of the Headache-Attributed Restriction, Disability, Social Handicap and Impaired Participation (HARDSHIP) structured questionnaires were administered to all the students available in participating in the study. The questionnaires were self-completed by pupils under supervision of their parents. Statistical analysis was performed with Jamovi 2.4.11 software. Continuous variables were expressed as the mean±standard deviation (SD), while categorical variables were presented as frequency or percentage.

Results: A total of 344 students were included in the study (mean age±SD 9.94±2.36, 53% females). Of these, 211 attended the primary school and 133 the secondary school. At least one headache attack in the past year was reported by 128 primary school children (61%) and by 118 adolescents attending secondary school (89%). In both the age groups, pain was mostly described as constrictive/gravative (53% primary school children; 51% adolescents), not strictly unilateral (46% bilateral pain; 37% vertex onset pain; unilateral 15%), lasting less than one hour (56% primary school children; 35% adolescents) and of mild intensity (52% primary school children; 62% adolescents). The most frequently associated symptom was phonophobia (77% primary school children; 79% adolescents), followed by photophobia (33% primary school children; 48% adolescents), nausea (23% primary school children; 25% adolescents) and vomiting (10% primary school children; 6% adolescents). A high proportion of participants (26%) reported at least one attack in the last 4 weeks (minimum 2 attacks – maximum 15 attacks).

Conclusion: Our results confirm that paediatric migraine shows a different clinical pattern as compared to adult migraine, presenting with shorter attacks, less pronounced lateralized and pulsating pain, and milder intensity. Headache-attributed burden in developmental age warrants investigation.

Familial visual snow syndrome: a case report

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Background: Visual Snow syndrome (VSS) is a condition described in ICHD3 and characterized by continuous tiny dots across the entire visual field persisting for >3 months with at least 2 between palinopsia, enhanced entoptic phenomena, photophobia and nyctalopia. It is frequently associated with migraine. Differentiating VSS from persistent migraine aura can be a challenge, as some symptoms are common to both conditions, including palinopsia, photophobia, nyctalopia, and tinnitus. Several studies support the hypothesis that patients with migraine aura present cortical hyperexcitability, and neuroimaging studies have shown that the lingual gyrus is involved in photophobia during migraine; these data suggest that VSS and migraine share several pathophysiological mechanisms that may justify the frequent association between the two conditions.

Case report: We describe the case of a boy who came to our attention at the age of 10 years for persistent headache with vomiting and evidence of papilledema. Previously, sporadic episodes of headache with migraine-like characteristics, the presence of migraine equivalents and a family history of migraine were reported. During hospitalization, brain MRI was performed with angiographic sequences which showed signs of intracranial hypertension, lumbar puncture with evidence of raised ICP (40 cmH20) and normal ERG-Flash and VEP. Once the diagnosis of idiopathic intracranial hypertension was confirmed, therapy with acetazolamide was started for about a year until the papilledema disappearance. Subsequently he continued to have occasional migraine episodes.
During a follow up visit at the age of 14 years he reported enhanced entoptic phenomena and photophobia and persistent colored dot vision in association with sporadic episodes of migraine lasting for 6 months. Brain MRI and ERG-Flash and VEP were repeated, with normal results.

Investigating the family history, the mother reports having the same type of persistent vision since she was a child and having undergone ERG-Flash and VEP, brain MRI, EEG and psychiatric evaluation over time, all reported normal. He also presents episodes of migraine with aura in which the reported visual symptom is scotoma.

Conclusion: The symptoms described by this patient and his mother meet the criteria for Visual Snow Syndrome with co-occurrence of migraine. To date, no other familial visual snow cases are reported in the literature. It would be interesting to evaluate a common genetic implication on a larger sample of patients with this diagnosis.

Intravenous Valproic Acid treatment in patients with chronic refractory migraine: our experience in pediatric age

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Background: Chronic migraine has high prevalence in children. In adults with migraine, valproic acid (VPA) is an effective prophylactic treatment. There are few pediatric studies that demonstrate the efficacy of intravenous VPA in chronic migraine.

Methods: We included 8 patients, 4 females and 4 males, with a median age of 15.6 years, with chronic refractory migraine. All patients underwent neuroimaging and lumbar puncture with measurement of intracranial pressure. A standardized protocol of repetitive infusion of VPA was applied (first dose at 15 mg/kg, in 30 minutes and thereafter at 5 mg/kg every 6 hours for 12 doses). Prophylactic therapy with oral VPA was initiated in patients with positive response to intravenous treatment. The response to treatment at VPA was evaluated by analyzing the severity, monthly frequency of headache and the use of attack medications before, during, after VPA infusions and during oral therapy.

Results: During VPA infusions, 4 patients reported a good response to treatment for pain reduction (median of visual analogue scale VAS 2/10, pre-infusion 9/10) and so oral treatment with VPA was continued. At the revaluation at week 12: 2 patients needed to undertake other prophylactic treatments because of a high frequency of migraines (28 attacks); 2 patients reported a decrease in monthly frequency and intensity of attacks (12 attacks, VAS 4/10). The headache frequency, as well as the intensity of pain and the use of drugs for the attacks did not show a significant reduction compared to before intravenous treatment with VPA in the 4 patients, who had a good response on the intensity of pain during infusion: the median of frequency of monthly attacks was 20 (pre-infusion 30), the median of intensity was 6.5/10 (pre-infusion 9/10) and the median of the use of drugs for the attack 16 (pre-infusion 22).

Conclusion: We observed how intravenous treatment with VPA in pediatric patients with chronic refractory migraine can reduce in acute the intensity of the attack during the infusion and in the days following treatment; while the continuation of oral treatment in the following three months did not show as much effectiveness in reducing frequency, intensity of pain and the use of drugs.

Headache in aseptic meningitis associated to MOGAD: thinking out of the box

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Introduction: MOGAD is an immune mediated inflammatory process of the CNS causing demyelination of optic nerves, brain and spinal cord. MOG is a component of myelin and found on the surface of oligodendrocytes. MOG antibody associated disease has been associated with multiple phenotypes including optic neuritis, transverse myelitis, seizures, elevated intracranial pressure, acute disseminated encephalomyelitis (ADEM) and aseptic meningitis.

Case report: Eleven-year-old healthy boy, presenting to the emergency room with a new onset severe headache associated with nocturnal awakenings and vomiting during sinus infection and tonsillitis. Fundus oculi showed bilateral papilloedema and brain MR documented indirect signs of intracranial hypertension. Lumbar puncture showed cerebrospinal fluid hypertension and pleocytosis. Suspecting an infectious meningitis the patient was treated with ceftriaxone and corticosteroid, associated with acetazolamide, with efficacy on headache and intracranial hypertension. At follow-up MRI was found leptomeningeal enhancement and blood tests showed seropositivity for anti-MOG antibodies. Suspecting MOGAD, therapy with high dose methylprednisolone bolus and then with IVIG was administered with efficacy, then the patient was discharged with oral corticosteroid therapy. After 4 months from onset, the patient presented a MOGAD relapse with optic neuritis in the left eye that again needed therapy with corticosteroid and IVIG, with resolution. Finally, a treatment was started with mycophenolate, as a prevention of new relapses.

Conclusion: Headache as a symptom of meningitis with intracranial hypertension could be an uncommon manifestation of MOGAD, that should be included into differential diagnosis of aseptic meningitis, in order to start an appropriate treatment as soon as possible. Our patient showed an excellent response to immunomodulating medical treatment, both in acute and during relapse, showing that accurate diagnosis can improve the efficacy of treatment and clinical improvement.

Hemiplegic migraine onset in pediatric age: a single-center clinical and neuroradiological perspective

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Background: Given the time dependence of specific treatments for stroke and for some stroke mimics, it is essential to have acute neuroradiological and clinical data to differentiate these conditions, including Hemiplegic Migraine. Hemiplegic Migraine (HM) is a rare form of migraine with aura, characterized by motor aura (transient motor weakness or hemiparesis) associated with other non-motor manifestations of aura (visual, sensory, speech/language or brainstem symptoms). It can be classified as sporadic (SHM) or familial (FHM). Headache is present in most patients and described more often as unilateral. It can be associated with nausea, vomiting, photophobia and phonophobia.

Methods: Retrospective analysis from 2013 to 2024 of patients (<16 years old) admitted to our hospital, which fulfilled the diagnostic ICHD-III criteria for HM.

Results: We included 15 patients (3 males and 12 females). Fourteen patients were diagnosed with SHM (12 females, 2 males), and 1 patient with FHM. The mean age at the first HM attack was 11 years.
In 7/15 subjects the headache onset occurred concurrently with motor aura, which manifested as hemiparesis in 10/15 patients. Ten patients presented with sensory aura, four patients had visual alterations and five patients presented with confusion. Moreover 12 out of 15 patients had speech abnormalities. Three patients out of 15 had a prolonged attack, lasting at least 72 hours. All of them were SHM.
MRI imaging at onset revealed alterations in the affected brain hemisphere in 6 out of 8 cases, including diffusion restriction, leptomeningeal contrast enhancement and cortical T2-FLAIR hyperintensity. EEG registration showed asymmetrical slow-wave activity in 9 out of 13 cases.

Conclusion: Clinical and neuroradiological findings have a crucial role in distinction of cerebrovascular event from typical migraine with aura. We recommend referring patients with acute focal neurological symptoms to centers that can guarantee MRI (including DWI, SWI FLAIR sequences) and MRA protocols in a time-dependent setting, to differentiate hemiplegic migraine from stroke. Proper diagnosis of hemiplegic migraine (HM) can also prevent inappropriate treatments. A multicenter case series would be appropriate for a better definition of diagnostic features.

Lost in transition: factors associated with effective transition from pediatric to adult headache care

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Background and aims: Since 2020, Campus Bio-Medico University Hospital and Bambino Gesù Children Hospital have created a joint outpatient clinic to favor a proper transition from pediatric to adult headache care. The present study aims to assess factors associated with ineffective transition.

Methods: This is a prospective cohort study. At the joint headache visit, we collected headache frequency, bothersome associated symptoms, aura, migraine onset age, comorbidities, number of previous preventive therapies, and family history in patients aged 17-22 who were still under pediatric care. All patients were instructed to perform a control visit at Campus Bio-Medico University Headache Center within one year.

Results: Ninety-one patients were considered (69.2% females, aged 17.9 ys; SD 2.7); of these, 52.8% of subjects also suffered from comorbidities, 54.9% presented migraine family history, and 17.6% had aura. Phonophobia was the most common associated symptom (90.2%). The mean onset age was 11.5 (SD 0.6). Subjects had experienced a median of 1 preventive therapy (IQR 2). Monthly migraine days (MMDs) were 2.7 (SD 0.5) at the joint visit. Only 29 patients (31.9%) performed a visit in the adult settings. Higher MMDs (4.8 SD 1.4 vs 1.5 SD 0.1 SD) was the only variable associated with an effective transition among the considered variables.

Conclusion: Most patients are lost in the transition from pediatric to adult care. Headache frequency is the main determinant of continuous takeover.

Prevalence of primary headache in school-aged children: preliminary findings from the REPICEF project

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Background: Assessing the prevalence of headaches in children and adolescents, along with the associated disability, is crucial due to the diagnostic challenges in this population. Additionally, there is a scarcity of high-quality epidemiological studies on this topic. The "Registro EPIdemiologico delle CEFalee in età evolutiva" project (REPICEF) aims to address this gap by providing a comprehensive analysis of the prevalence, characteristics, and comorbidities of headaches in school-aged children. This analysis focuses specifically on headache diagnoses and their prevalence.

Methods: REPICEF is a prospective study involving students aged 6 from 17 schools in the city of L'Aquila (Italy). Parents of the participating children provided informed consent. The Italian version of the child and adolescents Headache-attributed Restriction, Disability, Social Handicap and Impaired Participation (HARDSHIP) was used to evaluate the characteristics of headache and assess their headache diagnosis. The HARDSHIP questionnaire distinguishes between definite and probable diagnoses. To assess quality of life, the KINDL® test was employed. This test assigns a score from 0 to 100 based on responses to 11 questions answered on a 4-point Likert scale, with higher scores indicating a better quality of life.

Results: From January to May 2024, we included 286 students (55.2% female, mean age 11.6±3.4 years) and 244 (85.3%) of participants experienced at least one headache in the past year. Sixty-four (22.4%) were diagnosed with migraine and 27 (9.4%) with tension-type headache (TTH). Most of the children reported episodic migraine diagnosis (54; 84.3%) while the remaining had chronic migraine. Referring to probable diagnoses, 87 children and adolescents (30.4%) were diagnosed with probable migraine (pMigraine) and 66 (23.1%) with probable TTH (pTTH); 32 (11.2%) children and adolescents presented with unspecified headache. At the KINDL® test, children with headache reported a mean score of 29.1±3.7 points, corresponding to poor quality of life.

Conclusion: REPICEF project underscores the notably high prevalence of headaches among children and adolescents, highlighting a significant burden in terms of disability. Given this impact, it is crucial to educate families and teachers on the implications of this condition and to provide strategies for managing and supporting affected children. Furthermore, understanding the trajectories of headache in this population is essential for developing effective interventions and long-term management plans.

A retrospective analysis of paediatric patients with primary headache and chronic underlying disease

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Background: The management of children with primary headache can be influenced by underlying diseases, due to various factors (psychological, therapeutic). The aim of our study was to describe a population of children with primary headache and chronic underlying disease.

Methods: We retrospectively reviewed all the children with chronic underlying disease who were admitted for the first time to the Paediatric Headache Centre of the Regina Margherita Children's Hospital of Turin between January 2021 and December 2023.

Results: In the study period, 58 children with chronic disease were included (M 48%, F 52%); the mean age was 11.8 years (SD 3.3). Overall, 13 had oncohematological diseases, 10 had endocrinological disorders, 8 showed syndromes, 8 had neuropsychiatric disorders, 6 had Chiari I malformation, 5 suffered from an immune or reumatological disease, 5 had gastroenterogical disorders, and 3 had cardiological disorders. Twenty-five patients (43%) were on chronic therapy. Thirty-two children (55%) were diagnosed with migraine, 9 tension-type headache, 8 chronic-headache, 7 had a mixed form and 2 had a non-classified form. Forty-six patients (79%) needed prophylactic treatment for headache: all of them received nutraceutic therapy, principally with magnesium. Patients with chronic headache were referred to psychologists and were put on short-term follow-up in order to assess the need of pharmacological prophylaxis.

Conclusion: Children suffering from primary headache who have a chronic underlying disease are a heterogeneous population that need a multi-specialistic approach. In our group, we observed a higher percentage of chronic headache than in the general population and most of the children needed prophylactic treatment. Our findings confirm that headache progression or prognosis may be related to the presence of other chronic disorders.

Childhood migraine chronification: Is there a role for prophylactic treatment?

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Background: Childhood chronic migraine is a very debilitating condition. Prophylactic treatment could reduce the risk of chronification in adults, but this is still debated in childhood where the scenario is complicated by placebo response. In this study we wanted to investigate the effect of prophylactic therapy on migraine chronification.

Methods: We included 165 migraine children (age <18 years) evaluated at Bambino Gesù Children's Hospital from May 2021 to May 2023. The frequency of attacks, the use of analgesics and prophylaxis were recorded at T1 (4 months after baseline) and T2 (12 months after baseline). A screening for anxiety (GAD-7) and depression (PHQ-9) was performed. The patients were divided into 4 groups at T2: patients treated with prophylaxis when attack frequency was >4 and no chronification (P+ M-) or with chronification (P+ M+); patients not treated with prophylaxis when attack frequency was >4 and no chronification (P- M-) or with chronification (P- M-). Chi square test was used to compare the groups. We also investigate features associated to chronification.

Results: 123 patients were female and median age of migraine onset was 10 years. 63% had a positive screening for anxiety or depression but none received pharmacological treatment. Ninety-three patients received prophylactic migraine treatment (topiramate, flunarizine, amitriptyline, palmitoylethanolamide, tryptophan) when the headache frequency was >4 per month for at least 3 months. At T1, 43 patients had benefit and treatment was interrupted, while 50 continued (25 patients were switched to another drug). At the final follow-up visit (T2), 13 had a transformation to chronic migraine, of which 6 made excessive analgesic usage. Seventy-two patients were not treated and 64 had a chronification. The comparison between the two groups showed that the risk of chronification was significantly higher in the untreated group (OR 49.23, $P < 0.0001$). In our population female sex, age between 11-18 years, anxiety and depression were associated with chronification.

Conclusion: Our study showed that prophylactic treatment could reduce the risk of chronification in childhood. As already reported in previous study, anxiety and depression could contribute to the transformation in chronic migraine. This study has some limits, as the retrospective design.

Idiopathic intracranial hypertension in a pediatric Italian cohort: a retrospective study and what we have learnt

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Background: Idiopathic intracranial hypertension (IIH) is a condition characterized by increased cerebrospinal fluid pressure without an identifiable primary cause, making it a diagnosis of exclusion according to ICHD-3 classification. It is rare in the pediatric population. This retrospective study analyzes a cohort of patients from our Pediatric Neurology Unit.

Methods: We analyzed a cohort of 70 pediatric patients (38 females and 32 males) who were referred to our Pediatric Neurology Care Center from January 2007 to April 2024. Data were collected on personal and family medical history, clinical presentation, and various tests, including lumbar puncture (LP), fundus oculi, MRI, ERG, VEP, and optic nerve echography. The patients were divided into two subgroups based on age (8 years) due to significant differences found in the parameters considered, primarily body mass index, with older patients more commonly overweight or obese.

Results: Headache was the main symptom in pubertal and post-pubertal patients (81.4%), while prepubertal males primarily presented with diplopia and vertigo (11.4%; only one had a headache). The second most common symptom was diplopia with 6th cranial nerve palsy (28.6%). Other symptoms included nausea and/or vomiting (24.3%), transient visual obscuration/visual loss (21.4%), vertigo (11.4%), and neck pain (4.3%). The mean opening pressure (OP) was 40.8 cmH2O (SD 13.5; range 27-90), with higher OP in pubertal patients compared to younger children (42.9 vs. 33.4 cmH2O). OP was significantly higher in patients with headache and diplopia (mean 54.9 cmH2O; $P<0.01$).
All patients had papilledema (except for 3 who were symptomatic and confirmed by optic nerve echography). Therefore, 5 patients (7.1%) were asymptomatic, diagnosed by fundus oculi screening. Of the 56 patients who underwent MRI, 12 (21.4%) had normal results, while 44 (78.6%) showed abnormalities (bulging papilla with increased perioptic space 47.7%, empty sella 36.4%, tortuous optic nerves 15.9%, stenosis of the transverse sinus 4.5%, and other signs 20.5%). ERG was always normal, whereas VEP was altered, especially in patients with cranial nerve involvement. The treatment of choice was acetazolamide, with a mean treatment duration of 5.5 months, approximately one month after a normal fundus oculi was observed on follow-up. A notable increase in younger

child cases was observed during the COVID period, from 2020 to 2022 (P<0.01): particularly in the prepubertal age group (P<0.05) and in patients presenting without headache (P<0.01).

Conclusion: This study confirms previous data and provides new insights into the clinical presentation and standard care for this rare pediatric disease.

A project for the management of chronic headache in a Pediatric Headache Centre

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Background: Headache in children and adolescents shows different biological, psychological and environmental issues requiring integrated diagnostic and therapeutic management. In particular, even in children, chronic headache needs a psychodiagnostic evaluation, pharmacological and psychotherapeutic treatment. We describe a multi-specialist project for children with chronic headache ongoing in our Pediatric Headache Centre.

Results: A multi-specialist project part of the "*Progetto cefalea primaria cronica*" sponsored by Piedmont Region started in 2024 in the Paediatric Headache Centre of the Regina Margherita Children's Hospital of Turin. Children with a diagnosis of chronic headache at the first evaluation were also tested by a psychologist for anxiety and depression, respectively using the *Revised Children's manifest anxiety* and the *Children depression inventory* tests. The patients who showed clinically significant results started a specific psychological treatment consisting in 8 short-term sessions based on psychodynamic models, and relaxation and mindfullness techniques. At the same time, all the included children were evaluated by a neuropsychiatrist for pharmacological treatment, if necessary. This project also included parental involvement aimed at sharing the meaning of symptoms and an extended network intervention, such as the collaboration with local social workers and school.

Conclusion: The project started with the awareness of the importance of comprehensive and multidisciplinary approach for children with chronic headache and with the aim of improving their level of psycho-physical well-being and consequently also the characteristics of their headache. A network between hospital and outpatient service is essential to reduced school problems, which are frequent in such patients and can lead to massive school absences and school-phobia or social withdrawal due to the severity of symptoms and their consequences.

Hemiplegic migraine as presenting symptom of Evans syndrome: a case report

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Background: Hemiplegic migraine (HM) represents a rare form of migraine with aura presenting with episodes transient motor weakness/hemiparesis[1]. Evans syndrome[2] (ES) is an autoimmune condition that presents with two or more cytopenias, which include autoimmune haemolytic anaemia and thrombocytopenia. We report a case of ES with episodes of HM as symptoms of onset.

Case presentation: A 14-year-old young women, with no contributory history for hemiplegic migraine, referred to the emergency department for three episodes occurring in one week characterized by gradual development of scintillating scotomas, following by paraesthesia on left arm, then left hemiparesis and speech disturbance. Each symptom lasted approximately 10 min, were fully reversible and followed by a migrainous headache. CT brain excluded acute ischemic/haemorrhagic stroke. Haematochemical tests revealed anaemia (haemoglobin 6,2 g/dL), with increased LDH (1148 U/L), thrombocytopenia (136000/mmc) and reticulocytosis. A fourth episode of transitory left hemiparesis occurred, so she underwent an urgent multimodal brain MRI that excluded acute stroke, showing on the right hemisphere reduced flow signal representation at distal arterial branches A2/A3, M2/M3/M4, P3/P4 associated with perisylvian cortical venous congestion, and a concomitant hypoperfusion on the entire right hemisphere compared to contralateral hemisphere, as seen on pASL sequences (fig.1). Symptoms fully recovered and neurological examination was normal (NIHSS=0). On suspicion of an immune-mediated haemolytic process (Coombs test positive) therapy with IV immunoglobulin (0,5g/kg/die for five days), IV methylprednisolone (2,5mg/kg/die) and blood transfusions was started. Causes of secondary Evans Syndrome were ruled out. After starting specific therapy for ES, the patient no longer presented episodes of HM.

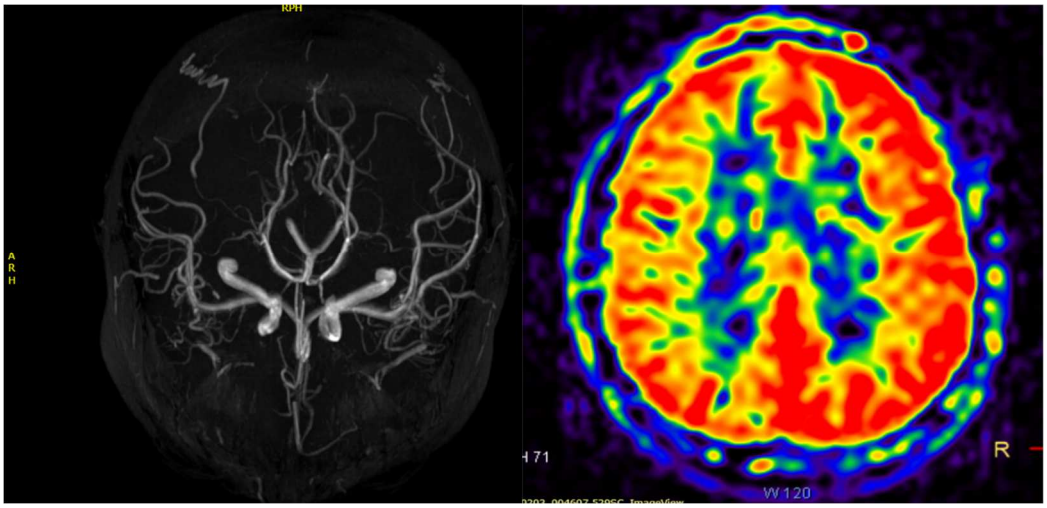

fig.1 MRA (A) and pASL(B) sequences

Conclusion: To the best of our knowledge, it is the first case of ES with episodes of HM as presenting symptoms. ES should be considered as a cause of HM of new onset.

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Management of headache in a patient with cystic fibrosis

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Background: Ivacaftor-tezacaftor-elexacaftor is the newest monoclonal therapy for cystic fibrosis. The efficacy demonstrated in clinical trials overcomes currently available therapies related to reducing exacerbations and improving pulmonary function and quality of life. Headache is one of the most common reported side effects.

Case report: We report the case of a 16-year-old boy suffering from cystic fibrosis, detected at birth through positive neonatal screening, with subsequent confirmation with sweat test and genetic analysis. He showed family history for headache in the maternal line. Before being put on therapy, he reported sporadic episodes of headache, mainly related to sinusitis. When he started monoclonal therapy with Ivacaftor-tezacaftor-elexacaftor, he began to experience episodes of pulsating vertex headache, associated with photophobia, resembling migraine without aura. The headache was poorly responsive to paracetamol, occurred weekly and lasted 2-3 days, with school discontinuation. The patient was referred to the Emergency Department several times due to this symptom. Brain Magnetic Resonance Imaging and fundus oculi evaluation proved negative. He was then referred to the Paediatric Headache Center of the Regina Margherita Children's Hospital of Turin: in agreement with pulmonologists, the monoclonal therapy was suspended after 3 months, and he was put on prophylaxis with magnesium. The headache improved after stopping the therapy; on follow-up the patient reported about one episode per month, well controlled with analgesic when needed.

Conclusion: Headache is one the most common side effects of Ivacaftor-tezacaftor-elexecaftor, together with cough, fever and skin rash. Our patient suffered from sporadic headache before starting the drug. We supposed that Ivacafactor-tezefactor-elexecaftor represented a triggering factor causing a clear worsening of his headache. Indeed, the symptoms were markedly reduced after discontinuation of the drug. This case confirms how challenging it is to take care of a patient with severe comorbidities who requires multiple drugs that can have intolerable side effects. Careful follow-up and multi-specialist evaluation is the key to enhance patient management and to get personalized therapy.

Migraine-mimicking headache in Tolosa-Hunt Syndrome: a case report

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Background: Tolosa-Hunt syndrome (THS) is a rare disease characterized by painful ophthalmoplegia caused by granulomatous inflammation in the cavernous sinus. Annual incidence of TSH is one case per million per year. Systemic symptoms associated with TSH are rarely described in reports in literature.

Methods: We describe the case of a 26-year-old woman presenting to the Emergency room (ER) of our hospital for a persistent and severe headache with typical migraine features (unilateral frontotemporal and retro-orbital pain associated with nausea, vomiting and photophobia, moderate to severe in intensity, up to NRS=10). The first time she visited the ER a brain CT scan was unremarkable and she was discharged with a diagnosis of migraine. Due to the persistence of symptoms and development of diplopia, she visited the ER a second time. A brain CT with contrast showed left cavernous sinus enlargement with no enhancement in the venographic scans. She was then admitted to Neurology department to undergo a brain MRI, laboratory tests, cerebrospinal fluid (CSF) analysis and ophthalmological evaluation. She was treated with intravenous corticosteroids.

Results: Brain MRI showed a focal mass expanding the left cavernous sinus with mild and late contrast enhancement and absence of signal in the angiographic sequences. CSF test was unremarkable. Autoimmune and microbiological screening tests were negative. The ophthalmological evaluation documented latent convergent strabismus due to the left VI cranial nerve deficit. Diagnosis of Tolosa-Hunt syndrome according to ICHD-3 criteria was formulated. We observed a remarkable improvement of head and eye pain (NRS at discharge=2) and diplopia resolution after corticosteroids treatment.

Conclusion: Due to its rarity, Tolosa-Hunt syndrome diagnosis can be challenging in clinical practice. Headache association with photophobia and nausea/vomiting in a young woman can easily be interpreted as migrainous manifestations. In this case, red flags consisted of a low response to acute treatment, no history of preexisting headache and association with diplopia after 10 days of head and eye pain. Our case shows that red flags must be carefully evaluated in the ER setting, even when typical migraine features are a prominent manifestation of a headache disorder.

Headache prevalence and phenotypes among a MOGAD population: a retrospective observational study

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Background: Pain manifestations are consistently being recognized as an important clinical feature in Neuromyelitis Optic Spectrum Disorders (NMOSD), while it has been less investigated in Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD); there is currently limited evidence about headache prevalence and features in MOGAD patients.

Methods: We selected 16 patients with a diagnosis of MOGAD and focused on clinical, radiological and laboratory findings regarding their disease course. Furthermore, we investigated the presence of onset-related headache and its characteristics (intensity, localization, quality of pain, accompanying symptoms and response to medications). We retrospectively collected data on history of preexisting primary headache disorders and focused on changes of both preexisting and newly diagnosed headache disorders after MOGAD onset.

Results: Ten patients (62.5%) presented headache preceding or accompanying the onset of other neurological manifestations. Among them, the most frequent MOGAD manifestation was optic neuritis (5), followed by brainstem involvement (2), encephalomyelitis (2), cerebellar involvement (1) and unilateral encephalitis (1). Duration of headache ranged from 24 hours to 10 days; qualitative aspects varied widely among patients, without a specific pattern. Eleven patients (68.7%) had a preexisting primary headache disorder. All patients with headache-related on reported different characteristics of pain in severity, localization and response to acute medications compared to their usual headache. Four patients had a newly-onset headache: among them, two never experienced headache again after MOGAD acute treatment, the others currently suffer from episodic migraine. Mean frequency of headache days/month was sporadic (<1 attack/month) for 5 patients; mean frequency for the remaining patients was 2.5 ∓ 1.3. Headache, preexisting or newly-onset, improved in severity and frequency for 6 patients after treatment.

Conclusion: The majority of patients presented headache at the onset and had a history of primary headache. Headache is an often-underestimated symptom; a careful evaluation can be helpful in early detection of central nervous system inflammatory disorders and, possibly, in predicting relapses in predisposed patients. Higher numbers and a longer follow-up period are required to validate our observations.

Herpes Zoster infection with monoclonal gammopathy: a complex case of ocular pain and cranial nerve palsy

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Background: A 78-year-old Caucasian male presented with a four-day history of left otalgia, initially misdiagnosed as an ear infection and inadequately treated with clavulanic acid and amoxicillin. One week later, he developed acute left eye pain, diplopia, and dysphagia, prompting an Emergency Department visit. Neurological evaluation revealed left-sided facial weakness, monocular diplopia, dysphagia, left sixth nerve palsy, and hyperalgesia on the left side of the face, without skin abnormalities.

Methods: Brain MRI and head and neck CT were performed to identify structural abnormalities and enhance visualization of cranial nerve involvement. To explore potential infectious causes, cerebrospinal fluid analysis was conducted via lumbar puncture, with samples subjected to cytological, cultural, and FilmArray testing to detect viral pathogens. Blood tests, including autoimmune screening, infectious disease screening, and tumour markers, were conducted to rule out other systemic conditions. Electrophysiological studies, including blink reflex and F wave assessments, were used to evaluate peripheral nerve involvement. Additional diagnostic evaluations included serum protein electrophoresis and immunofixation electrophoresis of serum and urine to detect monoclonal protein components.

Results: Brain MRI showed enhancement of the left seventh nerve near the geniculate ganglion and extradural hyperintense foci along the left petrous pyramid. Head and neck CT revealed soft tissue swelling at the palatine tonsil and oropharyngeal asymmetry. Electrophysiological studies confirmed left V cranial nerve involvement. CSF FilmArray was positive for Herpes Varicella-Zoster virus. The patient was treated with Acyclovir, Meropenem, Linezolid, and Prednisone, resulting in gradual improvement of facial weakness. Serum and urinary immunofixation identified a monoclonal IgG-K component, leading to a diagnosis of monoclonal gammopathy.

Conclusion: This case underscores the importance of considering Herpes Zoster infection in patients underlying monoclonal gammopathy and complex cranial neuropathies. Comprehensive diagnostic evaluations are crucial for accurate diagnosis and appropriate treatment, especially in atypical presentations where multiple cranial nerves are involved and no skin lesions are appreciable.

A severe case of IIH with an excellent response to the venous sinus stenting

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Background: We report the case of a 10-year-old girl who presented to our emergency department for walking instability who had experienced a fall followed by headache and vertigo. In her medical history: obesity (BMI 43.23 kg/m^2), hyperinsulinism, hypochromic anemia and dysmenorrhea.

Clinical Course: During the hospitalization, persistence of the pre-syncopal episodes described associated with cognitive regression and loss of vision in the right eye with dyplopia (medial rectus deficit). Brain MRI showed recent ischemic lesions in the right hemisphere (subcortical frontal, semioval center and periventricular) and previous ischemic lesions in the left hemisphere. Angio-MRI showed bilateral *ab extrinseco* stenosis of the venous sinus (trasverse-sygmoid junction). The fundus oculi showed bilateral papilloedema. The lumbar puncture documented an opening pressure of 100-140 cmH2O and the CSF analysis was negative. Idiopathic Intracranial Hypertension was the diagnosis and acetazolamide was started and then topiramate in add-on, due to the poor tolerability of acetazolamide. Since the patient experienced a further visual loss, right transverse venous sinus stenting was performed with improvement of the previous symptomatology and regression of the visual loss and right medial rectus deficit. Topiramate was stopped after 11 months while acetazolamide was maintained. An endocrinological and dietary follow-up was started, however with a poor control on the obesity (due also to a poor therapy compliance).

Conclusion: We described a case of a 10-year-old girl with severe IIH with a severe and sudden loss of vision, dyplopia and *ab extrinseco* stenosis of the transverse-sigmoid sinus junction that led to ischemic lesions in the right hemisphere. The severe clinical and radiological presentation was poorly controlled by the medical therapy, while the venous sinus stenting led to a fast and complete recovery of the clinical picture.

Headache and papilledema in IIH: an early integrated multidisciplinary management favors better outcome

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Background: Idiopathic Intracranial Hypertension (IIH) is characterized by increased intracranial pressure without an apparent cause, presenting with symptoms such as severe headache, visual disturbances, and papilledema. The incidence is 1-3 cases per 100,000 annually, primarily affecting young, obese women. Headache, reported by 84% of patients in studies, varies in nature (migraine, tension-type). Visual disturbances, including transient obscurations (68%) and diplopia (18%), are common in IIH. The condition poses severe morbidity, risking vision and causing intense headaches. Management options include weight loss, diuretics, and, in refractory cases, surgical interventions like ventriculoperitoneal shunting or optic nerve sheath fenestration. Given the variable prognosis, this study aims to assess the effectiveness of a timely, multidisciplinary approach involving neurologists and neuro-ophthalmologists.

Methods: We retrospectively investigated the management and outcomes of patients with confirmed IIH at our hospital from January 2020 to December 2023. Prompt patient assessment and collaboration between neurologists and neuro-ophthalmologists were documented. The effectiveness of early, multidisciplinary, conservative interventions was studied in terms of outcomes and the requirement for invasive treatment. Timely interventions included pharmacological therapies, weight management, lifestyle changes (e.g., smoking cessation), and invasive therapies when necessary.

Results: Twenty-two patients (17 females, mean age 35 ± 15, mean BMI 31 ± 7) were included. Neurological and neuro- ophthalmological evaluation within one month of symptom onset occurred in 91% of cases. Disabling headache attacks were experienced by 91%, papilledema by 96%, and visual disturbances by 96%. Pharmacological therapy (acetazolamide) was administered to 91%, 75% achieved weight loss, and 78% reduced or quit smoking (smokers = 10). Except for one patient with an arteriovenous dural fistula, invasive treatments were unnecessary, as 96% showed rapid improvement in both headache and papilledema.

Conclusion: Early multidisciplinary intervention yielded favorable outcomes in reducing papilledema progression and achieving symptom resolution, thereby minimizing the need for invasive procedures. Timely diagnosis and collaboration between neurologists and neuro-ophthalmologists are crucial for preventing disease progression and optimizing the management of IIH, enhancing the overall quality of life.

An unusual presentation of Giant Cell Arteritis

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Background: Giant Cell Arteritis (GCA) is the major form of systemic vasculitis affecting people older than 50 years. This granulomatous vasculitis affects the aorta and its major branches, with a predilection for the external carotid and ophthalmic arteries and, to a lesser extent, the vertebral arteries. Among the most serious complications of GCA are ischemic events, especially ophthalmic and cerebral ischemic events (CIE), often accompanied by vessel stenosis. Here, we describe the case of a patient with GCA presenting with cerebellar ischemic stroke.

Methods: An 88-year-old caucasian woman, with a history of systemic arterious hypertension and dyslipidemia, came to our attention due to the acute onset of subjective vertiginous symptoms, vomiting, postural instability, and dysarthria. Upon detailed questioning, the patient reported experiencing persistent fronto-temporal headache of mild to moderate intensity, widespread arthromyalgic pain particularly affecting the shoulder girdle, jaw pain exacerbated by chewing, and weight loss (from 45 to 40 kg) over the past month. Physical examination revealed hypopulsatile, thickened, and tortuous temporal arteries. The patient underwent brain CT scan, CT angiography of the intra- and extracranial circulation, color Doppler ultrasound of the temporal arteries, transthoracic echocardiogram, 24-hour Holter ECG, blood test, with extensive infectious-autoimmune screening, rheumatological evaluation, and right temporal artery biopsy.

Results: CT scan of the brain showed a right cerebellar ischemic lesion. CT angiography revealed progressive narrowing of the right vertebral artery starting 2 cm from its origin, leading to complete occlusion with reperfusion in the intracranial segment after the origin of the PICA, while the remainder was normal; blood tests revealed mild neutrophilic leukocytosis, an ESR of 35 mm/h, and a CRP of 3.7 mg/dl. Halo sign and compression sign were positive in the right frontal artery>left on ultrasound examination. Antiplatelet therapy and steroid therapy with prednisone 50 mg/day were initiated. Temporal artery biopsy showed muscular artery with chronic inflammation featuring macrophages within artery wall and lumen obliteration, findings compatible with the clinical suspicion of GCA. The other examinations showed no relevant findings.

Conclusion: GCA-related CIE has an estimated prevalence of 4%. Multiple stenoses/occlusions in the vertebrobasilar territory affect around 70% of stroke patients with GCA. Particular risk factors include the presence of low body mass index and jaw claudication. In the presented case, the vasculitic involvement of the vertebral artery was likely causative of the cerebellar ischemic event that brought the patient to our attention.

Migraine risk in Leber's Hereditary Optic Neuropathy patients and their relatives

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Background: The brain is one of the most energetically demanding organs and primarily uses aerobic metabolism. Migraine attack would occur when there is increased metabolic demand which cannot be sustained by the nervous tissue. Functional changes on magnetic resonance spectroscopy have shown that migraine has a relationship with mitochondrial deficiency. The objective of this study is to find out if Leber's Hereditary Optic Neuropathy (LHON) patients are more likely to suffer migraine attacks, with and without aura than people in the general population, and if first- and second-degree relatives of LHON patients are at higher risk for migraine auras or not depending on carrier mutation.

Methods: This cross-sectional, observational epidemiological study involved patients diagnosed with LHON and their first- and second-degree relatives (age ≥ 15 years) at the IRCCS Institute of Neurological Sciences in Bologna. A structured phone interview was conducted to collect data on headache patterns according to the International Headache Society criteria (2018). STATA® version 12.0 was used to perform statistical analysis.

Results: Out of 27 families (109 subjects) included in the study, 48% reported migraine without aura (39% definite, 9% probable), with a higher prevalence in females (63%). Only 3% reported migraine with aura. The standardized morbidity ratio (SMR) for migraine without aura was significantly higher in LHON patients and their relatives compared to Italian general population. No significant difference has been shown in migraine prevalence between affected and asymptomatic carriers or among different mutations.

Conclusion: The increased risk of migraine without aura in LHON patients and their relatives, regardless of symptoms, suggests a possible link between mitochondrial dysfunction and migraine. These findings need further research to confirm these results and explore the underlying mechanisms.

A case of glossopharyngeal neuralgia successfully treated with amitriptyline and gabapentin

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Background: Glossopharyngeal neuralgia is a rare condition which is characterized by a brief, intense, unilateral pain with abrupt onset and cessation in regions supplied by the glossopharyngeal nerve. It is a very rare condition, accounting for about 1% of all types of cranial neuralgias, with an incidence rate of 0.7 per 100000 population. The treatment of glossopharyngeal neuralgia can be pharmacological or surgical. As for trigeminal neuralgia, common analgesics are not effective and anticonvulsants are used as first-choice drugs. Nowadays, there are no clear treatment guidelines and glossopharyngeal neuralgia diagnosis is challenging.

Case presentation: A 64-year-old Italian woman was bothered by a burning sensation during swallowing. Her family doctor decided to start steroid therapy (betamethasone 4 mg/die), without any improvement.
In the following days, the patient complained of pain at the base of the tongue, extended to left ear and hypophonia. This pain was described as a short-lasting electric sensation of high intensity. The general practitioner recommended her to start carbamazepine (200 mg x 2), with slight benefit and the appearance of side effects. With a suspicion of glossopharyngeal neuralgia, she was referred to the Neurology Department. During the hospital stay, she underwent brain MRI with contrast showing left posterior inferior cerebellar artery contiguity with homolateral glossopharyngeal nerve without sure impingement. She was first treated with carbamazepine (400 mg x 2) associated with gabapentin (100 mg x 3). Despite an initial pain improvement, carbamazepine was stopped due to thrombocytopenia. Thus, gabapentin dosage was increased to 300 mg x 3 and it was associated with amitriptyline (25 mg/day). This therapy led to pain and other symptoms amelioration.

Conclusion: Craniofacial pain differential diagnosis and management can prove to be challenging. There is no consensus on the optimal treatment strategy, since current therapies can provoke significant side effects, requiring to switch agents and polytherapy in nonresponsive patients. In conclusion, we report a case of idiopathic glossopharyngeal neuralgia, a rare entity, that was successfully treated with gabapentin and amitriptyline. In these cases, carbamazepine can be an effective therapy but has many side effects, so it is essential to note possible alternatives.

New Answer for a Resistant Pathology – Chronic Migraine in NARP Syndrome

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Background: Migraine in mitochondrial pathology is an under-investigated, often drug-resistant entity whose therapeutic management is challenging [1].

Case report: A 46-year-old female with genetically diagnosed NARP syndrome (Neuropathy, Ataxia, and Retinitis Pigmentosa) presented with attacks of migraine, both with and without visual aura, since the age of 15, which were unresponsive to triptans (eletriptan, sumatriptan). Her medical history also included bipolar disorder with anxiety and panic attacks, and primary hypogonadism. At the time of our first evaluation, the patient had chronic migraine; attempts at preventive therapy with flunarizine, amitriptyline, and beta-blockers had been discontinued due to intolerance, and valproate sodium due to inefficacy, while OnabotulinumtoxinA was not considered due to the presence of a concomitant neuromuscular disorder. After a recent complication with medication overuse headache due to significant NSAID use (20 per month), a monthly injection of preventive therapy with Fremanezumab was also started but discontinued after three months due to inefficacy. At the time of discontinuation of anti-CGRP antibody therapy, she experienced 20 days of migraine per month (MIDAS 98) with an average VAS of 7 per migraine day. Then, following a concomitant worsening of her bipolar disorder, her psychiatrist suggested starting carbolithium 150 mg bid. After six months of therapy with carbolithium, she experienced a significant improvement in terms of frequency and intensity of the attacks, with 8 days of migraine per month and an average VAS of 5 per migraine day (MIDAS 28). Use of NSAIDs was reduced to 10 per month.

Discussion: Few limited experiences with common preventive therapies for chronic or high-frequency migraine in mitochondrial pathology are available in the literature [2]. Carbolithium is currently used in preventive therapy for cluster headache and is the first choice for the management of hypnic headache, while its experience in chronic migraine is limited [3].

Conclusion: This is the first case of improvement of chronic migraine associated with a mitochondrial disease using carbolithium. A possible role in the management of the pathology and its mechanism of action yet to be determined [4, 5].

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Reversible cerebral vasoconstriction syndrome presenting as a migraine with aura: a case report

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Background: Reversible cerebral vasoconstriction syndrome (RCVS) is a rare syndrome characterized by reversible intracerebral vascular spasms and recurrent severe headaches with or without neurologic signs and symptoms, most commonly in women aged 20–50 years. Neuroimaging shows constriction of the arteries of the Willis circle and their branches. When this condition is found to be idiopathic and occurs without any predisposing condition it is classified under Call–Fleming syndrome. Misdiagnosis as primary cerebral vasculitis, migraine with aura and aneurysmal subarachnoid hemorrhage is common for the overlapping features. Therapeutic management is by calcium channel blockers. Short course of high-dose glucocorticoid and magnesium sulfate as treatment are also advocated. Due to spontaneous resolution, the prognosis is good.

Case Report: A 22-year-old female with a history of migraine with aura and AF undergoing therapy with DOACs and antiarrhythmic drugs came to our attention for two episodes of transient aphasia and paresthesia followed by headache with migraine characteristics. She performed a first brain MRI which resulted negative. Subsequently, after a second episode with similar characteristics, she repeated brain MRI that showed a hyperintensity in the periventricular and subcortical temporo-parietal area, with restricted diffusion and contrast enhancement on FLAIR sequence and wall contrast enhancement of some insular cortical vessels. Neurological and laboratory examinations were normal. No symptoms occurred during hospitalization. The follow up brain MRI after 6 week showed complete resolution of the above-mentioned findings. The diagnosis of probable Call-Fleming syndrome was made, and calcium channel blocker therapy was introduced. After 7 months the brain MRI follow up was normal with a complete resolution of clinical findings. No episodes of migraine with aura occurred since calcium channel blocker therapy was stopped.

Discussion: This case report allows us to better understand how some neurological syndrome like RCVS could be misdiagnosed in patients with an history of migraine. It is important not to underestimate the possibility of a secondary headache even in patients with a known history of migraine.

Cervical meningioma underlying facial episodic paresthesia, tinnitus and vertigo

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Background: Meningiomas are the second most common primary intradural extramedullary neoplasms after schwannomas, with a higher prevalence in middle-aged women. Spinal meningiomas often present with slow-progressing symptoms such as weakness, sensory disturbances, and radicular pain. Surgical resection is the primary treatment for symptomatic meningiomas. We studied the case of a 62 year-old woman presented with a 1-year history of progressively worsening occipital headache without accompanying neurovegetative symptoms, who had previously received a diagnosis of tension type headache and had been treated with amitriptyline without improvement.

Methods: Persistent tinnitus in the right ear, inconsistent dizziness as well as paraesthesia in the right mastoid and mandibular regions emerged, while neurological examination showed slightly difficult tandem gait and hypoesthesia in the right great auricular nerve sensory area (C2-C3). A cervical spine MRI with and without e.v. gadolinium was performed and revealed the presence of pathological tissue characterized by intense and dyshomogeneous gadolinium-based enhancement in the right parasagittal intra-canal and extra-dural area from C2 to C4-C5, poorly dissociable from the right C3 and C4 roots, leading to a modest widening due to bone remodelling phenomena and extending into the extra-foraminal paravertebral site at C2-C3. The right vertebral artery appeared incorporated by the aforementioned tissue and slightly displaced anteriorly, not affecting intravascular flow signal.

Results: Morpho-structural features of the lesion supported the diagnosis of C3 nerve root schwannoma and a neurosurgical intervention was performed. Extemporaneous histological examination suggested the meningiomatous nature of the tissue and histological examination (characterized by absence for S100 and GFAP proteins) supported the diagnosis of grade I meningotheliomatous meningioma. At the 1-month clinical follow-up, patient reported a dramatic improvement in neck pain, tinnitus and vertigo and MRI follow-up showed no residual or recurrent neoplasm.

Conclusion: The case highlights the importance of considering spinal cord masses in patients presenting with neck pain, tinnitus, vertigo, and paraesthesia in the cranial region.

A rare case of cluster-like headache following intracranial endovascular procedure

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Background: Endovascular treatment of intracranial vascular malformations is increasingly expanding, and little is known about managing of headache as postprocedural symptom.

Case report: A 65-year-old woman presented at the emergency room with a new onset of nighttime, right orbital cluster-like headache with tearing and nasal congestion. Fifteen days before she underwent an endovascular procedure for a saccular aneurysmal formation of the right carotid siphon with the placement of a flow-diverter stent in situ. In her medical history, only an episodic migraine with visual aura was detected. At the time of admission, a brain CT scan + intracranial angio-CT and a brain MRI + intracranial angio-RM were unremarkable, showing good outcome from the previous vascular procedure. She was admitted to the Neurology Unit and iv methylprednisolone 250 mg, high-flow oxygen, and prophylaxis with Verapamil were started, resulting in the resolution of the headache. After 6 months after the discharge, she only complained about a worsening of her previous migraine, well controlled by prophylactic therapy with amitriptyline. No episodes of cluster headache were reported.

Discussion: Here we present a rare case of a new onset of typical cluster headache following an endovascular procedure. Little is known about new onset of headache as a postprocedural symptom after endovascular treatment of intracranial vascular malformations and differently from our case, newly onset headaches usually described are tension-type or migraine. According to ICHD-3, headache following endovascular procedures occur within 24 hours from the procedure. However, several studies have reported postprocedural headache episodes even beyond 24 hours, particularly within three months from the latter. Various factors such as local inflammation due to the placement of foreign objects, including stents, and mechanical stimulation of the arterial wall during the procedure has been hypothesized as potential risk factors.

Conclusion: This case highlights the possible onset of a new cluster headache as a post-procedural symptom after flow-diverter stenting for an intracranial aneurism, even after 24 h from the end of the intervention. The inflammatory genesis of the phenomena may be argued by the good response to corticosteroid therapy as well as the good outcome after prophylaxis.

Persistent Idiopathic Facial Pain. A challenging diagnostic entity: clinical experience from a Neuroalgology Department

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Background: Persistent Idiopathic Facial Pain (PIFP) is a challenging and often misdiagnosed clinical entity that leads to mistreatment, often invasive treatment, and delay in the correct approach. The diagnostic criteria are well established by the ICHD3 classification. However, not always clinical presentation is easy to handle. The aim of the study is to describe clinical phenotype and clinical history of patients with diagnosis of PIFP referrals to the outpatient dedicated service of an Italian third level headache center.

Methods: Sixty-three patients afferent to the Neuroalgology Department at the IRCCS Besta Institute from 2019 to 2022 were collected. Clinical information about type, pattern, site and onset of the pain, treatment received and previous diagnosis were assessed during the visit and recorded.

Results: We collected 63 patients followed at our dedicated outpatients service for Atypical Facial Pain (PIFP); 43 females, 19 males, median age 63 years. Patients had previously received different diagnoses: Trigeminal Neuralgia 70.4%, SUNCT 11.1%, Migraine 3.7%, only 14.8% had received the diagnosis of PIFP. The quality of pain was described as: in different modalities. The distribution of the pain was referred to as trigeminal territory for almost the entire sample: the most reported was the second-third branch distribution. Different pain triggers were reported for 45 out of 63 patients. Of 63 patients, 18 underwent dentistry procedures before the pain started. Patients received different treatments before presenting to our centre, not always significant clinical benefit. Eighteen patients underwent invasive procedures, also in this case without positive results

Conclusion: Patients with PIFP appear to be difficult to manage. Only 14% of them had received a correct diagnosis, receiving inadequate treatment. The diagnosis most often mistaken with is definitely trigeminal neuralgia (70.4%), often followed by aggressive pharmacological treatment. The most represented drug treatments in our sample are pregabalyn and carbamazepine, often in combination with antidepressant-type drugs (duloxetine and amitriptyline above all), with not optimal pain control. These patients need more attention from clinicians and the scientific community: further studies are needed to define the diagnostic pathway and to evaluate the most effective therapeutic interventions.

An unusual presentation of pituitary apoplexy: a case report

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Background: Headache is one of the most frequent causes of ER accesses. Although it is a very common symptom, it is mandatory to perform an accurate differential diagnosis, especially when facing a headache with unusual characteristics in a known headache patient.

Case report: We present the case of a 43-year-old man with a history of headaches, experiencing 4 attacks per month, responsive to NSAIDs. He accessed the emergency room for a recent-onset subcontinuous headache lasting 7 days, only partially responsive to anti-inflammatories, bilaterally located in the frontal, temporal, and vertex regions, worsening with orthostasis and the Valsalva maneuver. Neurological examination was negative, parameters were normal, and blood tests were within limits. A brain NCCT scan performed in the emergency room was negative. Symptomatic therapy was administered, followed by high-flow O2 without benefit. After neurological reevaluation, a brain MRI was performed, revealing an enlargement of the sella turcica cavity with an oval hyperintense formation in T1 and concurrent subacute blood collection, findings compatible with intralesional pituitary hemorrhage, which imprinted on the cerebrospinal fluid cistern but did not compress the optic chiasm. The suspicion of pituitary apoplexy was raised and later confirmed by MRI of the sella turcica.

Discussion: Pituitary apoplexy is a rare disorder due to ischemia or hemorrhage in the context of a preexisting pituitary adenoma, leading to rapid expansion within the sella turcica, increased intrasellar pressure, and compression of adjacent structures. Frequently presenting as a thunderclap headache or an acute headache with maximum intensity at onset, associated with visual or oculomotor disorders, presentations with headache different from thunderclap, particularly subacute throbbing headaches with nausea, vomiting, photophobia, and phonophobia have been reported, which can be easily misdiagnosed with a migraine state and treated as such.

Conclusion: In known headache patients presenting in ER with a headache with unusual characteristics it is pivotal to consider the possibility of a rarer and more serious condition such as pituitary apoplexy and perform a more detailed imaging examination, preferably MRI, to avoid delaying the diagnosis and subsequent pharmacological and surgical treatment.

Sex differences in the clinical features of 2841 patients with migraine: a retrospective, multicenter, cross-sectional study

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Background: Migraine is two to three times more common in women than in men. Women experience longer duration of attacks, higher risk of headache recurrence, greater disability, and need more time to recover. These different features between sexes could directly impact on diagnosis and treatments, as recently emerged for gepants. Therefore, exploring these differences, preferably in large cohorts due to the lower prevalence of migraine in men, is needed.
Herein, we report the preliminary results including 2841 patients with migraine from the RICe registry, to describe migraine sex differences in clinical features.

Methods: In 2019, the 'Italian Headache Registry' (*Registro Italiano per le Cefalee*, RICe) was established to evaluate primary headache disorders in Italy through a dedicated electronic platform. Among the aims of the registry, there is the possibility to conduct specific observational projects. The aim of this study was to explore the sex differences in the clinical features of migraine, both in episodic (EM) and chronic (CM) migraine with or without medication overuse (MO). Twenty-four

Italian headache centers contributed to data. For this exploratory analysis, demographic and clinical variables were collected, including: quality and intensity of pain (NRS 1-10 scale), localization at onset, accompanying symptoms and monthly headache days (MHDs). Categorical variables were dichotomized as appropriate (presence/absence). Intensity of pain was categorized for single variables (severe, moderate/severe and moderate/mild). Missing data was not computed. The primary objective was to explore potential sex differences in the collected variables.

Results: We included 2841 patients (80.0% females, 45.7±14.3 years, 26.5% with CM, MHDs 12.3±9.1). The 17.5% of patients with CM had MO. Including both EM and CM, significant sex differences were reported for the intensity of pain (NRS, higher in women [median 8, IQR 2] compared to men [median 7, IQR 2], p=0.001) and this difference is maintained when intensity is categorized (i.e., severe, moderate/severe and moderate/mild) (p=0.020). Subdividing intensity categories, the previous difference was due to the higher presence of moderate/mild intensity in men compared to women (14.9 vs 7.7%, p=0.003), whereas no differences were reported for moderate/severe (p=0.119) and severe (p=0.391) intensities. Including only patients with EM, the significant sex difference in intensity categories (p=0.001) was confirmed. For subdivided categories, mild/moderate intensity was still statistically significant (16.7% in men vs 7.6% in women, p=0.001).
Regarding accompanying symptoms, presence of photophobia/phonophobia and nausea/vomiting were different between sexes with a higher presence in women for both (72.7 vs 62.3% and 44.3 vs 36.0% respectively, p<0.001 each).
On the other hand, no sex differences have been reported between diagnosis (EM vs CM, p=0.071), prevalent headache localization (unilateral, p=0.736; bilateral p=0.252), MHDs (p=0.391), MO (p=0.339), age (p=0.274), age of onset (p=0.974). Other features such as aggravation by or causing avoidance of routine physical activity (p=0.292), pulsating quality (p=0.67), allodynia (p=0.624), dizziness (p=0.360), pressing or tightening quality (p=0.328) were not different.

Conclusion: In these preliminary results, we confirmed the higher presence of associated symptoms in women compared to men. We described that men have less severe attacks than women, a result still not consistent in previous studies. However, the small difference could be not clinically relevant. The frequency of CM was similar between sexes Further analyses are needed to optimize for confounding variables and explore other features and their different combinations.

Is there still a role for detoxification strategies in migraine therapeutic scenario?

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Background: Medication overuse headache (MOH) management relays on detoxification strategies able to withdraw from overused drugs but also to improve the responsiveness to subsequent acute and preventive treatments. Recent evidence supported the effectiveness of monoclonal antibodies acting on the CGRP pathway (CGRP-mAbs) regardless withdrawal from overused drugs and detoxification. However, it has been previously suggested that MOH can be distinguished in simple (MOH Type I) and complex (MOH Type II) phenotypes based on medication overuse duration, types and amount of overused medication, comorbid psychiatric conditions, and history of relapse after drug withdrawal. We evaluated whether detoxification strategy can still have a role in patients with complex MOH to improve or anticipate the response to preventive treatment with CGRP-mAbs compared to simple MOH.

Methods: During the run-in period and after the first, the third and the sixth month of treatment, two hundred chronic migraine patients affected by MOH and treated with subcutaneous CGRP-mAbs, underwent an extensive interview to assess clinical parameters of disease severity (headache days per month, monthly symptomatic medication intake, average headache pain intensity and headache attack duration). The primary endpoint of the study was the differences in the percentage of patients achieving a >50% reduction in monthly headache days at the end of the first, third and sixth month of treatment with CGRP-mAbs compared with the baseline among simple and complex MOH groups based on previous detoxification strategy.

Results: Dividing patients based on the diagnosis of MOH types and detoxification strategy (4 groups: patients with MOH type 1 performing or not detoxification strategy and patients with MOH type 2 performing or not detoxification strategy), no differences were found in the percentage of patients showing a >50% response in monthly headache attacks frequency nor after one month ($p=0.132$) nor after the third ($p=0.184$) and sixth months of treatment ($p=0.113$).

Conclusion: Our results support the emerging evidence that anti-CGRP monoclonal antibodies may be effective in MOH patients independently of detoxification strategies and irrespective from the "complexity" of medication overuse headache.

Cluster headache and COVID-19, a retrospective study on disease evolution during the pandemic

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Background: Cluster headache (CH) is a recurrent disease, characterized by severe intensity periorbital headache associated with ipsilateral autonomic signs and symptoms; attacks may occur several times per day, for periods of weeks (so-called cluster), with a relapsing periodic pattern during the year. COVID-19 pandemic has induced many lifestyle changes on the general population, especially related to the so-called lockdown. Aim of this study was to assess the clinical evolution of cluster headache patients during the lockdown period.

Methods: Patients included in this observational retrospective study had a definite diagnosis of cluster headache, with a minimum 5-year disease duration. Main collected data included diagnosis, age, disease duration, number of clusters per year, cluster duration, number of attacks per day and attack duration (both pre and post pandemic onset). Statistical analysis was performed to assess differences in cluster headache clinical manifestations before and after pandemic onset.

Results: The study included 44 patients, with mean age of 48.8 ± 12.6 years and male prevalence (35 male patients (79%)). Mean disease duration was 16.9 ± 8.5 years. Episodic CH was prevalent, with 40 patients with a diagnosis of episodic CH (91%) and only 4 patients with a diagnosis of chronic CH (9%). Comparing pre-pandemic period and lockdown period, mean cluster number per year was 1.6 ± 0.9 vs 0.7 ± 1.2 (p=0.001), mean cluster duration was 70.6 ± 98.4 days vs 24.4 ± 61.4 days (p=0.001), mean headache attacks per day were 2.8 ±1.2 vs 0.8 ± 1.0 (p<0.001), mean headache attack duration was 47.1 ± 31.0 minutes vs 15.3 ± 20.9 minutes (p<0.001). Pain intensity measured using the Numerical Rating Scale was 10 for all patients vs 4.3 ± 5.0 (p<0.001).

Conclusion: The results of this study showed a significant reduction in disease severity for cluster headache patients comparing the pre-pandemic and the lockdown period; this finding may be partly due to the lifestyle changes occurring as a consequence of the lockdown restrictive measures, even though the observed results were normalized considering the single-patient specific lifestyle and job activity performed during the lockdown, further underlining the peculiarity of this phenomenon.

Migraine prodromal symptoms, epidemiology and clinical significance; an observational multi-centre study

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Background: Migraine prodromal symptoms, previously described as warning migraine or premonitory migraine, usually manifest from 2 to 48 hours prior to the migraine attack. These symptoms have been classified in several categories, usually manifesting as general asthenia, cognitive slowing, irritability, difficulty in concentration, hunger, yawning and others. Given the paucity of studies assessing these clinical manifestations, aim of this study was to evaluate the clinical significance, manifestations and epidemiology of migraine prodromal symptoms in an outpatient setting.

Methods: This observational multi-centre study included patients suffering from migraine (with or without aura, episodic or chronic) evaluated in an outpatient setting, who reported the manifestation of some prodromal migraine symptoms. Main collected data included migraine diagnosis, monthly migraine days, current migraine preventive treatment, type of prodromal symptoms, symptoms duration, symptoms onset in relation to migraine attack. Descriptive statistical analysis was performed to assess the epidemiology of migraine prodromal symptoms.

Results: The study included 122 patients, with mean age of 39.4 y (SD 12.8 y) and 108 females (88.5%). Eighty-five patients (69.7%) had a diagnosis of migraine without aura, 15 patients (12.3%) suffered from migraine with aura and 22 patients (18%) had a diagnosis of chronic migraine. Mean monthly migraine days were 7.5 (SD 5.8). Prodromal symptoms onset ranged from 0.5 h to 48 h before headache onset (mean 9.9 h, SD 11.4 h), and duration of symptoms ranged from 0.3 h to 48 h (mean 6.3 h, SD 8.9 h). Regarding symptoms frequency, yawning and asthenia were the most frequent, observed in 46 patients respectively (37.7%); difficulty in concentration in 41 patients (33.6%), anxiety in 32 patients (26.2%), hunger in 26 patients (21.3%), depression in 23 patients (18.9%), vertigo in 20 patients (16.4%).

Conclusion: This study highlights the clinical significance of migraine prodromal symptoms (so-called warning migraine); these manifestations are observed and reported by many migraine patients, after a complete and thorough clinical interview by the clinician, and they play an important role in contributing to the burden of disease for the migraine patient.

Anti-CGRP monoclonal antibodies, migraine and mood disorders: an observational study

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Background: Migraine is frequently associated with psychiatric comorbidities; these are usually related to worse clinical outcome and migraine chronicization. Regarding therapeutic prophylactic options, anti-CGRP (calcitonin gene-related peptide) monoclonal antibodies are well known class of treatment but, whether these drugs could also have a positive impact on mood related disorders/symptoms, is still debated. Aim of the present study is to assess the benefit of anti-CGRP (calcitonin gene-related peptide) antibodies on migraine related symptoms and on anxiety and depressive symptoms, in patients with migraine with or without mood related comorbidities.

Methods: Two-hundred and six migraine out-patients in treatment with anti-CGRP antibodies for at least 6 months were included in this retrospective cohort observational study; patients were stratified according to the severity of mood disturbances [Group 1 = null/minor burden of depressive symptoms (Beck Depression Inventor -BDI 0-13) and Group 2 = moderate-to-severe depressive symptoms (BDI 14-63)]. Efficacy outcomes (monthly migraine days, MMDs; monthly headache days, MHDs; analgesics consumption; Numerical Rating Scale, NRS; Migraine Disability Assessment, MIDAS; Short-Form 36, SF-36; Headache Impact Test 6, HIT-6) and self-assessment anxiety and depression scales (BDI; Zung) were analyzed after 3 and 6 months of treatment.

Results: Efficacy outcomes showed a significant clinical improvement at T3 and T6, regardless of the presence of associated mood disturbances: ΔMHDs, ΔNRS, ΔMIDAS score, and ΔHIT-6 score were not statistically different in the two groups with the exception of ΔMMDs and Δ analgesic consumption as Group 2 reported a higher reduction compared to Group 1 both at T3 (ΔMMD: -9.58 ± 8.49 vs -7.33 ± 6.10; p = 0.003; Δ analgesic consumption: -14.86 ± 19.18 vs -12.02 ± 11.68 p = 0.026) and at T6 (ΔMMD: -8.96 ± 8.16 vs -7.51 ± 6.41 p = 0.044; Δ analgesic consumption: -15.00 ± 19.43 vs -11.22 ± 10.69 p = 0.050).
Anxiety and depressive manifestations improved during treatment; ΔBDI and ΔZung scales at T3 and T6 showed a relevant decrease in all patients' subgroups, especially in those with higher baseline values (ΔBDI in Group A: -1.30 ± 3.74 at T3, -1.67 ± 4.77 at T6 vs ΔBDI in Group 2: -6.35 ± 11.34 at T3, -8.06 ± 10.35 at T6; ΔZung Scale in Group A: -3.47 ± 5.58 at T3, -3.68 ± 7.82 at T6 vs ΔZung scale in Group 2: -4.96 ± 6.07 at T3, -5.08 ± 6.51 at T6).

Conclusion: This study confirms anti-CGRP antibody treatment efficacy in migraine patients, regardless of the associated mood related comorbidities. The positive impact of this treatment is also evident in the persistently beneficial course of mood symptoms severity and intensity during treatment.

Daily and night functioning improvement after 6 months of treatment with Anti-CGRP/R mAbs in pharmacoresistant migraine patients

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Background: Migraine is a complex pathology, often associated with psychiatric symptoms, sleep quality impairment, fatigue and symptoms of central sensitization, as for allodynia.
This study evaluated the efficacy of monoclonal antibodies (mAbs) acting on calcitonin-gene related peptide (CGRP) or its receptor (anti-CGRP/R mAbs) not only taking into account traditional outcome parameters (i.e. migraine monthly days -MMD- and migraine related disability), but also further daily and night functioning descriptors such as fatigue and subjective sleep quality, allodynia as marker of sensitization and psychiatric symptoms.

Methods: The open-label longitudinal study enrolled 59 pharmacoresistant migraine patients (78% females, median age 49.81). Clinical parameters and allodynia, fatigue, psychiatric symptoms, subjective sleep quality were assessed with headache diary and specific validated questionnaires (Migraine Disability Assessment Scale – MIDAS -, Allodynia Symptom Checklist 12 - ASC-12 -, Fatigue Severity Scale – FSS -, Generalized Anxiety Disorder 7 - GAD7 -, Patient Health Questionnaire 9 - PHQ9 -, Pittsburgh Sleep quality index – PSQI -) at baseline and after 6 months of treatment.
Patients were divided into 4 categories based on response rate expressed in MMD percentage decrease after 6 months of treatment: non-responders (response rate < 30%), mild-responders (30-50%), responders (50-75%) and super-responders (> 75%).

Results: Nine patients resulted non-responders (15%), 5 mild-responders (9%), 19 responders (32%) and 26 super-responders (44%). No significant differences were noted in age, migraine burden and comorbidities between groups at baseline.
After 6 months of treatment, there was a significant reduction in MMD and in migraine related disability score in responders and super-responders, which was associated with a significant improvement in descriptors of daily and night functioning (fatigue and subjective sleep quality), allodynia and comorbid psychiatric symptoms ($p < 0.05$).
No statistically significant differences were noted in daily and night descriptors and comorbid psychiatric symptoms in non responders and mild responders.

Conclusion: Anti-CGRP/R mAbs treatment improves migraine clinical picture beyond migraine monthly days; improving several coexisting conditions they significantly contribute to reduce migraine interictal burden in pharmacoresistant migraine patient. Further studies are needed to verify the putative role of CGRP on affective and sleep related symptoms.

Acute confusional migraine in a patient with pulmonary sarcoidosis: a case report

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Background: Acute confusional migraine (ACM) is a rare type of migraine that primarily affects children and adolescents. It is characterized by sudden onset confusion and other neurological symptoms that typically resolve in 24 hours. Although migraine is common in sarcoidosis, ACM has not been described: we report a case thereof.

Methods: A 25-year-old male was admitted to our hospital with acute confusional state and a migraine-type headache. His medical history included subclinical hyperthyroidism, ankylosing spondylitis, migraine without aura and previous use of cocaine. On admission, he was not taking any medication. On neurological examination the patient was disoriented, agitated, irritable and unable to follow conversations.
Anterograde and retrograde amnesia were also present. Urgent brain CT scan with angiographic and perfusion imaging was normal as blood tests and toxicological screening. Cerebrospinal fluid analysis and brain MRI were also unremarkable. Serial electroencephalograms documented only nonspecific slow activity in the left hemisphere without epileptiform abnormalities, even after sleep deprivation. Meanwhile, neurological impairments spontaneously resolved within 24 hours from onset. Among further investigations, electrocardiography monitoring and transthoracic echocardiogram were normal, while a chest CT scan revealed multiple pulmonary nodules and mediastinal lymphadenopathy, which showed increased uptake on subsequent total body 18-FDG PET study. A mediastinal lymph node biopsy was then performed, with histological examination suggestive of sarcoidosis.

Results: Based on the clinical picture and the exclusion of other potential causes, a diagnosis of ACM was considered. A prophylactic therapy with Topiramate was then initiated and as-needed treatment with triptans was recommended. No recurrence of neurological symptoms has been found on successive follow-up. Regarding the incidental diagnosis of pulmonary sarcoidosis, oral corticosteroid therapy was initiated and further investigations were prescribed.

Conclusion: ACM is a rare migraine variant primarily affecting children and adolescents. The diagnosis of ACM is based on the exclusion of other major causes of acute encephalopathy. It should be considered when patients with sarcoidosis present with recurrent headaches accompanied by acute confusion, since an adequate treatment could improve their quality of life. Whether specific investigations for sarcoidosis should be considered in adult patients with ACM is a meaningful issue that warrants further studies.

Lack of association between primary headache disorders and dementia risk: results from a case-control study on a Memory Clinic patient cohort

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Introduction and Objective: Recent evidence suggests that primary headache disorders may increase the risk of dementia, but existing studies are conflicting. A recent systematic review and meta-analysis conducted by our group showed the presence of a link between primary headaches and dementia [1]. Considerable heterogeneity has also emerged, especially in terms of the diagnostic criteria used, design of the studies and results obtained. Based on these assumptions, we conducted a case-control study on a population of well characterized patients referred to our memory clinic.

Methods: We recruited patients who underwent diagnostic lumbar puncture with cognitive symptoms referring to our Memory Clinic of the Department of Neuroscience of University of Turin from 2023 to date. Research criteria for Alzheimer's disease (AD) [2] and the most recent diagnostic criteria for other neurocognitive disorders were applied. Specifically, non-AD patients were grouped into the following categories: frontotemporal lobar degeneration spectrum disorders (FTLD); dementia with Lewy bodies (DLB); mild cognitive impairment (MCI A-/T-); patients with probable multiple-cause cognitive decline were classified as "mixed". All subjects underwent a structured questionnaire to assess the current or anamnestic presence of a primary headache disorder (migraine or tension-type headache), based on the ICDH-3 criteria [3]. Caregivers of patients were included as controls.

Results: We recruited 106 patients and 99 controls. Specifically, 17 patients met the criteria for MCI (A-/T-), 44 AD, 20 FTLD, 4 DLB and 20 mixed dementia. Of these, 41 patients (38.68%) and 37 controls (37.37%) were found to have a tension-type headache or migraine. Headache did not appear to be associated with an increased risk of cognitive decline (OR=1.06; CI:0.60-1.86, p= 0.96). Furthermore, there was no group differences based on the diagnostic subgroups (χ^2=0.66, p=0.96). At logistic regression analysis, headache disorder was not found to be a significant predictor of cognitive decline (β=-0.19, p=0.56; R^2=0.19).

Discussion and conclusion: The results of our study did not support the hypothesis of an increased risk of cognitive decline in patients with primary headaches; however, further studies are needed to examine the role of primary headaches as a possible risk factor for neurodegenerative dementia.

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Orofacial pain, temporomandibular disorders and sleep quality in migraine patients compared to controls: preliminary findings from an observational study

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Background: The relationship between orofacial pain, temporomandibular disorders (TMD), and migraine involves shared pathophysiological mechanisms, potentially exacerbating each other's symptoms. Similarly, sleep quality significantly impacts migraine severity and frequency. However, the prevalence and risk of comorbidities in migraine patients is not well understood. The aim of the study is to assess the risk of orofacial pain, temporomandibular disorders, and poor sleep quality in adult (>18 years) patients with migraine attending an Italian Headache Center.

Methods: Patients were diagnosed by a neurologist following the ICHD-3 criteria. 21 subjects with migraine (mean headache frequency: 12.9 days/month) and 24 controls were enrolled. Presence of orofacial pain was assessed through questions 1 and 7 of the Craniofacial Pain Disability Index (CF-PDI). Presence of painful TMD and joint TMD were assessed through the Temporomandibular Disorder Pain Screener and questions 9, 10, and 13 of the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) Symptom Questionnaire. The Pittsburg Sleep Quality Index (PSQI) was used to evaluate sleep quality. Subjects with a ≥5 score were categorized as having poor sleep.
The presence of a statistically significant association between the analyzed variables was estimated by odds ratio (OR) with a 95% confidence interval (CI).

Results: Orofacial pain was reported in 66.7% of migraine patients and in 8.3% of controls (OR 22; 95% CI 4.09-106.2; P<0.0001). Painful TMD was reported by 47,6% of migraineurs versus 12.5% of non-migraineurs (OR 6.4; 95% CI 1.49-23.99; P=0.0192). Cases and controls reported non-significant associations for Joint TMD prevalence (57.1% vs 33.3%; OR 2.7; 95% CI 0.74-9.15; P=0.1397). Migraine patients showed a higher risk of poor sleep quality (prevalence 71.4% vs 37.5%; OR 4.2; 95% CI 1.11-12.76; P=0.0362).

Conclusion: Migraine patients are at higher risk of orofacial pain, painful temporomandibular disorders, and poor sleep quality, but not joint TMD. Identification and management of comorbidities in migraine should be considered.

Diaphragmatic small bowel disease in a patient with resistant migraine and medication overuse treated with galcanezumab

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Background: Monoclonal antibodies directed against Calcitonin Gene Related Peptide (CGRP) or its receptor have greatly improved migraine patients' quality of life, but they should be administered with caution in patients with constipation or inflammatory bowel disease, also considering that non-steroidal anti-inflammatory drugs, widely used by patients with migraine for treating attacks, which have gastrointestinal side effects.

Methods: This is a case report.

Results: We report a case of a patient with a clinical history of migraine with and without aura, paroxysmal hemicrania, and overuse of indomethacin. Due to multiple therapy failures, galcanezumab 120 mg was prescribed, with a significant reduction of migraine days. Twenty days after the start of this therapy, the patient began to complain of severe abdominal pain associated with vomiting. She had never experienced these symptoms in the past. For the persistence of symptoms, the patient underwent an esophagogastroduodenoscopy (EGDS) showing cardiac incontinence and hyperemic gastropathy of the antrum related to Helicobacter pylori. However, abdominal pain with vomiting, and constipation did not resolve with a progressive associated weight loss. Colonoscopy showed signs of active inflammatory bowel disease of the ileum. In March 2022, the patient underwent exploratory laparoscopy with ileal resection of approximately 45 cm of intestinal loops. The pathological examination of the surgical specimen showed diaphragmatic disease of the small intestine, a morphological and clinical picture compatible with chronic overuse of NSAIDs. Despite the concomitant situation described, until October 2022, the patient never wanted to interrupt the monthly administrations of galcanezumab. However, at the follow-up visit at our center in October 2022, we decided not to renew the treatment with galcanezumab. Upon discontinuation of the drug, the migraine returned to a chronic frequency, for which we prescribed treatment with OnabotulinumtoxinA according to PREEMPT protocol.

Conclusion: This case report recommends being extremely cautious when starting mAbs anti-CGRP treatment in patients with a longstanding medication overuse with NSAIDs and abdominal symptoms, as blocking the CGRP pathway can facilitate a possible underlying intestinal dysfunction. In this light, a careful medical and pharmacological history and close follow-up of these patients are necessary.

Headache characterization in elderly patients: description from a frailty-oriented Rehabilitation centre

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Background: Primary headaches management currently represents a challenging topic due to increased patients' referral to headache clinics. However, epidemiological data describing patients' profiles remained limited. Here we present clinical data and therapeutic challenges on elderly headache patients referring to a frailty-oriented institution.

Methods: We acquired data from consecutive patients over 4 years. Demographic data were collected, along with headache diagnosis and characteristics according to ICHD-3, previous tried acute and preventive therapies, number and type of contraindications to either acute or preventive therapies. Patients' follow-ups were closely scheduled up to dropout or censored at 1 year.

Results: We collected data from 86 patients (F = 85%). Mean age was 74.2 ± 7.6 years: 61-70 y.o. 36.5%; 71-80 y.o. 36.5%; >80 y.o.: 27%. Headache onset ranged from 1 month to 60 years prior to first visit (mean 25.1 ± 24.3 years). Primary headaches affected 88% of patients: 34% had chronic migraine (CM) with or without medication overuse (MOH), 34% episodic migraine (EM), 7% tension-type headache (TTH) and 2.3% TTH-MOH. Remaining 10.7% patients had other primary headaches (e.g., 3.6% primary stabbing headache). About 10% had a diagnosis of migraine with aura; 27.6% of migraine patients used acute treatments, 29.4% were under prophylaxis, with amitriptyline (12%) as the most prescribed (also in non-migraine headache: 8.2%). Mean headache frequency in EM was 9.55 ± 7.5 monthly days, while 23.5 ± 8.4 days in CM, and 25.1 ± 7.0 days in MOH. Preventive therapy was started in 56% of patients; candesartan, amitriptyline, botulinumtoxin, topiramate and beta-blocker were the most prescribed options. Median number of comorbidities was 5 for each patient, of which at least 1 in each patients represented a contraindication to both acute and preventive treatments. Median first follow-up time was 4 months later with a return rate of 63.3%, of which 17% patients had >30% and another 17% a >50% frequency reduction.

Conclusion: Primary headaches (particularly CM, MOH) affects the largest share of elderly headache outpatients. Comorbidities and contraindications to treatment hampered the response chance. Response rate is about 1 out of 3 patients at the first therapeutic try.

A case of remitting headache

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Background: A 58-year-old woman presented to the Emergency Department (ER) for severe headache and visual disturbances. The diagnostic process to pinpoint the etiopathogenesis was long, coming to a diagnosis of exclusion based on the evolution of the clinical picture and on neuroimaging.

Methods: A Caucasic 58-year-old woman presented to the ER for left pulsating headache, associated with photophobia, blurred vision and scotomata. A head computed tomography and an Ophthalmology consult were permed, in the latter suspicion of a retrobulbar optic neuritis was raised. Magnetic Resonance Imaging + Angiography were performed: no acute lesions were detected, in the presence of pathological contrast enhancement of left optic nerve meningeal sheath and anterior clinoid, marked flow reduction at the level of the right internal carotid artery, with an irregular vascular profile that seems to attach the middle meningeal artery to the carotid siphon, of unknown significance. Cerebrospinal fluid analysis was only significant for mild hyperproteinorrachia. Oligoclonal bands, autoimmune and infectious diseases screen were performed and not significant. Suspecting a left retrobulbar optic neuritis a course of high-dose steroids was prescribed. Headache and visual acuity markedly improved after treatment. After about 2 months patient developed headache again and a third cranial nerve palsy. A lumbar puncture was repeated with the same results, MRI and MRA showed contrast enhancement of the left orbital apex, anterior clinoid and fronto-basal meninges, with asymmetrical cavernous sinuses (left enlargement). A stenosis of both carotid syphons was detected. The neuroimaging picture, together with the neurological clinical evolution, raised the suspicion of Tolosa-Hunt syndrome, so high-dose steroids were administered with good response, followed by an oral tapering. The patient was then evaluated for steroid-sparing treatment.

Discussion and Conclusion: Tolosa-Hunt syndrome is an idiopathic granulomatous inflammation of the cavernous sinus, orbit and/or adjacent meninges. The disease is rare (incidence: 1/million/year) and a bilateral involvement of the carotid arteries even more so. The clinical picture can be the same in a wide variety of pathological processes, including malignancy, infection or vascular and inflammatory processes of different aetiologies. A high level of suspicion is necessary to ensure a prompt diagnosis and treatment.

Covid-19 related headache and long Covid headache: real-life experience at Tertiary Headache Center

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Background: COVID-19 is a heterogenous infective syndrome frequently showing headache as a symptom, that can occur at the beginning or develop later, and sometimes persist after the infection has resolved (Covid related/Long Covid Headache).
We report the experience of the Pisa University, Neurology Department during the pandemic period.

Methods: Between June 2020 and December 2021, we evaluated 1350 patients for "headache" (72 pharmacoresistant migraine patients treated with anti-CGRP(R)-mAb), of which only one out of three reported COVID-19. Among 450 patients, half of the patients experienced headache infection related; we selected 87 patients with persistent disabling headache (defined as > 8 days of pain per month for more than 3 months infection resolved).

Results: We described the clinical course of 87 patients, 7 males and 80 females, with mean age of 52.42 years. Seventy-two had previous history of migraine, while 15 patients manifested a New Daily Persistent Headache. In both cases we noticed a migraineous pattern of headache; 26 patients showed a high frequency episodic headache and 61 patients a chronic form. After 3 months follow-up, 38 patients improved (50% reduction in monthly migraine days compared to baseline) after changing their preventive treatment; 20 patients improved without any modification of the ongoing therapy and 9 patients improved spontaneously. Twenty patients reported no changes at 3 months despite pharmacologic treatment. Among the patients treated with anti-CGRP(R)-mAb (N=72), 14 showed an initial clinical worsening but finally only 4 patients did not recover after 3 months follow-up.

Conclusion: Headache in the setting of Covid-19 pandemic has globally increased the burden of headache disorders. Our report, according to the literature, charted that Covid-19 can be a risk factor for migraine worsening. Clinical data about patients treated with anti-CGRP(R)-mAb support the possible CGRP involvement in Covid-19 related/long Covid headache pathogenesis.

Memory assessment in osmophobic migraineurs

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Background: Migraine often presents with neurovegetative symptoms like osmophobia, occurring during or between episodes. Memory and olfaction share certain neural pathways. Nonetheless, memory of migraineurs with osmophobia has not been extensively assessed, hence the aim of this study.

Methods: Patients with ictal or interictal osmophobia referred to the Headache Centre of Trieste within six months were enrolled. Exclusion criteria were chronic migraine, nasal or olfactory disorders and conditions or medications (e.g., antiepileptics and antidepressants) affecting memory. Demographic and migraine-related data were collected. Cognitive abilities were assessed using the MoCA test, followed by evaluations of memory, visuospatial skills, attention and executive functions using the Rey Auditory Learning Verbal Test (RALVT), Rey-Osterrieth Complex Figure (ROCF), Multiple Features Target Cancellation (MFTC) and Stroop Color and Word Test (SCWT).

Results: Twenty-four patients (21 females, 3 males; mean age 39±9 years), all with medium to high education (17±4 years), participated. All experienced ictal osmophobia; 54% also reported interictal osmophobia. Approximately 60% consistently avoided specific odors; smoke was the most frequently cited as bothersome (83%) or triggering (42%). Thirty-seven percent of patients used migraine prophylaxis, with improvement of ictal osmophobia in 50% of them. All patients scored normally in the MoCA test. Most scored normally in RAVLT immediate recall (42% pE4; 13% pE3; 33% pE2; 0% pE1; 13% pE0), delayed recall (54% pE4; 25% pE3; 4% pE2; 8% pE1; 8% pE0), delayed recognition (100% pE4) and ROCF delayed recall (75% pE4; 4% pE3; 8% pE2; 8% pE1; 4% pE0). No deficits were observed in visuospatial tasks: all patients scored in the upper normal range on the ROCF copy (100% pE4). Attention was evaluated through accuracy, false alarms and execution time in MFTC. Accuracy was below the education-adjusted cutoffs in 4 patients (17%<0.869; 83%>0.869); execution times/false alarms resulted normal. Most patients were accurate in the SCWT (only 8% had pE0 and 13% pE1), with normal speed in all cases.

Conclusion: Osmophobic migraineurs showed normal cognitive performance. In few patients isolated deficits in memory (RALVT immediate and delayed recall, ROCF delayed recall), attention (MFTC accuracy) and executive functions (SCWT accuracy) were found, but their cognitive functions were overall preserved.

Evaluation of migraine related cognitive symptoms in patients with high frequency episodic and chronic migraine

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Background: Migraine patients often complain of cognitive symptoms such as deficits in concentration, attention, executive or phasic functions during migraine attacks. To date, however, it is unclear whether cognitive symptoms can be constitutional migraine symptoms, expression of severe pain perception or, even, whether they can be adverse effects of symptomatic treatment. In the present study we aimed to explore the presence, the time of onset and the course of cognitive symptoms during migraine attacks in order to achieve a putative pathophysiological interpretative hypothesis.

Methods: This is a retrospective observational study enrolling 280 patients with high frequency episodic migraine or chronic migraine interviewed to obtain information regarding the presence of cognitive symptoms (deficits in attention or concentration, executive or phasic functions and word retrieval) both at the beginning of migraine attack and at the pain peak as well as after symptomatic treatment.

Methods: At baseline, the 73.5% of patients present cognitive symptoms in the course of migraine attacks. Among these, 33% of patients manifest cognitive symptoms at the beginning of migraine attacks when pain is mild to moderate, 45% of patients at pain peak and 27% of patients only after symptomatic treatment. Interestingly, among patients experiencing cognitive symptoms in the course of migraine attacks independent of symptomatic medication and acute medication intake, a change in cognitive symptoms resulted in 57% of them (73.3% improved while 29.3% worsened).

Conclusion: Based on the above mentioned descriptive findings, we speculate on the possibility that the pathophysiology of cognitive symptoms in the course of migraine attacks could be complex and multifactorial with a significant inter-individual variability.

Effectiveness of multimodal physical therapy for episodic and chronic migraine with prevalent occipital migraine pain: randomized clinical trial

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Background: It is very common that migraine patients could refer neck pain as part of the migraine attack, suggesting that migraine pathophysiological mechanisms could be effective in activating also the neck pain pathways. In a previous report we demonstrated a higher prevalence of musculoskeletal dysfunctions in subjects with prevalent occipital migraine pain. Due to the therapeutic effect of multimodal physical therapy (mobilization and/or manipulation plus exercises) on several pain conditions arising from articular and/or muscular structures involved in the neck pain, and given the close clinical, anatomical and pathogenetic bi-directional relationship between neck pain and migraine, it would be of interest to evaluate the effectiveness of the multimodal physical therapy of the neck region in migraine pain. The purpose of this study was to evaluate the efficacy of a combined multimodal physical therapy approach plus usual care vs. usual care alone in subjects with episodic and chronic migraine with prevalent occipital migraine pain.

Methods: A total of 50 subjects aged 18-65 who met criteria for episodic or chronic migraine with prevalent occipital migraine pain were randomized and assigned to receive musculoskeletal focused multimodal physical therapy (16 sessions over 8 weeks) plus usual care treatment (MPhT) vs. usual care alone (SoC). Main outcomes were number of monthly migraine days (MMD) and symptomatic drugs intakes per month (MDI) after 30 and 60 days of treatment. Secondary outcomes including disability scale scores for musculoskeletal dysfunctions and migraine were also considered.

Results: No differences in migraine and musculoskeletal dysfunctions parameters were detected between study groups before the study treatment. We found a significant reduction in MMD (F: 9.550; $p<0.001$) and MDI (F: 8.78; $p<0.001$) in MPhT group after 30 and 60 days of multimodal physical therapy when compared to SoC group.

Conclusions: Our results suggests that a multimodal physical therapy could be an effective complementary treatment opportunity in subjects with episodic and chronic migraine with occipital migraine pain and possibly musculoskeletal dysfunctions.

Serotonergic tone and extracranial pressure pain thresholds are surrogates of response to pain education in chronic migraine patients

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Background: Pain neuroscience education (PNE) has been recently added as an option for different chronic pain conditions. To date, however, no standard content or methods for PNE have been developed for chronic migraine (CM). This study aims at highlighting mechanisms responsible for PNE effect in CM.

Methods: We recruited consecutive CM patients aged 18-65. We excluded those with other headache diagnosis (except medication-overuse headache, MOH), migraine prophylaxis started in the last 3 months, concomitant neurological or psychiatric conditions, language barrier. Patients' assessment included headache frequency and medication use, validated questionnaires (CSI, HADS, PCS, HIT-6, MIDAS), neurophysiological evaluations with nociceptive blink reflex (nBR), intensity dependence of auditory evoked potentials (IDAP), and clinical evaluation with pressure pain thresholds (PPTs) and wind-up ratio (WUR) at baseline (T0), midway (T1) and at the end of the treatment (T2). PNE was administrated in ten lessons, once a week. Patients were treated in groups. Data from Responders (R) and Nonresponders (NR) were further analyzed.

Results: We recruited 14 female patients (mean age 43.4±16.4 years; mean schooling years 15.5±3.8). Headache days reduced from 18.5±5.2 to 13.4±7.5 (p=0.002) and HIT-6 from 63.1±3.3 to 56.0±6.0, p=0.013). Other evaluations were not significant. Serotonergic tone tended to reduce from T0 to T1 (p=0.13), while WUR significantly decreased from 3.1±1.8 at T0 to 1.8±1.6 at T1 (p=0.002) and negatively correlated with HIT-6 value at T2 (rho=-0.5, p=0.02). IDAP at midway negatively correlated with headache days' reduction at T2 (rho=-0.5, p=0.04). Values of PPT on tibialis anterior (but not on temporalis muscle or metacarpophalangeal tendon) recorded midway to treatment positively correlated with ipsi- (rho= 0.73, p=0.002) and contralateral (rho=0.6, p=0.007) nBR at the same time point but not in other time-points.

Conclusion: PNE resulted effective in reducing migraine days and disability in a sample of CM patients as stand-alone preventive therapy. Early determination of the serotonergic tone though IDAP could represent a predictive biomarker of response since, as in other studies, it correlated with later clinical benefit. PPT values on tibialis anterior could serve as a proxy of nNR, allowing for an intra-subject evaluation of central sensitization in CM also at clinical bed-side level.

Safety and feasibility of non-vestibular physical therapy in vestibular migraine

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Background: Vestibular migraine (VM) has a therapeutic indication to vestibular rehabilitation for the control of vestibular and pain symptoms. However, availability of vestibular rehabilitation remains limited. Pharmacological prophylaxis for VM can reduce both pain and vestibular symptoms, therefore it is possible that also pain-oriented physical treatments could be effective in VM.

Methods: We recruited consecutively episodic and chronic VM patients aged 18-65. We excluded those with other headache diagnosis (except medication-overuse headache, MOH), migraine prophylaxis started in the last 3 months, concomitant neurological or psychiatric conditions, language barrier. Patients' assessment included headache frequency and number of acute medications, questionnaires such as SF 36-100 for quality of life, DASS-21 for anxiety and depression, dizziness handicap inventory (DHI) for vestibular symptoms at baseline (T0) and at the end of the treatment (T1). Pain pressure thresholds with a digital algometer were recorded on temporalis muscle, second metacarpal joint and tibialis anterior muscle.
Two different physical therapies were administered twice a week for 4 weeks. Group A received unilateral pressure on C1-C3 spine and neck muscle reinforcement, Group B received trigger-points compressions and muscle treatment on trapezius bilaterally plus neck reinforcement.

Results: We recruited 5 female patients (mean age 49.0±21.3 years). Baseline MIDAS was 14.8±18.4, HIT-6 was 59.8±10.7. DASS-21 reported a mild level of anxiety (5.8±4.2) and stress (8.6±3.8) and a moderate level of depression (7.6±3.7). Patients tolerated the treatments, one patient of Group B dropped for worsening of the headache. Both groups experienced a reduction of all clinical parameters (including headache scale and vestibular symptoms), no significant differences were found. However, depression scale improved significantly from 7.6±3.7 to 4.8±3.3 meaning a shift from moderate to mild depression. PPTs values on the tibialis muscle at the end of the treatment inversely correlated with the scores on the DHI scale (rho=-0.9, p=0.034) indicating that the stronger the vestibular component, the higher the sensitization process.

Conclusion: Non vestibular manual therapy seems a safe and feasible option in VM patients and should be further explored in larger study. PPTs could serve a useful biomarker of response.

The long-term treatment of migraine with ketogenic diet: a single-centre, retrospective study

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Background: Metabolic dysfunction and insulin resistance are significantly associated to migraine, influencing attack severity and disability. Previous studies have highlighted the efficacy of ketogenic diet on migraine however, they involved small numbers of patients, were mostly limited to episodic migraine, and with a short time window of observation. This study aims to evaluate the long-term effectiveness of the modified Atkins ketogenic diet (MAD) in the treatment of drug-resistant episodic and chronic migraine.

Methods: A non-randomized, single-centre, retrospective study was conducted. Fifty-two episodic or chronic migraineurs were observed in the nutritional outpatient clinic of the University Hospital of Padua from January 2021 to May 2023 and treated with modified Atkins ketogenic diet (MAD). Migraine assessment (frequency and severity of attacks), migraine medication intake count, BMI, blood pressure and laboratory data were collected before the start of dietary treatment and after 1, 3, 6, 9 and 12 months.

Results: Forty-five (87%) patients were females and 7 (13%) males. Twenty-eight patients (54%) had chronic migraine and 24 (46%) had episodic migraine. At the start of treatment, the mean body mass index (BMI) was 27.9 ± 6.8 kg/m^2. Frequency of migraine attacks was 14.3 ± 8.1 days per months, length of attacks was 17.0 ± 14.5 hours per day, intensity of pain was 8,3 ± 1.4, intake of pain medications was 20.7± 15.1 doses per month. After six months, 41 patients were still following MAD, showing a marked improvement in the number of episodes per week ($p<0.001$), their duration ($p<0.005$), intensity ($p<0.001$) and pain medication intake ($p<0.001$); BMI, hsPCR, fasting plasma insulin and HOMA index were also significantly reduced. The improvement of migraine was independent of BMI loss. After twelve months of MAD, 33 patients were still on the diet; BMI was significantly reduced and benefit on migraine persisted.

Conclusion: MAD determines a significant benefit on migraine frequency, severity and on reducing intake of pain medications; this benefit is independent of BMI loss and persists in the long term (12 months), in both episodic and in chronic migraineurs. The positive metabolic changes observed in lipid profile, insulin resistance, inflammation and blood pressure may be an additional benefit of this diet.

A novel approach to analgesic withdrawal in medication overuse headache: a case report

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Background: Chronic headache due to overuse medications (MOH) is defined by the International Headache Society as a headache occurring 15 or more days per month for at least 3 months, triggered by the regular use of symptomatic headache medication. If migraine prophylactic drug therapy is ineffective, patients should take a medication pause or be withdrawn from medication. Tricyclic antidepressants, neuroleptics (antiemetics), and steroids are recommended for managing withdrawal symptoms or headache during the medication pause, based on expert consensus rather than controlled trials. Headache practitioners frequently use peripheral nerve blocks to treat various headache disorders in both acute and outpatient settings, often with positive results. There is no consensus on the technical aspects of administering these blocks. Four greater occipital nerve blockade significantly reduced the average number of headache and migraine days in patients with chronic migraine compared to a placebo. This treatment, in addition to prophylaxis with Topiramate, has shown additional benefits compared to oral prophylaxis alone. Adverse effects were generally mild, transient, and self-limiting. We aimed to evaluate a novel approach to facilitate analgesic withdrawal in a difficult-to-treat patient diagnosed with MOH.

Methods: We identified a patient with MOH experiencing more than 15 headache days per month and severe triptan overuse (Frovatriptan, 60 doses per month). This patient was refractory to multiple lines of treatment (oral medications, Onabotulinumtoxin A, subcutaneous anti-CGRP antibodies). Before initiating secondary prophylaxis with Rimegepant, we aimed to achieve analgesic withdrawal. As is customary at our center, we treated the withdrawal symptoms and rebound headache with an intravenous infusion therapy, which included the following medications: Diazepam 5 mg, Methylprednisolone 250 mg, Metoclopramide 10 mg, Pantoprazole 40 mg, and B vitamin supplementation. Following this therapy, we decided to prevent patient's rebound headaches and avoid early relapse into analgesic overuse by treating the patient with two sessions, spaced 7 days apart, with anesthetic blockades of the greater occipital nerve (GON) and lesser occipital nerve (LON) administering 2 cc of Lidocaine 2%, 2 cc of Ropivacaine 0.75%, and limited to the first treatment 80 mg of Methylprednisolone. After 3 weeks from the start of these treatments, prophylaxis with Rimegepant 75 mg, one tablet every 48 hours, was initiated. The patient was evaluated weekly.

Results: The patient remained headache free starting from the third day of the intravenous disaddictive therapy and until the day of the second nerve block therapy (day + 12 from the start of therapy). From day +14 onwards the migraine returned to the usual levels of intensity and frequency and the patient resumed triptan abuse. Concomitant initiation of Rimegepant (day + 19) did not substantially change this condition.

Discussion: In this case the therapy with anesthetic blockade of the GON and LON failed to prevent the early rebound headache from withdrawal of analgesics and to keep the patient free from symptomatic therapies. However, we believe that this approach could be useful in achieving the aforementioned objectives in selected patients.

Observational study of patients with chronic migraine treated with mindfulness as a complementary therapy

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Introduction: There is a growing body of research demonstrating that for a number of patients with chronic pain, mindfulness-based approaches can be an effective tool among those proposed for pain management. It can be said that mindfulness improves mood, subjective well-being, and quality of life, also mindfulness improves anxiety, depression, activity inhibition, negative body image, and reduces physical and emotional pain. Additionally, in some cases, it can help reduce the use of pain medications.

Background: The concomitant use of pharmacological and non-pharmacological techniques improves the state of health of patients with chronic migraine, teaching and strengthening to put into practice alternative procedures to deal with headache attacks. Non-pharmacological treatments, cognitive behavioral therapies, relaxation techniques and mindfulness, have given stimulating results. Mindfulness is a process that cultivates the ability to bring attention to the present moment, awareness, and acceptance of the present moment, helping patients manage pain, avoiding abuse of drugs and increasing pain awareness. Mindfulness also allows patients to live with their pain and accept their present experience in a docile and above all non-judgmental way.

Methods: Two groups took part in the study. One group received only pharmacological prophylaxis, the other group in addition to the pharmacological prophylaxis, received 8 weekly sessions of guided training based on Mindfulness.

Conclusion: The hypothesis is that a treatment with the addition of Mindfulness leads to a higher reduction in the frequency of headaches and drugs consumption in 3 months.

The specific pattern of comorbidities in patients with resistant and refractory migraine - Results from the REFINE study

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Background: Resistant and refractory migraine identify two difficult-to-treat conditions whose epidemiology is still not well known due to their varying definitions. The presence of comorbidities such as psychiatric disorders might favor migraine progression from episodic to chronic. We aimed at assessing comorbidities of resistant and refractory migraine in a real-world setting.

Methods: REFINE is an international prospective observational study involving 18 centers across Europe. The study consecutively included one half of patients with either resistant (ResM) or refractory migraine (RefM), while the remaining half was of patients with non-resistant and non-refractory migraine (NRNRM). The present analysis focused on baseline patients' data. The prevalence of 20 previously defined comorbidities was compared among the three patient groups – ResM, RefM, NRNRM – with the chi-squared test.

Results: We included 689 patients; (570 women; 82.8%) with a median age of 47 years (interquartile range [IQR] 38-56); 262 patients (38.0%) had ResM and 73 (10.4%) RefM. Referring to psychiatric comorbidities, depression was present in 88 (34.1%) patients with ResM, 29 (39.7%) with RefM, and

56 (15.8%) with NRNRM (p<0.001), while anxiety was present in 65 (25.2%) patients with ResM, 25 (34.7%) with RefM, and 40 (11.3%) with NRNRM (p<0.001). Sleep disturbances were present in 104 (40.3%) patients with ResM, 24 (33.3%) with RefM, and 99 (28.0%) with NRNRM (p=0.025). Referring to pain comorbidities, muscular trigger points were present in 55 (21.3%) patients with ResM, 24 (33.3%) with RefM, and 44 (12.4%) with NRNRM (p<0.001). Referring to medical comorbidities, thyroiditis was present in 35 (13.6%) patients with ResM, 20 (27.8%) with RefM, and 43 (12.1%) of those with NRNRM, while cerebrovascular disorders were present in 6 (2.3%) patients with ResM, 12 (16.7%) with RefM, and 8 (2.3%) with NRNRM (p<0.001).

Conclusion: Many psychiatric and medical comorbidities were more prevalent in patients with RefM compared with ResM and NRNRM. Although coming from a cross-sectional study which is only designed to detect associations –not causations– our data suggest that there might be an association between some comorbidities and resistance to migraine preventive treatments.

Association of apolipoprotein E genotype with the risk of migraine related to menstruation in women with episodic migraine

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Background: Migraine is a complex neurological disorder for which there is currently no reliable specific biomarker. Recently, interest has been drawn to apolipoprotein E (ApoE), a protein whose serum levels are higher in episodic migraine patients compared to healthy controls, especially during migraine attacks. In addition, ApoE is an important supplier of cholesterol precursors for the production of steroid hormones including ovarian estrogen, the withdrawal of which can trigger migraine attacks in the premenstrual phase. In the present study, we aimed to investigate the influence of ApoE genotype on the risk of migraine related to menstruation (MRM) in a cohort of reproductive-age women with episodic migraine.

Methods: Genomic DNA was extracted from peripheral blood samples. The ApoE genotype status was determined based on the combination of rs429358 and rs7412 polymorphisms, which were genotyped by TaqMan real-time polymerase chain reaction. The univariate statistical analysis of explanatory variables was conducted by chi-square test in case of dichotomous variables, while independent samples t-test or the Mann-Whitney U test were used for continuous variables, as appropriate. Factors found to be significant in the univariate analysis were included in a multivariate logistic regression model to detect predictors of MRM. The threshold for statistical significance was set at $P<0.05$.

Results: The study involved 136 women with episodic migraine, with a median age of 39 (IQR, 29-45), which were divided into two groups: 63 (46.3%) women with MRM and 73 (53.7%) women with migraine not related to menstruation (MNRM). In the univariate analysis, ApoE ε4 allele carrier status (P= 0.017), age (P= 0.004), dysmenorrhea (P= 0.007) and insomnia (P= 0.045) significantly differ between MRM and MNMR patients. In the multivariate logistic regression analysis, ApoE ε4 allele carrier status (OR: 3.55; 95% CI: 1.30-9.73; P= 0.014), age (OR: 1.05; 95% CI: 1.01-1.09; P= 0.020) and dysmenorrhea (OR: 2.84; 95% CI: 1.32-6.09; P=0.008) were found independent predictors of MRM.

Conclusion: Carrying the APOE ε4 allele confers an increased risk of migraine related to menstruation in women with episodic migraine. These findings should be replicated in a larger study and further investigated to elucidate the underlying pathogenic mechanism.

Alexithymia increases the risk of chronification in women with migraine: preliminary results

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Background: Alexithymia is a multidimensional psychological construct, characterized by a deficit in identifying and communicating feelings and distinguishing between feelings and bodily sensations. Emerging data suggest a role for alexithymia in migraine, in a complex interplay with psychiatric comorbidity. This study is aimed at investigating the relationship between alexithymia and migraine chronification in female migraineurs.

Methods: Ninety-seven female patients, fulfilling the diagnostic criteria for migraine (with/without aura, episodic/chronic), were enrolled to date in this observational, cross-sectional study. Each patient underwent a psychological assessment for alexithymia (TAS-20 scale), anxiety and mood comorbidity (STAI-Y1/STAI-Y2, BDI-II), migraine-related disability (HIT-6) and apathy (Starksteln's Apathy scale). Data on headache attack frequency/intensity and medication/s were recorded. A multivariate analysis (using a logistic regression model) will be performed to assess the association among alexithymia (independent variable) and the probability of chronic migraine (dependent variable), taking into account BDI-II, STAI-Y1/STAI-Y2, HIT-6 scores, age, disease duration and medication use (covariates).

Results: The main clinical and demographic features were: mean age (n=96): 43.64 (±SD:13.14) years; diagnosis of episodic migraine: 56/95 (58.95%), chronic migraine 27/95 (28.42%), medication overuse headache: 7/95 (7.37%); mean monthly headache frequency (n=91): 10.31 (±SD:6.76) days; mean monthly drug days (n=91): 7.51 (±SD:5.45).
Interestingly, alexithymia was diagnosed in 39/90 (43.33% of the sample).
According to the preliminary monovariate analysis (88 subjects), alexithymia increased the odds of chronic migraine by 21.6% (p: 0.75).

Conclusion: Although these preliminary results require confirmation by a multivariate analysis on the whole sample (expected 350 patients), this study suggests that alexithymia, which is highly prevalent in female migraineurs, may play a role in increasing the risk of migraine chronification. Moreover, these findings may support a novel therapeutical approach, targeting alexithymia, for migraine prophylaxis.

Phenotyping interictal migraine patients according to clinical and psychophysical characteristics

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Background: This study aims to 1) assess migraine patients in different phases and identify those with increased pain sensitivity; 2) identify variables that could predict the presence of IPS independently by the phase of the assessment could be identified.

Methods: This observational study included Episodic (EM) and Chronic Migraine (CM). In the first part of the study, patients were divided into two distinct cohorts according to the phase in which the evaluation occurs (interictal; ictal/perictal). In each cohort, we performed a cluster analysis approach to identify distinct subgroups of migraine patients according to clinical and psychophysical characteristics. In the second part of the study migraine patients were treated as one cohort, and a Chi-squared Automatic Interaction Detection decision tree analysis was used to identify clinical predictors to be included in the NoIPS or IPS group. To assess the internal validity of the model, a tenfold cross-validation was applied.

Results: Part 1: 198 EM and CM were included (98 assessed during the interictal phase, while 100 assessed during the ictal/perictal phase). The cluster analysis approach identified distinct subgroups of migraine patients according to clinical and psychophysical characteristics. In both cohorts, we identified 18-19% of patients who had No Increased pressure-Pain Sensitivity (NoIPS), while the remaining 81-82% of patients had Increased pressure-Pain Sensitivity (IPS). In both cohorts, the IPS groups had reduced pressure pain threshold (PPT) over all tested areas (temporalis, cervical spine, hand, and leg) compared to NoIPS and a group of healthy subjects, while the NoIPS groups had either no difference or increased PPT compared with healthy subjects.
Part 2: Migraine patients with: 1) PPT over temporalis <= 130 kPa; 2) PPT over temporalis > 130 kPa and <= 197.5 kPa and PPT over the hand <= 347.33 kPa; 3) PPT over temporalis > 197.5 kPa and PPT over the hand <= 315 kPa; were correctly included in the IPS group with a sensitivity of 96%, a specificity of 81%, a positive predictive value of 96 %, and a negative predictive value of 81%. The overall accuracy of the model was 93% (model error: mean= 0.07; Standard error=0.02). The result of the cross-validation analysis revealed an overall accuracy of 92% (model error: mean= 0.08; Standard error= 0.02.

Conclusion: The high internal validity suggests that our model could precisely predict the presence of IPS independently by the phase in which the assessment occurred. These results suggest that

trigeminal and hand PPT cut-off values could be used in a clinical setting to identify patients with IPS. However, future longitudinal studies assessing the same patients across different migraine phases should be performed to confirm the validity of these cut-off values.

Pain catastrophizing in parents and their children: a comparison between parents with and without migraine

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Background: We aimed to: 1) explore pain catastrophizing in children and its potential association with (a) attack frequency, (b) pain intensity, and (c) efficacy of pharmacological treatment for attacks; 2) compare pain catastrophizing between patients and parents (subdivided into: migraine-affected, non-migraine-affected); 3) analyze potential relationships between domains of catastrophizing between patients and parents.

Methods: We included 90 children (mean age 12.30 ± 2.60 years; 65 females and 25 males) who met the diagnostic criteria for migraine without aura, along with one of their parents (65 with migraine, 25 without migraine). The patients were divided into: (1) high frequency and low frequency; (2) mild and severe pain; (3) effective attack medication and ineffective attack medication; (4) children of migraine-affected parents and children of non-migraine-affected parents. Pain catastrophizing was assessed using the PCS/PCS-C (Pain Catastrophizing Scale/ Pain Catastrophizing Scale-Child).

Results: In our sample, there were no significant differences in catastrophizing domains according to migraine pattern except for pain intensity. Patients with severe pain intensity showed higher scores in the "Magnification" domain (p=0.004). No differences emerged in the catastrophizing domains among patients based on headache family history (p=>0.050). However, migraine-affected parents had significantly lower scores compared to non-migraine-affected parents in the "Rumination" (p=0.003) and "PCS-total score" (p=0.025) domains. Comparing patients and their migraine-affected parent, we observed significantly higher scores in patients in the “PCS-total score” (p=<0.001) and "Helplessness" (p=<0.001) domains. While the catastrophizing tendency of migraine-affected parents did not correlate with that of their children, we observed a positive correlation between the “Helplessness” of non-migraine-affected parents and some domains in their children, such as “Magnification” (p=0.025), “Helplessness” (p=0.004) and “PCS-total score” (p=0.004). Additionally, a positive correlation is also present between the “PCS-total score” of the non-migraine-affected parent and the “PCS-total score” of their child (p=0.030).

Conclusion: Migraine-affected parents exhibit lower levels of catastrophizing compared to non-migraine-affected parents. Additionally, although not significantly different, patients with a migraine-affected parent show slightly lower levels of catastrophizing compared to patients with a non-migraine-affected parent. Therefore, it can be hypothesized that migraine-affected parents may transmit and influence the approach to pain management.

Psychopatological features and bipolar disorder spectrum traits in outpatients suffering from primary headaches: cluster headache versus migraine

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Background: Although numerous studies have been conducted over the last 20 years on the psychological characteristics and psychiatric comorbilities of primary headaches, migraine and tension-type headache, research focused less on cluster headache, a severe and rarer subtype.

Objectives: This study aims to assess psychopathological variables and to investigate the co-occurrence of bipolar disorder spectrum traits in patients with cluster headache disorder as compared with other primary headaches.

Methods: The cross-sectional phase of this observational study is in progress. Adult patients with cluster headache or migraine attending the Headache Outpatient Clinic of Neurology Service (Department of Human Neuroscience AOU Policlinico Umberto I, Rome) were consecutively enrolled. An *ad hoc* questionnaire on socio-demographic variables and the following psychometric tools were administered: Headache Impact Test 6 (HIT-6), Mood Disorder Questionnaire (MDQ), Patient Health Questionnaire 9 (PHQ-9), Stress-related Vulnerability Scale 9 (SVS-9), items on alcohol/substance abuse (modified from M.I.N.I), Portrait Values Questionnaire 11 (PVQ-11) and MIDI Personality Trait Scales 30-item. Student t-test and Pearson chi-square test were used to compare the two subgroups represented by males due to the high probability of gender bias.

Results: The study revealed that cluster headache patients are more prone to the value Achievement ((t=-2.334; p=0.020), slighly to Self-Direction (t=-1.942; p=0.052) and to Agentivity (t=-2.566; p=0.010). Also, an increased prevalence in life-time of periods characterised by higher mood (14%) as compared to the migrainous group (0%; $\chi^2 = 6.947$, df = 1, p = 0.008) and to general population (4%) was found. The results indicate a relationship between the way of being of the patient with cluster headache (more open-to-change and self-enhanced) and the manifestation of the headache itself as well as with humoral fluctuations.

Conclusion: Cluster headache patients have personality traits that indicate an outward disposition rather than towards themselves and, in addition, show greater mood lability. Clinicians should be aware of possible (sub)clinical expressions of mood disorder in the personological features of cluster headache and possibly identify of a bipolar disorder. Treating the disorder may improve the intensity and frequency of cluster headache itself. Pending analysis of the definitive data of the project just presented, and further in-depth studies and ampliation of the sample are needed.

Neurophysiological and neurobiological correlates of analytic style of processing visual information in healthy subjects and in migraine sufferers: focus on visual cortical habituation and neurotrophins levels

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Background: Previously we highlighted a link between analytic cognitive style and migraine. Moreover, impaired habituation, earlier linked to migraine, has been shown in analytic healthy subjects**.** On the other hand, it is known that Nerve Growth Factor (NGF) has a role in pain transmission and higher levels of this neurotrophin have been highlighted in saliva and plasma of migraineurs. It is noteworthy that NGF and Brain Derived Neurotrophic Factor (BDNF) are involved in cognitive processing and can be upregulated by behavioral arousal and environmental stimuli. Currently, however, no study has examined whether analytic cognitive style is associated with neurotrophins alterations in human plasma and saliva. We investigated this issue in a group of migraineurs and healthy subjects.

Methods: We enrolled 24 subjects as below: 8 migraineurs (N=4 with aura; N=4 without aura) and matched them with 16 healthy volunteers (N=8 characterized by analytic cognitive style and N=8 by a global one, as preliminary assessed by cognitive psychological questionnaires: Sternberg, Amos test). The same questionnaires were employed to explore cognitive style in the migraine group. All subjects underwent recording of visual habituation trough visual evoked potentials (VEPs), and evaluation of NGF and BDNF plasmatic and salivary levels (ELISA Kit).

Results: All migraineurs showed analytic style at cognitive questionnaires. We found significant higher levels of NGF in saliva of analytic healthy subjects similarly to migraine group, versus global group. At the same time, VEPs recording highlighted significant potentiation instead of habituation in analytic subjects and in migraineurs versus the global group. Analytic scores are positively correlated with higher salivary NGF levels and potentiation to VEPs in migraine groups and in healthy subjects. ANOVA test: ($p<0.05$).

Conclusion: We highlight for the first time a correlation between analytic style of processing visual information, visual habituation patterns and NGF and BDNF salivary and plasmatic levels in healthy subjects and in migraineurs, warranting further investigation. Such research might shed some more light on the role of both NGF and analytic visual information processing on pain mechanisms, potentially indicating them as targets for new integrated therapeutic strategies, pharmacological and non, for primary headaches.

Real-world application of Short Term Psychodynamic Psychotherapy (STPP) as chronic migraine preventive therapy: Profiling responders and predictive factors

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Background: Chronic migraine (CM) is a difficult-to-treat condition. Non-pharmacological treatments represent valuable assets for CM patients. Short-term psychodynamic psychotherapy (STPP) showed excellent results in CM and, particularly, in interrupting medication overuse (MO). In this study, we aim at identifying predictive factors to stratify CM patients according to their STPP response chance.

Methods: We designed a prospective observational study on CM patients undergoing STPP. We collected clinical data related to migraine burden (baseline headache days, number of acute medications used, MIDAS, HIT-6), as well as psychiatric comorbidities (by means of MINI) and mentalization level obtained by the STPP interview to use them as predictive factors by univariate and multivariable discriminant function analysis at 3 (early) and 6 months (sustained response).

Results: We recruited 119 patients (mean age 39.90 ± 14.4., F=102); 94% (n=103) completed the STPP treatment. All patients presented a low-to-intermediate mentalization level. STPP was effective in reducing monthly headache days and in lasting interruption of MO at 3 and 6 months. Mentalization level didn't affect the STPP outcome (p=0.40). Baseline headache days, alternative therapies' use, and the Hamilton Depression scale score were predictors of response at 3 months: the more headache days at baseline, the higher the chance of response. Sustained response was predicted by current use of preventive therapy, pain intensity, HIT-6 score, hypomania, and dysthymia.

Conclusion: In real-world, STPP is effective in patients with a high migraine burden in all types of patient-specific stratification. STPP may represent a further interesting and useful approach to the treatment of CM.

Anti-CGRP monoclonal antibodies and psychiatric symptoms in migraine: The EMIPSY22 Project

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Background: Mood, anxiety, and sleep disorders, as well as personality traits or clear-cut personality disorders, are primarily linked with migraine. Individuals with migraine and comorbid psychiatric conditions often have a history of multiple therapeutic failures with conventional preventive treatments and are at a heightened risk of developing chronic migraine and medication overuse headache. The EMIPSY22 project aims to investigate: (i) whether psychiatric comorbidities and baseline psychopathological characteristics influence the response to treatment with anti-CGRP monoclonal antibodies (mAbs); (ii) changes in psychopathological characteristics and symptom severity following treatment with mAbs.

Methods: We enrolled 36 consecutive patients eligible for mAbs treatment who attended our Headache Center from June 2022 to June 2023. Subjects underwent clinical evaluation at the Headache Center and psychiatric assessment at the Psychiatry Section, at two time points (at baseline and after six months of therapy). Data regarding migraine characteristics and the degree of disability caused by headache were recorded, and a comprehensive psychiatric assessment was conducted. Specifically, at baseline, we evaluated the presence/absence of psychiatric disorders (using SCID-5-CV), including personality disorders (SCID-5-PD), as well as the presence and severity of depressive symptoms (BDI-II and HAM-D), anxiety symptoms (HAM-A, STAI-Y), hypomanic/manic symptoms (MRS, MDQ), obsessive-compulsive symptoms (OCI-R), and sleep disturbances (ISI). After six months of treatment, tests were repeated to assess changes in the severity of psychiatric symptoms.

Results: In our sample, nearly one-third of the subjects were diagnosed with a psychiatric disorder (30.6%). Among these, the most frequent diagnoses were adjustment disorders, followed by depressive and anxiety disorders; 5.6% of the overall sample were diagnosed with personality disorders (pathological personality traits were prevalent in 33.3% of cases, especially cluster C characteristics). Of the sample, 64% responded to mAbs treatment at 6 months. The prevalence of baseline psychopathological characteristics did not differ between responders and non-responders. We observed a significant reduction in the severity of depressive and anxious symptoms, as well as sleep disturbances, after six months of treatment.

Conclusion: We may hypothesize that psychiatric symptoms do not impact the response to mAbs therapy and, furthermore, that the observed improvement in psychiatric symptoms is not solely attributable to the improvement of headache but also suggests functional and structural changes involving both trigeminal pain modulation pathways and neurolimbic-pain-network structures implicated in processing the multifaceted pain experience.

The effect on the medication overuse profile of Short-Term Psychodynamic Psychotherapy compared to pharmacological therapy in CM patients: a propensity score matched study

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Background: Medication Overuse (MO) is a common complication of chronic migraine (CM). Patient's advice and early start of preventive therapy is a valuable strategy. Add-on Short-Term Psychodynamic Psychotherapy (STPP) has been proved useful in prevent MO relapse at 1 year. Here, we tested the early effect of stand-alone STPP to interrupt MO compared to pharmacological therapies.

Methods: A sample of 430 CM (±MO) patients screened at the first visit were addressed to an oral preventive therapy: amitriptyline (AMI), flunarizine (FLU), topiramate (TOP), valproate (VPA) [before FDA warning] or stand-alone STPP. Propensity score matching (PSM) was used to pair pharmacological group with STPP by age-, sex- and migraine disability. Headache days and medications intake were reviewed at 3 (t-3) and 6 (t-6) months after the first visit.

Results: PSM paired with STPP patients 49 patients with TOP, 68 with AMI, 49 with FLU, 20 with VPA. Groups didn't differ from STPP controls for aura (p=0.85), STPP groups used more triptans/combination than TOP and AMI group, while it was not significant for FLU e VPA group. The use of previous prophylaxis didn't differ among groups. Groups didn't differ from STPP for HIT-6 (p=0.07) and MIDAS (p=0.36) scores. At t-3 the headache day reduction for all STPP groups was equal to that obtained by pharmacological counterparts, but a t-6 all STPP groups returned in average to a chronic pattern while in average pharmacological groups remained episodic ($F[14,430]=8.97$, $p=0.0001$). On the other hand, acute treatment consumption remained equally low in both STPP and pharmacological groups at both t-3 and t-6 ($F[14,390]=1.78$, $p=0.038$) with an average of 7 vs 6 between all STTP controls and all pharmacological groups.

Conclusion: At 3 months follow-up, stand-alone STPP was as effective as other oral pharmacological preventive therapies in reducing MO and facilitate remission from CM to episodic form. After 6 months, patients treated with STPP show a worsening of the frequency of attacks but maintain the benefit on medication overuse. This data could underline a specific action of the STPP on the profile of abusers.

Anti-CGRP antibodies counteract interoceptive awareness of malaise

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Background: Dysfunctional processing of interoceptive cues has a key role in disease pathogenesis. CGRP regulates interoceptive information and emotional states encoded by neural pathways projecting to the amygdala from lateral parabrachial nucleus and thalamus. Here, we investigated whether anti-CGRP mAbs modulate interoception and malaise sensations.

Methods: Rats were exposed for different times to anti-CGRP antibodies at 100 mg/kg s.c, and Western blotting adopted to investigate pharmacokinetics of anti-CGRP antibodies upon transcardial perfusion. Gene array was adopted to evaluate the impact of fremanezumab on gene expression profiles in trigeminal ganglion and different brain regions. Conditioned taste aversion was used as a model of aversive memory and awareness of malaise. Lastly, exposure to cycles of cisplatin allowed to evaluate the impact of anti-CGRP mAbs on chemotherapy-induced anorexia and weigh loss.

Results: We report that systemically administered anti-CGRP mAbs reach the rat brain cortex and hypothalamus at concentrations in keeping with those reported in the literature for IgG and about one order of magnitude lower than those present in the skin and gut. Accordingly, subcutaneous fremanezumab alters transcriptional homeostasis of the trigeminal ganglion as well as that of brain cortex, hypothalamus and amygdala. Interestingly, Gene Ontology enrichment analysis demonstrated that, among the tissue biomarkers evaluated, those showing upregulation were exclusively related to the nervous system, highly represented in the hypothalamus and included the amygdala. We also found that both fremanezumab and galcanezumab counteracted conditioned taste aversion, a learning process sustained by CGRP release in the amygdala. Finally, both antibodies reduced anorexia and weight loss in rats exposed to two cycles of cisplatin exposure.

Conclusion: Data indicate that anti-CGRP mAbs modulate interoception and sensation of malaise, and disclose the translational potential of these biologics to treatment of mental, eating and oncological disorders.

Psychiatric comorbidities in migraine patients with medication overuse

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Background: Medication overuse headache (MOH) is often a complication of chronic migraine, especially in patients who suffer from psychiatric disorders. The study evaluated psychiatric comorbidities in chronic migraineurs, comparing clinical characteristics between patients with and without MOH.

Methods: We enrolled 75 patients with chronic migraine (CM) from the Headache Center at the Hospital of Pisa. All patients were assessed using psychometric scales (the brief version of Temperament Evaluation of Memphis, Pisa, Paris and San Diego self-questionnaire - brief TEMPS-M -, the Reactivity Intensity Polarity Stability Questionnaire - RIPoSt-40 -, the Adult Self-Report Scale - ASRS-v 1.1 -, the Morningness-Eveningness Questionnaire Self-Administered - MEQ-SA -, the Wender-Reimherr Adult Attention Deficit Disorder Scale – WRADDS -, the Clinical Global Impression – CGI -, the Global Assessment of Functioning Scale – GAF -, the Headache Impact Test - HIT-6 -, the Allodynia Symptom Checklist - ASC-12 -, and the Fatigue Assessment Scale – FAS). The participants were classified into two groups based on MOH comorbidity to identify specific clinical and psychiatric characteristics.

Results: The study found significant differences between MOH group (n=41) and non-MOH group (n=34) in migraine onset age (15 vs 23 years) and prevalence of mood disorders comorbidities (75.6% vs 52.9%), especially bipolar spectrum disorders (mostly cyclothymia). There were significant discrepancies in cyclothymic temperaments (7% vs 6.75%) and affective instability (11.8% vs 10.52%). MOH patients showed an early chronotype less frequently than N-MOH subjects (41.5% vs 67.6%). Between the two groups there were no significant differences in education and marriage state, neither in psychiatric family history.

Discussion and Conclusion: The results of the study highlight a strong association between psychiatric disorders and MOH in CM patients. In our study patients with MOH reported higher rates of bipolar spectrum disorders and cyclothymia, as well as higher levels of affective instability and emotional dysregulation. Due to the higher rates of comorbid mood disorders in patients with MOH, our study seems to suggest that a systematic assessment of psychiatric comorbidity in MOH patients may lead to a more appropriate management of these complex subset in patients.

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