ABSTRACTS

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ORAL COMUNICATIONS

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Cortical effects of erenumab in migraine

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Background: Subcutaneous injection of monoclonal antibody against CGRP receptor erenumab (Aimovig®) has been approved for the prophylactic treatment of migraine. Although different studies have shown that this treatment is highly effective and safe, the neurophysiological mechanisms underlying its clinical efficacy are still debated widely. In particular, it is not yet clear whether the neurophysiological effects of the drug are exclusively confined to the periphery of the trigeminal system or also occur centrally, at the cortical level. This study assessed the cortical effects of erenumab injection in a group of patients with migraine unresponsive to at least 2 prophylactic treatments.

Methods: We prospectively enrolled 10 migraine patients (4 with chronic migraine and 6 with high-frequency episodic migraine). In all participants, we recorded the non-noxious somatosensory evoked potentials (SSEPs) after repetitive electrical stimulation of the median nerve at the wrist. We measured N20-P25 amplitudes from 3 blocks of 100 sweeps and assessed initial cortical activation from the amplitude of the 1st block and habituation from amplitude changes between the three sequential blocks. Neurophysiological measurements were recorded before each monthly erenumab injection, for 3 months.

Results: At month 3, erenumab significantly reduced the mean monthly headache days, severity of headache (0-10), and the mean monthly tablet intake (all p=<0.001). A significant increase in delayed SSEP amplitude decrement (habituation), but not in the initial cortical activation, was noted 3 months after the beginning of the treatment compared to the baseline (slope baseline = +0.13, month 3 = -0.37, p = 0.009).

Conclusion: In this preliminary study, we showed for the first time that clinical improvement induced by erenumab injection in migraine patients is accompanied by neurophysiological changes that occur at the cortical level. It remains to be confirmed if this treatment may favour the cortical response amplitude decrement, possibly via a normalization of the activity of the first-order trigeminovascular neurons.

Safety and tolerability of erenumab for migraine in mitochondrial disorders

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Background: Monoclonal antibodies against calcitonin gene-related peptide (CGRP) or its receptor are innovative specific therapies for migraine prophylaxis, meeting the longstanding need for effective and tolerable preventive options. Migraine is the most frequent Central Nervous System clinical manifestation of patients affected by mitochondrial diseases (MDs), with a higher prevalence in MDs compared with general population[1]. We report the six months treatment outcomes of the first patient affected by a mitochondrial disease to be treated with erenumab for migraine.

Methods: A 37 year old woman, followed by our Headache Centre for chronic migraine without aura, was recently diagnosed with Progressive External Ophthalmoplegia (PEO) associated with POLG mutation. Previous trials with several migraine prophylactic drugs had been discontinued for tolerability issues or contraindicated due to her medical history. The patient was offered treatment with erenumab 70 mg monthly and previous prophylactic treatment with cinnarizine was withdrawn. Mean monthly headache days, mean monthly acute medication use days and mean severity of pain using the Visual Analog Scale (VAS) were assessed at baseline and after 6 months of treatment with erenumab. The patient was administered with Migraine Disability Assessment Questionnaire (MIDAS), and Headache Impact Test-6 (HIT-6), at baseline and after 6 months. The patient was evaluated for adverse events and tolerability concerns on a monthly basis.

Results: The frequency of headache attacks changed from 17.25 ± 2.21 days/month at baseline to 6.33 ± 1.52 after 6 months of treatment. There was a reduction in the monthly acute medication use days, from 20.5 ± 1.91 to 6.67 ± 2.08. Median VAS was 9.67 ± 0.47 at baseline and 7.33 ± 0.47 at sixth month follow-up. The patient reported improvements in quality of life as measured by the MIDAS and HIT-6. No serious nor minor adverse events occurred and the treatment was well tolerated.

Conclusion: In this patient, with a history of poor tolerability of traditional migraine prevention drugs and with an underlying mitochondrial disorder restricting the possible therapeutic choices, erenumab showed to be a safe and well tolerated option, confirming the safety data also in fragile subjects such as patients affected by Mitochondrial Disorders.

Effects of Erenumab on trigeminal A-delta fibers conduction assessed by Laser Evoked Potentials: preliminary analysis and results

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Background: Following the recent discovery of the CGRP's role in trigeminovascular system, CGRP targeted therapies, have been developed which gave rise to groundbreaking treatments for migraine. Erenumab is the first monoclonal antibody against CGRP receptor approved for episodic and chronic migraine prophylaxis. Its action results from inhibition of meningovascular Adelta fibers CGRP receptors. The aims of this work were to observe the clinical efficacy of Erenumab and to explore neurophysiological effects on migraine pathophysiology.

Methods. We enrolled 12 patients affected by migraine according to ICHD-3 of which 4 with episodic and 8 with chronic migraine. The group consisted of 10 females and 2 males (M age= 38.7 years, DS= 11.7). We adopted the CO_2 Laser Evoked Potentials to elicit an activation of cutaneous A-delta fibres. According to our hypothesis the antagonist CGRP receptors could have an indirect inhibition effect on nociceptive evoked responses. The patients received laser stimuli on the right and left forehead before Erenumab administration (time 0), after 10 minutes (time 1) and after 15 days (time 2) by injection. The time 1 evaluation served as placebo session
We performed the repeated measures ANOVA for N1, N2 and P2 amplitude, according to the EEGlab tool of Matlab software.

Results: We presently evaluated LEPs from 12 patients. The N1 and the N2 component appeared to be modulated by Enerumab, as both waves seemed to be reduced in amplitude at the time 2. The later wave was unaffected after Enerumab injection. Due to the small size of evaluated groups, the statistical differences were eluded by multiple comparison correction.

Conclusions: These preliminary data show a trend toward an inhibiting action of Enerumab on trigeminal A-delta transmission, exerted after 15 days from injection. The action on N1 and N2 waves, suggests a possible partial inhibition of A-delta afference. Further analysis in larger sample could confirm the statistical robustness of these data and their possible correlation with clinical outcome.

Erenumab in a patient with Chronic Migraine and Relapsing Multiple Sclerosis: a case report

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Background: Erenumab is the only human monoclonal antibody directed against the calcitonin gene-related peptide (CGRP) receptor to be approved for migraine prevention. It is indicated in patients with at least four migraine days per month, after proved inefficacy of at least two prophylactic drugs. At the moment no studies concerning its use in multiple sclerosis (MS) patients are available. Herby we present a relapsing-remitting (RR) MS patient with chronic migraine (CM) treated with Erenumab.

Clinical case: We describe the case of a 41-year–old woman referred to our Headache Centre. She suffered from migraine without aura since she was 12-years-old. Her family history was positive for migraine. Attacks consisted of supraorbital pulsating pain, spreading in frontal and temporal region with bilateral location. Pain was moderate or severe with nausea, vomit and photo-phonophobia, lasting 24-72 hours, if not treated. Initially frequency was 5 days per months, but after pregnancy, became of about 15. She experimented several migraine preventive drugs (amitriptyline, flunarizine, pizotifen, citalopram, cynnarizin, and botulinum toxin) with unsatisfactory response, while her headache becoming daily and a depressive syndrome occurring.
In May 2000 she was diagnosed with RR-MS, initially treated with Interferon beta-1a (discontinued 4 years later for pregnancy planning), then with Natalizumab, discontinued spontaneously for disease stability. In September 2019 she was selected to start Erenumab 70 mg subcutaneously/monthly. After two doses of Erenumab, she reported a significant decrease in the intensity of attacks (from 7-8/10 VAS to 4/10) but not in frequency. So she switched to Erenumab 70 mg 2 fl subcoutaneusly, with a 12 attack reduction compared to baseline and an intensity of 2/10 VAS. Since Erenumab start no new neurological signs or symptoms suggesting a MS clinical relapse were recorded. No side effects were reported.

Discussion and conclusions: Erenumab demonstrated its efficacy and its tolerability in our patient suffering from drug resistant CM, without impact on MS course. Currently no data are available about Erenumab use in patients with MS. We aim to continue the treatment with a regular clinical and imaging follow-up, in order to monitor both Erenumab efficacy persistence and any possible adverse event or MS course modifications.

Erenumab in refractory Chronic Migraine patients: Real life results from the Bologna Headache Center

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Background: Randomized controlled trials have proven effecacy and safety of erenumab as preventive treatment in chronic migraine (CM).The aim of the study is to evaluate effectiveness and safety of erenumab in refractory CM patients in real-life.

Methods: Between May and September 2019, all eligible consecutive CM patients received Erenumab 70 mg subcutaneously once every 4 weeks in our Tertiary Headache Center. Erenumab was increased to 140 mg at week 8 in poor-responders and non-responders. We evaluated changes in monthly migraine days, monthly analgesic intake and >50%, >70% responder rates at week 8 and 12 compared to baseline.

Results: 67 patients (47 female, 20 male; mean age 50.8±9.48) received at least one Erenumab dose. Mean previous failed pharmacologic preventive treatments was 7.5 and mean previous failed non-pharmacologic preventive treatments was 3.2. 49/67 (73%) patients received at least 2 doses. At week 8, there was a >50% response rate in 26.5% (13/49) and a >70% response rate 12.2% (6/49), respectively. Monthly migraine days decreased from baseline 20.75±6.36 to 13.47±7.60 ($p<0.0001$) and monthly analgesic intake decreased from baseline 27.04±18.97 to 16.35±11.85 ($p=0.0002$). 31/67 (46.2%) patients received at least 3 doses. At week 12, there was a >50% response rate in 32.2% (10/31) and a >70% response rate 9.6% (3/31), respectively. Monthly migraine days decreased from baseline 20.46±6.52 to 13.00±7.91 ($p=0.0001$) and monthly analgesic intake decreased from baseline 27.04±18.54 to 15.27±11.41 ($p=0.0002$). 2/67 discontinued treatment due to ineffectiveness. There were few reported side effects. No serious adverse event were reported.

Preventing migraine with erenumab: real-life data of 3-month treatment in 170 patients from 6 headache centers of Southern Italy

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Background: Migraine represents one of the first causes of disability worldwide. Several treatment options are available, but, likely due to tolerability problems or partial efficacy, adherence to therapy remains far from optimal. Erenumab is a fully human monoclonal antibody that showed safety and efficacy for the preventive treatment of both episodic and chronic, even refractory, migraine.

Methods: Here we report real-life data about the effect of 3-month preventive treatment with erenumab in migraineurs from six Headache Centers of Southern Italy regions (Campania, Puglia, Calabria, Sicilia). A total of 170 patients (119 females; mean age: 48yrs) have been included. 139 of them were affected by chronic migraine (90% with drug overuse). The majority of chronic patients failed at least 3-4 preventive treatments (mean 3.5). Concerning dosage, most of the patients were given 70 mg/month, while 140 mg/month was used in 21 of them.

Results: after 3-month treatment, headache days consistently reduced (mean 10 days less) with a responder rate (more than 50% reduction) of about 65%. An even more relevant effect was observed in acute migraine drugs assumption (mean 11 less, 67% of responders). Moreover, disability, measured by HIT6 scores, consistently reduced too. No difference in the mentioned outcomes measures was observed between patients treated with 70 and 140 mg at 3-month evaluation. However, 140 mg group showed a slightly greater effect in acute drug reduction and a faster effect in migraine days and drug consumption reduction (comparison after 1-month treatment). Treatment was well tolerated, no serious adverse event has been reported, the more frequent side effects being constipation (15%) and cramps (10%).

Conclusion: According to this preliminary experience, both 70 and 140 mg erenumab doses seem to be well tolerated and effective as preventing treatment in migraine, even in chronic and refractory patients. 140 mg dose may perhaps induce a faster amelioration and lead to a slightly more reduction of acute monthly drugs use. However, more data are needed to define the efficacy and safety of erenumab and the potential advantage of the higher dosage schedule.

Refractory chronic migraine: Could it be idiopathic intracranial hypertension? Data from a tertiary Headache Center

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Background: Idiopathic intracranial hypertension (IIH) is a chronic condition characterized by raised intracranial pressure (ICP) in the absence of a known etiology [1]. We aimed to investigate the prevalence of IIH in patients with chronic migraine unresponsive to medical treatment.

Methods: We included consecutive patients, referring within a 3-month period to our headache center and who met ICHD diagnostic criteria for chronic migraine (CM) and had failed or not tolerated at least 4 classes of previous preventive treatments. Those patients entered a diagnostic path including 1) brain MRI with magnetic resonance venography (MRV); 2) fundus oculi examination and 3) lumbar cerebrospinal fluid (CSF) opening pressure measurement (reserved to patients with at least 3 imaging signs of IIH, including perioptic nerve sheath distention, vertical buckling of optic nerve, globe flattening, asymmetric transverse sinuses, and empty sella) [2].

Results: Over the study period, 19 patients met the criteria to enter the IIH diagnostic path. They were all women, with a median age of 54 years (interquartile range 21-71). The prevalence of overweight or obesity was 10.5%. Ten (52.6%) of them had failed treatment with onabotulinumtoxinA treatment failure and 8 (42.1%) treatment with erenumab. All patients had fundus oculi examination which was normal. Nine (47.4%) patients performed had MRI with MRV; for the other patients the exam is scheduled but not yet performed. At brain MRI, 3 patients had features of possible IIH. Lumbar puncture was performed in 2 of them while 1 refused the exam. Both patients had an increase in the CSF pressure which was of 30 and 33 mmHg respectively.

Conclusion: IIH may be one possible explanation which may contribute to drug failure in patients with CM. Further data are needed to understand appropriateness and timing MRI with MRV and CSF pressure measurement in patients with CM.

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Altered electroencephalographic fractal dimension in migraine patients between attacks

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Background: In patients with episodic migraine, previous studies have detected abnormalities in the electroencephalographic (EEG) signal in different nodes of the somatosensory pathway. Despite this evidence, little is known about the functional nature of these alterations in migraine. Peculiar EEG properties for each specific signal component derived from the EEG trace can be investigated by using a multi-angle approach, capable of integrating time and frequency information, as well as complexity measures like Higuchi's temporal Fractal Dimension (FD). The FD is an index used to describe non-periodic and irregular time series, such as EEG spectra variability.

Methods: EEG recordings with eyes open were performed in 25 healthy volunteers (HVs) and 22 migraine without aura patients (MO), the latter were recorded interictally. We initially performed an independent component analysis in order to extract, between groups, significant EEG-derived resting-state networks (RSNs). Thereafter, we used the functional source separation technique (FSS) to identify four ad-hoc functional constraints in order to extract the brain activity along the sensorimotor pathway, of two subcortical (Brain Stem (BS) and Thalamus (Th)) and two cortical nodes (Primary sensory [BA 3b or S1] and primary motor [BA4 or M1] areas). We calculated non-linear fractal dimensionality (FD) – expressly suited to describe the dynamics of brain electrical activity – for each RSNs and for each node of the sensorimotor pathway.

Results: Eight EEG-derived RSNs showed significantly higher FD values in the MO group compared to the HVs. When the analysis was restricted to the various nodes of the somatosensory pathway, patients presented an increase in FD values only at the level of the brainstem source, while only a tendency to augmentation in the FD values was revealed at the thalamic level. No relevant differences were found in both cortical sources between the two examined groups.

Conclusion: We have observed that migraineurs interictally experience increased complexity of the EEG signal, especially at the brainstem level. This increase may reflect an alteration in connectivity of the migraine brain, which is linked to abnormalities in rhythmic EEG activity.

Altered short-term visual paired associative plasticity in migraine patients between attacks

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Background: In healthy volunteers (HVs), we recently observed that the same time-dependent paired-associative plasticity rules found within the sensorimotor system are valid for the visual system. Here, we have tested whether dysfunctioning associative plasticity might characterize the visual system of episodic migraine without aura patients (MO) where abnormalities in both inhibitory and excitatory paired-associative sensorimotor plasticity have been observed between attacks.

Methods: In 14 MO between attacks and in 15 HVs, we performed a visual paired associative stimulation (vPAS) protocol by coupling 90 black-and-white checkerboard reversals with low-frequency TMS pulses over the occipital cortex at 2 interstimulus intervals in separate sessions by subtracting or adding 25ms to the visual evoked potential (VEP) P100 latency. We recorded VEPs (600 sweeps) before, after, and 10-min later each vPAS session. VEPs were partitioned in 6 blocks of 100 sweeps. We analysed VEP N1-P1 first block amplitude and delayed habituation.

Results: While vPAS-25 significantly enhanced and vPAS+25 reduced VEP amplitude habituation in HVs, they both did not significantly change VEP amplitude habituation in MO between attacks.

Conclusion: We provide evidence for lack of excitability depressing and enhancing short-term associative plasticity mechanisms within the visual system in interictal migraine.

The "true" Trochlear Migraine: three case reports.

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Background: Trochlear Migraine is the association of two concurrent painful disorders represented by unilateral trochlear pain and ipsilateral migraine attacks, where the appearence of the first worsen the second pain as well as the migraine improve after succesful treatment of trochleodynia.

Methods: We collected clinical data of three children admitted to our Pediatric Headache Centre of "ISMEP"Palermo, Italy in the last three years.

Results: we reported three pediatric patients which showed a clinical migrainous syndrome with strict trochlear localization of pain, exactly as intended by the nosographic term. The first case was a 12-year old male, affected also by tipe 1 diabetes, with severe left infraorbital pain, nausea and vomit at the admission to Hospital. He reported an history of episodic headache caracterized by gradual onset, pulsating quality, severe intensity, localization strictly limited to the unilateral superior-inner angle of orbit associated with selective sensitivity elicited by pressure over infratrochlear zone, alternating side and association with nausea, photophobia, phonophobia and rarely vomit. The second case was an 11-year old male presented several migrainous attacks from an early age. He reported episodic attacks of migraine with pulsating quality and severe intensity, many of which strictly localized in the unilateral superior-inner angle of orbit associated to pressure tenderness over the same area. These attacks lasted several hours and often are associated with nausea, photophobia, phonophobia and unilateral cranial autonomic symptoms. The third case was a 16-year old female affected since seven years by recurrent unilateral headache attacks with the following features: pulsating quality, trochlear localization with rarely irradiation on the same frontal side, association with nausea, vomit photophobia and phonohobia. All the cases described above had familiarity for migraine and a negative neurological examination.

Conclusion: Although the term "Trochlear Migraine" refers to the association of two concurrent painful disorders that have causal relationship each other, just few cases and no one pediatric has been reported with this particular correlation. In our opinion it would be more useful if the term was referred to the relationship between topographical localization (strictly in trochlear region) and other clinical features, just like in the above described cases.

MIDAS and HIT-6™ as a measure of erenumab effectiveness in clinical setting

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Background: Migraine is a highly prevalent neurological pain syndrome, underestimated and disabling. Calcitonin gene-related peptide (CGRP) plays a crucial role in the pathogenesis. Recently, researchers have shown an increased interest in the development of monoclonal antibodies against CGRP and CGRP receptors for the treatment of migraine, such as the CGRP-receptor monoclonal antibody erenumab. The aim of our study is to assess the effectiveness and the impact on Quality of Life (QoL) of erenumab, compared to the routine preventive medical care.

Methods: Twenty patients (aged 18 and older) diagnosed with migraine according to ICHD-3 classification, 10 of them on erenumab (70 or 140 mg monthly) and 10 on other preventing therapies, will be tested at baseline-pretherapy and every three month. Neurological follow-up visits will be performed together with the psychologist, in order to reinforce the therapy compliance. The main outcome of our study will be the reduction in days lost due to migraine-related disability, according to the Migraine Disability Assessment Test (MIDAS) score and the reduction of negative effects of headache on normal activity of daily life, measured by the Headache Impact Test (HIT-6™).

Results: Using a liner regression model, a positive response to treatment with erenumab versus other therapies will be considered as a statistically significant reduction in MIDAS and HIT-6 scores.

Effects of multisensory overload on cortical excitability in healthy humans

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Background: Merging of sensory information is an important process towards the production of learning and memory. In animal models, co-application of tactile and visual stimulations enhances the magnitude of responses to somatosensory stimulations. This multisensory integration process takes place at a thalamic level, under cortical control. Here, we have sought evidence for the existence of the same process of multisensory integration in humans, by evaluating the potential ability of concurrent visual and somatosensory stimulations to affect the mechanisms of habituation, a basic form of learning.

Methods: We recorded somatosensory evoked potentials (SSEPs) in 18 healthy volunteers (HVs) before (T0), during, and 5 min (T1) after simultaneous visual stimulation (black-and-white checkerboard pattern-reversal). Six-hundred sweeps were acquired for each condition and partitioned off-line in blocks of 100 sweeps for the calculation of habituation as the slope of the regression line between the 1st and the last block of averaged N20-P25 SSEP amplitude response.

Results: SSEP N20-P25 habituation, i.e. amplitude decrement, which was obvious in most HVs during the T0 recording session, was deficient (amplitude increment) during the visuo-somatosensorial stimulation. During the T1 recording session, the SSEP amplitude linear trend was not different from that observed at T0.

Conclusion: Our study is the first to report the existence in healthy humans of the same cross-modal interaction previously observed in animal models, which manifests as an augmenting response to somatosensory stimuli. We suggest therefore that multisensory integration may enhance short-term memory mechanisms. Extending our study from HVs to patients with migraine between attacks would offer a unique opportunity to investigate defensive strategies against multisensory overload under conditions when baseline habituation is already absent.

Cortical effects of erenumab in migraine

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Background: Subcutaneous injection of monoclonal antibody against CGRP receptor erenumab (Aimovig®) has been approved for the prophylactic treatment of migraine. Although different studies have shown that this treatment is highly effective and safe, the neurophysiological mechanisms underlying its clinical efficacy are still debated widely. In particular, it is not yet clear whether the neurophysiological effects of the drug are exclusively confined to the periphery of the trigeminal system or also occur centrally, at the cortical level. This study assessed the cortical effects of erenumab injection in a group of patients with migraine unresponsive to at least 2 prophylactic treatments.

Methods: We prospectively enrolled 10 migraine patients (4 with chronic migraine and 6 with high-frequency episodic migraine). In all participants, we recorded the non-noxious somatosensory evoked potentials (SSEPs) after repetitive electrical stimulation of the median nerve at the wrist. We measured N20-P25 amplitudes from 3 blocks of 100 sweeps and assessed initial cortical activation from the amplitude of the 1st block and habituation from amplitude changes between the three sequential blocks. Neurophysiological measurements were recorded before each monthly erenumab injection, for 3 months.

Results: At month 3, erenumab significantly reduced the mean monthly headache days, severity of headache (0-10), and the mean monthly tablet intake (all p=<0.001). A significant increase in delayed SSEP amplitude decrement (habituation), but not in the initial cortical activation, was noted 3 months after the beginning of the treatment compared to the baseline (slope baseline = +0.13, month 3 = -0.37, p = 0.009).

Conclusion: In this preliminary study, we showed for the first time that clinical improvement induced by erenumab injection in migraine patients is accompanied by neurophysiological changes that occur at the cortical level. It remains to be confirmed if this treatment may favour the cortical response amplitude decrement, possibly via a normalization of the activity of the first-order trigeminovascular neurons.

Mouse model of migraine induced by proinflammatory agents

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Background: Administration of endogenous mediators or exogenous chemicals in migraine patients provokes early headaches and delayed migraine-like attacks. Despite breakthroughs in our understanding of the pathogenesis of migraine and in the development of treatment options, considerable gaps remain in our knowledge of the signaling pathways involved, and specific biomarkers of migraine are lacking. Sustained mechanical allodynia is a common response associated with the local administration of various proalgesic substances in experimental animals and humans. Here, we investigated the ability of a series of endogenous autacoids which have been implicated in migraine mechanism to provoke or do not provoke mechanical allodynia upon their injection in the mouse periorbital area.

Methods: Different stimuli were given by subcutaneous injection in the periorbital area of C57BL/6J mice. Spontaneous nociceptive behaviour was assessed by measuring the time that animals spent face rubbing the injected area with its paws after local administration of prostaglandin E2 (PGE2), prostacyclin (PGI2) and prostaglandin F2α (PGF2α) and histamine Mechanical allodynia in the periorbital area was assessed with the von Frey filament assay. Different antagonists were given by local and systemic administration.

Results: Local (periorbital) injection of PGE2, PGI2, PGF2α, but not histamine evoked spontaneous nociception. Histamine, PGE2 and PGI2, but not PGF2α evoked a dose-dependent periorbital mechanical allodynia. The painful responses were attenuated by systemic or local (periorbital) administration of selective antagonists of the histamine (H1), PGE2 (EP4), and PGI2 (IP) receptors, respectively.

Conclusion: The ability of histamine, PGE2, PGI2 to provoke migraine-like attacks in patients and periorbital allodynia in mice suggests that the study of allodynia in mice may provide information on the proalgesic mechanisms of migraine-provoking agents in humans. Failure of PGF2α to elicit PMA in mice is consistent with the observation that such prostanoid does not provoke migraine-like attacks in humans.

Efficacy and safety of erenumab in the real-life settting of the Abruzzo region, central Italy

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Background: We aimed to assess the efficacy and safety of erenumab, a fully human monoclonal antibody inhibiting the calcitonin gene-related peptide receptor (CGRPr), for the prevention of migraine in a real-life setting with adequate (6-month) follow-up.

Methods: We included in our observational study all patients treated with erenumab during the year 2019 in the Abruzzo region, central Italy. All included patients had a 6-month follow-up and received erenumab in the absence of reimbursement criteria.

Results: Among the 89 included patients, 76 (85.4%) received 6 doses of erenumab, 11 (12.4%) autonomously withdrew the drug due to perceived inefficacy, and 2 (2.2%) due to adverse events. Among the 76 patients completing treatment, 66 (86.8%) were female, with a mean age of 46.6±10.7 years; 71 (93.4%) had chronic migraine, and 55 (72.4%) medication overuse. All patients had ≥2 prior preventive treatment failures. Thirty-three patients (43.4%) increased the dose from 70 to 140 mg monthly, 10 (13.2%) withdrew the concurrent oral preventive medication, and 8 (10.5%) started a new one. Fifty-three patients (69.7%) had a 50% decrease in monthly migraine days (MMDs) within the first three doses; 46 (83.6%) of 55 patients withdrew medication overuse. In the 76 patients who completed a 6-dose treatment, erenumab decreased median MMDs from 19 (interquartile range [IQR] 12-27.5) to 4 (IQR 2-9.5; P<0.001), median monthly days of analgesic use from 10 (IQR 4.5-20) to 2 IQR 0-5; P<0.001), and median monthly days of triptan use from 5 (IQR 0-15.5) to 1 (IQR 0-4; P<0.001). We recorded 24 adverse events in 20 (22.5%) patients, the most common being constipation (14.2%). Two adverse events led to treatment discontinuation, namely allergic reaction in one patient and vertigo in one further patient.

Conclusion: Our data confirm the efficacy of erenumab for the prevention of migraine, especially in patients with chronic migraine and medication overuse, in a real-life setting. The treatment was well tolerated over a 6-month period. Further data are needed to assess the contribution of dose escalation and of oral add-on treatments, and to assess the impact of future reimbursement criteria by the Italian National Health Service.

Combined treatment with erenumab and subcutaneous immunoglobulin in a patient with comorbid chronic migraine and myasthenia gravis

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Case report: SCIg act as immunomodulators by neutralizing circulating autoantibodies; therefore, hypothetically, SCIg may also inactivate therapeutic monoclonal antibodies, even if anti-CGRP antibodies are designed to avoid acting on the immune system. However, there is no clinical experience of co-prescribing SCIg and therapeutic monoclonal antibodies. We here report the case of a 30-year-old obese woman with chronic migraine (CM) and myasthenia gravis (MG) due to thymoma reported at her first visit about 25 headache days per month (12 with migrainous features). Most of the attacks were disabling and had a poor response to triptans and nonsteroidal anti-inflammatory drugs; however, she had no medication overuse.
The patients' MG was associated with thymoma and positive to anti-acetylcholine receptor autoantibodies. Due to her chronic steroid use, she developed obesity, Cushing syndrome, osteoporosis, and cataracts. In March 2019, because of her multiple treatment failures, she was started on 70 mg monthly erenumab. There was an immediate reduction of monthly migraine days from 25 to 3 without adverse events. In June 2019, she underwent steroid tapering because of the steroid-related side effects. With steroid tapering she experienced worsening of her migraine with 12 migraine days in one month. Thus, the erenumab was increased to 140 mg per month in July 2019 with a new improvement in the frequency of migraine attacks. At the end of the same month, she was started on monthly SCIg treatment. She had an excellent response. At the last follow-up (January 2020), the patient was continuing treatment with erenumab 140 mg monthly and SCIg. Her migraine continued improving, with only two migraine days during the last month of follow-up. The control of the myasthenic symptoms with SCIg was excellent.

Discussion: To our knowledge, this is the first case of concurrent treatment with erenumab and SCIg in the same patient; the two treatments remained effective for their conditions and there were no clinically evident interactions or adverse events. Given the comorbidity between migraine and systemic autoimmune diseases, the use of concurrent treatments like that of our patient might be frequently required.

Erenumab in chronic migraine: efficacy and response predictors from a real life observational study

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Background: Randomized, placebo-controlled trials demonstrated erenumab safety and efficacy in the prevention of chronic migraine (CM). However, real life clinical data is still missing. Aim of the present study was to asses erenumab efficacy in CM prevention and characterise the clinical and demographical profile of erenumab responders and non responders.

Methods: The present study was conducted at the Headache Centre of Spedali Civili of Brescia. Patients were treated with erenumab 70 mg every four weeks. If no clinical response was observed after 12 weeks, a dose increase to 140 mg was attempted. Data about outcome, adverse events, abortive medication consumption and disability (Migraine Disability Assessment Score Questionnaire – MIDAS) were collected. The clinical characteristics analyzed were: age, gender, education, body mass index, migraine localization, disease duration, triptans response, medication overuse, allodynia, psychiatric comorbidities, autoimmune disorders, previous prophylaxes, hormonal therapies, relationship status, shift work and add-on therapies.

Results: Twenty-seven consecutive patients were enrolled (18 female, 9 male), with a mean age of 45.4 (± 7.4) years. Mean headache days per month was 21.1 (± 6.3). Medication overuse was documented in 24 patients (82.7%), with a mean monthly analgesic consumption of 23.5 (± 14.2). A statistically significant reduction from baseline to week 4, 12 and 24 in total headaches days ($p<0.0001$), severe headaches days ($p=0.001$), analgesics consumption ($p<0.0001$), and pain intensity ($p=0.001$) per month was found. Patients were classified according to the percentage of headache days reduction as non-responders (< 30%), partial-responders (< 50%) and responders (> 50%) at week 4, 12 and 24 of treatment. At week 24, 77.3% of patients were classified as responders, of whom 31.8% documented a reduction greater than 75% (super responders). Mood disorders ($p=0.01$) and absence of a stable relationship ($p=0.005$) were more frequent in non-responders compared to responders.

Conclusion: Our data confirm erenumab efficacy in CM prophylaxis, with over 70% of patients documenting a significant clinical response at week 24. However, psychiatric comorbidities and relationship status were found to significantly affect its efficacy in our cohort.

Schwann Cells and TRPA1 orchestrate ethanol-evoked neuropathic pain in mice

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Background: Alcohol abuse and dependence are among the major healthcare problems in the world and around 60% of alcoholics exhibit neuropathic pain. Alcohol dehydrogenase (ADH) converts ethanol into the reactive and toxic product acetaldehyde, which is rapidly metabolized to acetic acid by the mitochondrial aldehyde dehydrogenase-2 (ALDH2). Acetaldehyde is considered as the major contributor of the detrimental effects produced by acute and chronic alcohol consumption, including flushing, headache, cirrhosis and cancer. The transient receptor potential ankyrin 1 (TRPA1) channel, can be activated by acetaldehyde generated by alcohol dehydrogenase (ADH) in the liver and other tissues. However, the pathways by which acetaldehyde causes ethanol-evoked pain are poorly understood.

Methods: Periorbital mechanical allodynia was assessed with the von Frey filaments after acute and chronic ethanol ingestion in C57BL/6 and in mice with TRPA1 genetic deletion. The presence of ADH was assessed in neuronal tissue and Schwann cells by immunofluorescence. The content of by-products of oxidative stress (H_2O_2 and 4-hydroxynonenal (4-HNE)) was determined by immunofluorescence and colorimetric assay.

Results: Acute and chronic ethanol ingestion caused delayed periorbital mechanical allodynia in mice. Inhibition of ADH or deletion of TRPA1, a sensor for oxidative and carbonyl stress, prevented allodynia. Acetaldehyde generated by ADH in both liver and Schwann cells surrounding nociceptors was required for TRPA1-induced nociception. Schwann cell- (*Plp1-Cre*;*Trpa1*$^{fl/fl}$) specific deletion of TRPA1 revealed that channel activation by acetaldehyde results in NADPH oxidase-1 (NOX-1)-dependent production of H_2O_2 and 4-HNE, which sustain allodynia by paracrine targeting of nociceptor TRPA1. Human Schwann cells express ADH/TRPA1/NOX1 and recapitulate the proalgesic functions of mouse Schwann cells.

Conclusion: The presence of ADH in Schwann cells that express TRPA1/NOX1 and their ability of generating oxidative stress identifies an autocrine pathway that we propose as a major contributing mechanism in alcoholic painful neuropathy.

Are paediatric headaches in the emergency department increasing? An Italian experience

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Background: The aim of this study is to assess admissions, for headache, to the emergency department (ED) of the Di Cristina Children's Hospital in Palermo over a decade. The total number of ED admissions for headache was retrospectively analysed considering two periods of 2 years each: 2009-2010 and 2017-2018. The significant increase in admissions for paediatric headache is probably due to limited efficacy of the Italian and international guidelines and of the educational strategies implemented in this setting, and also due to communication difficulties, both with patients and between primary care networks and hospitals.

Methods: We retrospectively analysed the total number of admissions to the ED at the G. Cristina Children's Hospital in Palermo during two periods of 2 years each. We selected all admissions for headache and analysed those requiring assessment by a child neuropsychiatrist or/and an imaging examination.

Results: Total admissions to the ED decreased from 55,613 to 50,096 between the two periods considered, while the number of admissions for headache increased by 63.56%. There was also a significant increase in the number of multiple ED admissions by single children and the number of headache examinated with CT.

Conclusion: The comparative analysis of our ED admission data showed a significant increase in the admissions for headache and in CT examinations. A growing awareness, among families, of headache symptoms, together with inappropriate use of the paediatric ED by family paediatricians and general practitioners, could lead to unjustified overcrowding of the paediatric ED. The number of CT examinations performed was more than double; possible explanations for our data may be the defensive attitudes on the part of our ED paediatricians and neuropsychiatrists, and also the recent (2015) introduction of high-definition CT with very fast execution times.

Paralytic ileus after open abdominal surgery in a patient treated with erenumab

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Background: CGRP is involved in numerous biological functions other than pain. Among the several functions, CGRP modulates the enteric motility. In fact, one of the reported side effects of monoclonal antibody acting on CGRP is constipation. Constipation if present may range from mild to severe and in some cases lead to treatment discontinuation.

Case description: We present the case of a female 39 year-old patient with history of migraine with and without aura since her childhood. Her migraine worsened over time and became chronic. At the time of the visit in our Headache Center, she reported about 20 headache days per month (15 with migrainous features). Most of the attacks were disabling and had a poor response to acute phase treatments. She had no medication overuse. She had failed 3 previous migraine preventatives. Pre-existing comorbidities were urticaria, alopecia and anxiety disorder; she was on treatment with cetirizin, spironolactone, minoxidil, lorazepam and escitalopram. She started treatment with erenumab 70 mg in March 2019. She had an immediate reduction of monthly migraine days from 20 to 5. The attacks became also less severe. As side effect she reported mild constipation. In November 2019 she received the diagnosis of uterine myomas which was treated with open surgery in December. After surgery, she had paralytic ileus, which slowly recovered within few weeks. The scheduled administration of erenumab was cancelled.

Conclusion: In the described case, it is possible that erenumab contributed to development of paralytic ileum after open abdominal surgery. Up to now there are no other reports of such adverse event and causation cannot be proved. Anyhow our case raises the hypothesis if it is worth to stop anti-CGRP monoclonal antibodies before planned abdominal surgery especially in patients who already have constipation.

Pre-Ictal Migraine in a case of cervicocranial Fibromuscular Dysplasia

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Background: Fibromuscular dysplasia (FMD) is a rare vascular disease that affects small- and medium-sized arteries, most commonly renal and cerebral arteries. Cerebral vessels are involved in 25-30% of the cases. We describe the case of a woman who came to our observation for incoming seizures triggered by a migraine attack.

Methods: Clinical, neuroradiologic and neurophysiological observations were performed, including CT scan, brain and spine angiographic-MRI, brain selective angiography, video-EEG and polygraphic recordings.

Results: A 46 years-old woman was admitted to our Emergency Department for incoming seizures. Ten years earlier, the patient started experiencing episodes of typical migraine systematically followed by a 2-minute generalized tonic-clonic seizure, beginning about 20 to 50 minutes after the onset of headache. Antiepileptic therapy with Phenobarbital and Valproic Acid was started. The patient continued frequently to experience focal motor seizures with secondary generalization, accompanied by transient impairment of consciousness. Few months later, the patient voluntarily discontinued the therapy. Other pharmacological treatments, alone or combined, were tried without complete control of the seizures.
At the time of our examination, the patient was in post-ictal state, presenting drowsiness and confusion. The patient had a mild left hemiparesis, which progressively resolved in the following 2 hours. The CT scan performed at the Emergency Department showed no parenchymal abnormalities but revealed several vascular malformations. Brain and spine angiographic-MRI scan and Brain selective angiography were consistent with the cervicocranial FMD. EEG showed intermittent, irregular focal theta slowing in temporal regions. Occasional right sharp waves were present. Therapy was reintroduced with Valproic Acid and it was effective in reducing the frequency and severity of both seizures and headache attacks. The patient reported that the seizures and migraine attacks ceased after a period of 3 weeks. The embolization of the vascular malformations could not be performed because of the tortuosity of vessels.

Conclusion: Our patient suffered from seizure preceding by typical Pre-Ictal Migraine. In our patient the close association between seizures and headache attacks, as major clinical features of FMD, permit to hypothesize an underlying common pathogenic mechanism for both of them.

The acyl-glucuronide metabolite of ibuprofen has analgesic and anti-inflammatory effects via the TRPA1 channel

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Background: Ibuprofen is a widely used non-steroidal anti-inflammatory drug (NSAID) that has an analgesic and anti-inflammatory action. Ibuprofen is indicated to relieve inflammation and several types of pain, including headache, muscular pain, toothache, backache, and dysmenorrhea. Therapeutic effects of ibuprofen are attributed to inhibition of prostanoid synthesis by a non-selective, reversible inhibition of both cyclooxygenase 1 (COX1) and 2 (COX2). The transient receptor potential ankyrin 1 (TRPA1) channel, expressed primarily in nociceptors, mediates the action of proalgesic and inflammatory agents also produces during migraine/headache attacks. The metabolism of ibuprofen produces the reactive compound, ibuprofen-acyl glucuronide, which, like other TRPA1 ligands, interacts covalently with macromolecules. We investigated the ability of ibuprofen-acyl glucuronide to antagonize TRPA1 activation and, via this mechanism, its contribution in the analgesic and anti-inflammatory actions of ibuprofen.

Methods: To test the ability of ibuprofen-acyl glucuronide to interact with the TRPA1 channel, we used *in vitro* tools (TRPA1-expressing human and rodent cells and molecular modeling) and to explore its analgesic and anti-inflammatory actions we used *in vivo* mouse models of inflammatory pain (carrageenan and formalin test).

Results: Ibuprofen-acyl glucuronide, but not ibuprofen, inhibited calcium responses evoked by reactive TRPA1 agonists, including allyl isothiocyanate (AITC), in cells expressing the recombinant and native human channel and in cultured rat primary sensory neurons. In addition, molecular modeling studies suggested the key cysteine residue C621 as a probable alkylation site of TRPA1 channels for ibuprofen-acyl glucuronide. Local administration of ibuprofen-acyl glucuronide, but not ibuprofen, in the mouse hind paw attenuated nociception by AITC and other TRPA1 agonists (acrolein and hydrogen peroxide) and the early nociceptive response (phase I) to formalin. Systemic ibuprofen-acyl glucuronide and ibuprofen, but not indomethacin, reduced phase I of the formalin response. Carrageenan-evoked allodynia in mice was reduced by local ibuprofen-acyl glucuronide, but not by ibuprofen, whereas both drugs attenuated PGE_2 levels.

Conclusion: The reactive ibuprofen metabolite by blocking TRPA1, suggests that this novel action of ibuprofen-acyl glucuronide might contribute to the analgesic and anti-inflammatory activities of the parent drug.

Migraine-provoking substances evoke periorbital allodynia in mice

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Background: Migraine is a pain disorder that affects about 15% of the adult population worldwide. Although migraine provoking substances are normally vasodilators, dilation of arterial vessels does not seem to be the sole contributing factor, and the underlying mechanisms of the delayed migraine pain are mostly unknown. Here, we investigate a series of neuropeptides including calcitonin gene-related peptide (CGRP), adrenomedullin, amylin, pituitary adenylyl cyclase activating peptide (PACAP) and vasoactive intestinal polypeptide (VIP), which have been found to provoke or not provoke migraine-like attacks in patients, to elicit or do not elicit delayed and prolonged periorbital mechanical allodynia (PMA) after their injection in the periorbital skin of mice.

Methods: CGRP, adrenomedullin, amylin, PACAP and VIP were administered locally in the periorbital area of C57BL/6J mice. Spontaneous nociception was assessed by measuring the time (seconds) that the animal spent face rubbing the injected area with its paws, mechanical allodynia was assessed with the von Frey assay. Antagonists were administered by local and systemic injections.

Results: The periorbital injection of CGRP did not evoke an acute spontaneous nociceptive response but it did cause a robust, dose-dependent and sustained PMA lasting 4 hours after the injection. Systemic intraperitoneal or local injection of the CGRP receptor antagonist, olcegepant, or the monoclonal anti-CGRP prevented PMA. Local administration of adrenomedullin or amylin at the same pro-allodynic dose of CGRP, was unable to produce any measurable acute nociceptive response and PMA, over the entire period of observation (6 hours). Local injection of PACAP, which did not provoke any detectable spontaneous nociceptive behaviour even at the highest dose, induced a marked, dose-dependent and sustained (1-6 hours) PMA prevented by pretreatment with the selective PACAP receptor antagonist, PACAP6-38. VIP was unable to produce either acute nociception or PMA.

Conclusion: The correspondence between neuropeptides that provoke (CGRP; PACAP), or do not provoke (VIP), migraine-like attacks in patients and periorbital allodynia in mice suggests that the study of allodynia in mice may provide information on the proalgesic mechanisms of migraine-provoking agents in humans. Results underline the ability of migraine-provoking substances to initiate mechanical allodynia by acting on peripheral terminals of trigeminal afferents.

The potentials of nursing case management within a multidisciplinary approach to headache patients

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Headache disorders have been estimated by the World Health Organization to affect about 50% of the worldwide population. These disorders are also severely disabling, and migraine is the first cause of disability in subjects aged ≤50 years. These concerning data led to a worldwide call for action, highlighting the need for an empowerment of dedicated healthcare resources, as well as structured and multidisciplinary management of headache patients. Besides, headache disorders require a holistic approach to their clinical, functional, social and economic implications on patients.

In the near future, nursing competencies are anticipated to evolve and specialize through new educational programs based on a systematic patients' approach using the nursing process in different clinical areas, and innovative organizational models. In this context, referring to outpatient settings, such as Headache Centres, nurses are expected to increasingly participate in patients' health management. In particular, nurses may act as coordinators of multidisciplinary teams to ensure an effective meeting of patients' needs. 'Case managers' nurses might during the first referral to the Headache Centre, perform a systematic and holistic assessment of patients' needs, leading to a take-in-charge of patients. Afterwards, individual patient education and support might be the key activity for case managers, mainly aiming to provide patients with enough knowledge and self-confidence to adequately manage their disease and the proposed treatment also considering the new migraine targeted therapies. Moreover, nurses might directly communicate with patients and educate them to identify and avoid triggering-pain factors, manage pain, impaired functionality, and quality of life. Nurses might also monitor, early recognize, and manage clinical outcomes, complications, and adverse events. As patients' managers, nurses might request other professionals' assessment and jointly act with primary care providers such as family physicians and family nurses.

In Headache Centres, expected results of this evolution include an improved management of patients who will receive a customized, high-quality and holistic care, will better manage their disease, and will report improvements in self-perceived health status. Moreover, an early recognition of patients' complications and issues is expected, with their quicker management. Finally, nurses' activities could reduce neurologists' burden and contribute to face medical doctor shortage.

Visual cortical excitability in chronic migraineurs treated with erenumab: preliminary results of a study with sound induced flash illusions

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Background: Perception of the surrounding environment results from the interaction of multiple sensory stimuli. The modulation of perception can be explored by sound-induced flash illusions (SIFI): when a single flash is presented with two or more beeps, it is often perceived as multiple flashes (fission illusion); such illusory perception is associated to changes in visual cortical excitability. It is known that migraineurs show an abnormal visual cortical excitability, even interictally, so, here, we aim to evaluate whether there are SIFI changes in chronic patients treated with erenumab.

Methods: We enrolled 17 chronic migraine patients without aura (mean age 49.3 yo ±8.4; 13 females) who started prophylactic treatment with Erenumab (140mg monthly) and 17 control subjects (14 females) in the same age range. We used a software able to show a transient single flash presented together with concurrent beeps. Subjects had to count aloud flashes seen each time (5 tests randomly presented several times: 1FxB, where *x* goes from 0 to 4; F=flash, B=beep). We compared such scores using repeated measures ANOVAs: i) healthy controls vs baseline migraineurs (t0); ii) baseline migraineurs vs the same ones three months after treatment start (t3); iii) t3 migraineurs vs healthy controls. Moreover, we performed a post-hoc Duncan's test analysis

Results: First rmANOVA showed that healthy controls refer a higher number of flashes compared to chronic migraineurs ($p=0.0004$), while the second analysis did not show significant changes of such scores before and after 3 months of Erenumab treatment ($p=0.5405$), but post-hoc analysis showed an almost significant augmentation of scores between 1F4B tests ($p=0.0716$). Last rmAnova showed a less significant difference between t3 migraineurs and healthy controls ($p=0.0018$).

Conclusion: Data obtained suggest that chronic migraineurs manifest more fission illusions than healthy controls, consistently with previous studies. Furthermore Erenumab is a drug that may restore, partially, fission illusions and, consecutively, normalize visual cortical excitability, but, possibly, a wider sample is needed to highlight such effect.

Note: Authors of this abstract have nothing to disclose.

Cortical laminar necrosis in a 14-year old patient with status migrainosus

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Background: Cortical laminar necrosis (CLN) is necrosis of neurons of the cortex, radiologically defined as high intensity cortical lesions on T1 weighted MRI images following a gyral distribution. It occurs when supply of oxygen and glucose is insufficient to meet regional demands. In children, cortical laminar necrosis has been reported to be associated with hypoxic-ischemic encephalopathy, metabolic disorders, hypoglycemia, renal and hepatic dysfunction, immunosuppressive chemotherapy and encephalitis, but it's an uncommon finding in migraine and status migrainosus with or without aura.
We present the case of a 14-year old male patient, without known history of migraine or neurologic issues, who came to our attention for the manifestation of an acute and long persistent (>72h) symptomatology characterized by headache, confusional state, dysarthria, aphasia and visual disturbances.

Methods: Clinical evaluation, laboratory tests and instrumental examinations were performed during the hospitalization.

Results: A first emergency MRI showed a localized edema in the supramarginal gyrus in left brain hemisfere that has been identified as a possible vascular etiology. Supramargynal gyrus (Broadmann's area 40), a portion of the parietal lobe, is considered to be part of Wernicke's area and it is probably involved with language perception and processing. At a MRI control, it was possible to highlight a laminar necrosis of the cortical-pial zone in that area.

Conclusion: This case is interesting for the uncommon correlation between cortical laminar necrosis and status migrainosus with aura as well as for the site of the hypoperfusion revealed through MRI and for the atypical progression of the aura.

Migraine-provoking substances evoke periorbital allodynia in mice

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Background: Migraine is a pain disorder that affects about 15% of the adult population worldwide and represents one of the most prevalent and disabling neurological disorders. Although migraine provoking substances are normally vasodilators, dilation of arterial vessels does not seem to be the sole contributing factor, and the underlying mechanisms of the delayed migraine pain are mostly unknown. Here, we investigate a series of neuropeptides including calcitonin gene-related peptide (CGRP), adrenomedullin, amylin, pituitary adenylyl cyclase activating peptide (PACAP) and vasoactive intestinal polypeptide (VIP), which have been found to provoke or not provoke migraine-like attacks in patients, to elicit or do not elicit delayed and prolonged periorbital mechanical allodynia (PMA) after their injection in the periorbital skin of mice.

Methods: CGRP, adrenomedullin, amylin, PACAP and VIP were administered by local injection in the periorbital area of C57BL/6J mice. Spontaneous nociception was assessed by measuring the time (seconds) that the animal spent face rubbing the injected area with its paws, mechanical allodynia was assessed with the von Frey filament assay. Antagonists were administered by local and systemic injections.

Results: The periorbital injection of CGRP, even at the highest dose, did not evoke an acute spontaneous nociceptive response but, it did cause a robust, dose-dependent and sustained PMA lasting 4 hours after the injection. Systemic intraperitoneal or local injection of the CGRP receptor antagonist, olcegepant, or the monoclonal anti-CGRP prevented PMA. Local administration of adrenomedullin or amylin at the same pro-allodynic dose of CGRP, was unable to produce any measurable acute nociceptive response and PMA, over the entire period of observation (6 hours). Local injection of PACAP, which did not provoke any detectable spontaneous nociceptive behaviour even at the highest dose, induced a marked, dose-dependent and sustained (1-6 hours) PMA prevented by pretreatment with the selective PACAP receptor antagonist, PACAP6-38. VIP was unable to produce either acute nociception or PMA.

Conclusion: The correspondence between neuropeptides that provoke (CGRP; PACAP), or do not provoke (VIP), migraine-like attacks in patients and periorbital allodynia in mice suggests that the study of allodynia in mice may provide information on the proalgesic mechanisms of migraine-provoking agents in humans. Results underline the ability of migraine-provoking substances to initiate mechanical allodynia by acting on peripheral terminals of trigeminal afferents.

Red flags and secondary headache

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Background: We describe the case of a 77 years old man who was admitted to our Neurologic Clinic for a recent-onset headache appeared twenty days before, with an unremitted course. Headache was pulsating, of moderate-severe intensity located in fronto-temporal and periorbital right side. Furthermore, the patient started to present pollakiuria and nocturia one week before the admission to the hospital. The patient also referred episodes of diplopia lasting few minutes on the right lateral gaze. At the neurological examination no abnormalities emerged.

Methods: The patient underwent a brain CT scan, which showed inflammatory material completely obliterating the right sfenoidal emisinus. The case was interpreted as a secondary headache attributed to sfenoidal sinusitis. Intravenous antibiotic treatment with ceftriaxone and moxifloxacin was therefore started. After three days of antibiotic administration, diplopia became constant and cranial nerve examination showed right partial III and right VI cranial nerve palsies. Moreover, the patient started to present fever (38 grade centigrade), polyuria and polydipsia. Due to fever persistence, i.v. ceftriaxone and moxifloxacin were substituted with i.v. ampicillin, cefotaxime and metronidazol. We performed a brain MRI examination, which showed a slightly irregular enhancement in the sellar region, predominantly on the half right of the adenohypophysis, the pituitary stalk as well as the ipsilateral cavernous sinus. Laboratory tests showed plasma hyperosmolarity (>300 mosmo/L), associated with urine hypoosmolality (<300 mosm/l), suggesting a diabetes insipidus.

Results: Based on brain MRI findings and laboratory tests results a Headache attributed to hypothalamic or pituitary hyposecretion according to ICHD 3rd edition was suspected; it was confirmed by the water deprivation test. Treatment with desmopressin was thus started and in few days headache remitted, fever disappeared and plasma and urine osmolarity normalized.

Conclusion: Based on patient headache history and clinical and laboratory red flags, considering that 10% of headache could be secondary, the above case report suggests that it is mandatory do not include only CT scan in the clinical workup but rely on brain MRI and more specific laboratory tests for a correct diagnosis and more targeted treatment.

A case report on how to increase the efficacy of migraine target therapy

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Background: Monoclonal Antibodies binding Calcitonin Gene Related Peptide (CGRP) or its receptor are changing the therapeutic scenario for migraine because of their efficacy and good tolerability. However, successful migraine management cannot be reached unless the target therapy is associated with thorough consideration of comorbidities and triggers. We report an example of a patient successfully treated with a combination of migraine-specific and hormonal treatment.

Case description: We describe the case of a 32-year old woman with a medical history of polycystic ovary, polygenic hypercholesterolemia and lymphocytic colitis. She has suffered from migraine since the age of 6 years and was diagnosed with chronic migraine in 2008.
At the time of her first visit at our Headache Center in 2014 she was experiencing almost daily headache and had medication overuse. She was treated with amitriptyline and topiramate but had to stop them because of side-effects. Treatment with cinnarizine was not effective. Thereafter she started onabotulinumtoxinA showing partial improvement. In January 2019, onabulinumtoxinA was stopped and she started erenumab 70 mg. After the first two administrations, headache days were reduced from 15 to 3 per month. The 3 migraine days occurred during menstruation, were very severe, disabling, and unresponsive to triptans and antinflammatory drugs. Therefore, she was started with an extended-regimen of combined hormonal contraception. With ongoing hormonal treatment, she experienced 1-2 headache days per month which were very mild not needing treatment or when needed with quick and strong response. After 1 year of treatment, the benefits of the combination between erenumab 70 mg and extended combined hormonal contraceptives still persisted.

Conclusion: This case report highlights the importance of a comprehensive approach for optimal migraine management. In our case, we have achieved such remarkable results thanks to the combined therapy which targeted separately menstrual-cycle and chronic migraine. Further data are needed to understand the effect of the new migraine targeted treatments on menstrual attacks.

A new diary to evaluate patients' functional disability, headache trends, and pain management in a Headache Centre: an observational study project.

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Background: Headache-related functional disability (HRFD) is one of the most concerning health issues worldwide. However, the currently used instruments for the assessment of HRFD refer to long periods of time; therefore, they depend on patients' recall of the previous months or weeks. In the modern context of holistic healthcare, a more accurate measure of headache-related disability is needed to obtain a proxy measure of patients' resilience and ability to cope with their disease. Therefore, we aimed to develop a new headache diary which allow to collect with an easy visual approach daily HRFD together with attack frequency, intensity, and use of medications.

Methods: Within the nursing educational activities of our regional referral Headache Centre, we elaborated a new version of the diary (attached) to be provided to headache patients. In the diary, patients will be asked to report headache days, pain intensity (10-levels Likert scale), number of medications taken, and HRFD (3-levels scale). After the Internal Review Board approval, data from diaries will be prospectively collected during scheduled visits, along with patients' written informed consent. The association between disability and headache days, pain intensity, and number of painkillers taken will be assessed with parametrical or not parametrical tests, as needed.

Results: Expected results will outline the profile of headache patients according to their level of disability and contribute to understand the impact of headache disorders on patients' life. In particular, patients' HRFD levels will provide a proxy measure of their resilience and coping skills.

Conclusion: A detailed and quick assessment of patients' disability during headache attacks could be a valid adjunct to current patients' assessment and care, especially when considered along with headache trend and patients' strategies to manage the disease. Therefore, the awareness of the existing associations between these factors and patients' disability could improve patients' management and education, especially during nursing activities at follow-up.

v. Headache Diary

Dear patient, we ask you to fill this diary (as a calendar) to monitor your headache.

Last and first name_____

Starting date___/___/____

When an headache occurs, please write down:

- Pain **intensity** from 1 to 10, where:

1	2	3	4	5	6	7	8	9	10

Very minor pain — **Bigger pain possible**

- Add 'A' if you experienced an **aura**
- Add 'X' for each **medication** taken for the pain
- For women: add 'M' if you also have **menstruation**

- Headache **impact on daily-life** activities:

Add 'D0', if you are able to perform all daily-life activities

Add 'D1', if you are able to perform some daily-life activities

	Jan	Feb	Mar	Apr	May	June	July	Ago	Sept	Oct	Nov	Dec
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
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18												
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25												
26												

Caro paziente, ti chiediamo di compilare questo diario per tenere sotto controllo la tua cefalea.

Cognome e nome _____

Data inizio___/___/____

Nei giorni in cui hai cefalea, per favore riporta:

- **Intensità** del dolore da 1 a 10, dove:

1	2	3	4	5	6	7	8	9	10

Dolore molto lieve — **Dolore estremamente forte**

- Aggiungi 'X' per ogni farmaco **antidolorifico** usato
- Aggiungi 'A' sei hai un'**aura**
- Per le donne: aggiungi 'M' se hai le **mestruazioni**

- **Impatto della cefalea sulla funzionalità**:

Segna 'D0', se hai svolto le tue usuali attività

Segna 'D1', se le tue attività sono state limitate o compromesse

	Gen	Feb	Mar	Apr	Mag	Giu	Lug	Ago	Set	Ott	Nov	Dic
1												
2												
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TRPA1/NOX in the soma of trigeminal ganglion neurons mediates migraine-related pain of glyceryl trinitrate (GTN) in mice

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Background: GTN causes prolonged mechanical allodynia in rodents, which temporally correlates with delayed GTN-evoked migraine attacks in patients. Several mechanisms have been proposed to explain GTN-evoked headaches, including degranulation of meningeal mast cells, delayed meningeal inflammation sustained by induction of nitric oxide (NO) synthase and prolonged NO generation, and the release of calcitonin gene-related peptide (CGRP), a primary migraine neuropeptide. GTN also generates oxidative stress.

Methods: In vivo assessment of periorbital mechanical allodynia after GNT and systemic and local treatment with different antagonists.

Results: We showed that systemic, intrathecal or local administration of selective enzyme inhibitors revealed that NO, liberated from the parent drug by aldehyde dehydrogenase-2, initiates but does not maintain allodynia. The central and the final phases of allodynia were respectively associated with generation of reactive oxygen and carbonyl species within the trigeminal ganglion which target TRPA1. Knockdown of neuronal TRPA1 by intrathecally administered antisense oligonucleotide and selective deletion of TRPA1 from sensory neurons in *Advillin-Cre;Trpa1$^{fl/fl}$* mice revealed that NO-dependent oxidative and carbonylic stress generation is due to TRPA1 stimulation, and resultant NADPH oxidase-1 (NOX1) and NOX2 activation in the soma of trigeminal ganglion neurons. Early periorbital vasodilatation evoked by GTN was attenuated by aldehyde dehydrogenase-2 inhibition but was unaffected by TRPA1 blockade. Antagonists of the CGRP receptor did not affect the vasodilatation but partially inhibited allodynia.

Conclusion: Although both periorbital allodynia and vasodilatation evoked by GTN are initiated by NO, they are temporally and mechanistically distinct. While vasodilatation is due to a direct NO action in the vascular smooth muscle, allodynia is a neuronal phenomenon mediated by TRPA1 activation and ensuing oxidative stress. The autocrine pathway, sustained by TRPA1 and NOX1/2 within neuronal cell bodies of trigeminal ganglia, may sensitise meningeal nociceptors and second order trigeminal neurons to elicit periorbital allodynia, and could be of relevance for migraine-like headaches evoked by GTN in humans.

Efficacy of Erenumab treatment in migraine patients with depressive symptoms

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Background: Depression is a common comorbidity in migraine. The aim of the present study was to evaluate the outcome of erenumab treatment in migraine patients with depressive symptoms as compared with those without.

Methods: We included in our study all patients with episodic or chronic migraine treated with erenumab. Patients were considered positive for depressive symptoms if they were experiencing, at baseline, a depressed mood together with ≥3 of the following symptoms: diminished interest or pleasure in their daily activities, significant weight loss, fatigue, feelings of worthlessness, and diminished ability to concentrate [1]. We evaluated patient outcomes at 3 months of treatment. Beck Depression Inventory-II (BDI-II) [2] was used to evaluate the evolution of depressive symptoms after 3 months of treatment.

Results: Among the included 66 patients with migraine on treatment with erenumab, 30 (45.5%) had depressive symptoms at baseline. There were no significant differences between the characteristics of two groups of patients with and without depressive symptoms.
At the third dose of erenumab, patients with depressive symptoms showed a significant decrease of MMDs (20, interquartile range [IQR] 15-25, vs 10, IQR 5-20, p=0.001) and analgesic use days (13, IQR 8–24, vs 8, IQR 1–11; P=0.009) as compared to baseline. There was no difference in the proportion of patients who achieved at least ≥50% reduction in MMD between patients with or without depressive symptoms (16 [53.3%], vs 24 [66.7%], p=0.270).
At third dose of erenumab, there was a non significant improvement in depressive symptoms as compared to baseline (median BDI 9, IQR 7.5-12.5, vs 6, IQR 5-12.5; p=0.397).

Conclusion: Erenumab confirms to be effective in patients with depressive symptoms. Depression should not be an exclusion criterion, and it should not be considered a poor prognostic factor for erenumab treatment.

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Efficacy of anaesthetic block of the greater occipital nerve in migraine and cluster headache: Results from a tertiary Headache Center

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Background: The Greater occipital nerve anaesthetic block (GONB) consists on the local administration of lidocaine and steroids. It is considered a preventive or rescue therapy for several headache disorders, including chronic migraine (CM) and cluster headache. We aimed at evaluating the efficacy of this treatment in a retrospective case series.

Methods: We included in our study consecutive patients treated with GONB from May 2019 to January 2020. GONB was performed in all patients bilaterally with a solution of metilprednisolone and lidocaine. Injections were repeated every month for three months. The efficacy of GONB was evaluated in terms of reduction of intensity (measured on a scale from 1 to 10) and frequency of the episodes (number of monthly headache days for migraine and number of daily episodes for cluster headache).

Results: During the study period, 18 patients were treated with GONB. In the 13 patients with CM, after the first course, four patients reported an excellent response (75% reduction of intensity or frequency of attacks), which persisted after the following courses. Three patients had a good response (50% reduction of intensity or frequency of attacks). Six did not get any benefit; among them one patient improved after the second course.
In the 5 patients with cluster headache, in 3 patients, there was pain relief and complete remission of the cluster within 24 hours from the first administration. One patient reported no efficacy at all and discontinued the treatment.
Notably, the unique side effects reported were hair loss and transient local pain, but there were not severe adverse events.

Conclusion: In our study GONB resulted to be effective and well-tolerated. Further studies with larger population and better-defined outcomes are required to confirm these results.

Contribution of right-to-left shunt to migraine features

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Background: Migraine is associated with a higher prevalence of right-to-left shunt (RLS) compared with the general population. However, the nature of this association remain elusive. RLS may trigger some migraine attacks but the exact nature of this association remain unclear. We aimed to assess the impact of RLS on migraine features.

Methods: We included consecutive patients with migraine referring to our tertiary Headache Center. For each patient, we recorded sex, age, and vascular risk factors, together with migraine characteristics including frequency, aura, and age at onset. Each patient underwent a transcranial Doppler examination to detect RLS in basal conditions and under Valsalva maneuver. We quantified RLS as absent (no bubbles), mild (<10 bubbles), moderate (10-20 bubbles), or severe (shower effect). We performed Spearman's correlation tests among the collected variables.

Results: We included 78 subjects, 87.2% were female, with a median age of 45 (IQR 34-50) years and a median age at migraine onset of 18 (IQR 14-25) years. 36 patients had RLS, which was mild in 15, moderate in 10 and severe in 11. We did not find any difference in migraine characteristics (migraine type, presence of aura, frequency of attacks severity of attacks, age at migraine onset) according to RLS presence and severity. Only, in patients with CM there was a trend towards a negative correlation between age at migraine onset and monthly frequency (R= -0.225; P=0.071).

Conclusion: According to our data, RLS is highly prevalent in patients with migraine. However, RLS does not seem to affect migraine characteristics. Advanced functional studies are needed to clarify the role of RLS in migraine.

The Clinical experience of Perugia Headache Center

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Background: Monoclonal antibodies acting on the calcitonin gene-related peptide or on its receptor are new drugs to prevent migraine. Therefore, we focused on CGRP target therapy , in particulary Erenumab (anti-CGRP receptor); Our study'aim is to demostrate it's clinical effectiveness. This preliminary study included 22 patients with chronic migraine (CM, day per month 19.4± 4.8), 17 of them with MO (NSAIDs, combination analgesics, triptans) and 16 patients with high frequency episodic migraine (HFEM, day per month 8.8± 2.7). All of these patients underwent erenumab treatment 70 mg s.c., monthly; we evaluated the efficacy of this therapy at three months, comparing the days of headache per month before and after treatment, using specific scales.

Methods: We evaluated the erenumab efficacy for the first three months by using two scales, MIDAS and HIT-6 score. At balseline, we have administered these two scales and headaches diary to our patients.

Results: In the group of CM patients, we recorded at the baseline MIDAS 35.4± 10.6 values and HIT-6 score 78.7±6.7 values; MIDAS values of HFEM patients were 17.1±0.6, those of HIT-6 were: 59.8±5.3; a significant reduction was detected for both groups in headache days per months at the 3rd month of treatment (-5.6 for CM patients and 4.2 for HFEM ones); we have obtained MIDAS total scores improvement in both patient groups at the 3rd month, −19.8 ± 7.5 for CM patients and − 5.5 ± 0.8 for HFEM ones. Significant mean changes in HIT6 score was described in both patients groups: - 6.1 for CM patients −5.6 for HFEM ones.

Conclusion: Our preliminary datas obtained in a limitated group of patients supports erenumab effectiveness in clinical practice in the first 3 months of therapy, above all in CM population.