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ABSTRACTS

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Classification and pathogenesis

Migraine in children under 6 years of age: a long-term follow-up study

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Background: Migraine received poor attention in very young children, specially under the age of 6. Early starting of migraine is frequently associated with higher frequency of attacks and worse clinical picture with respect to later onset, and seems predictive for less favorable outcome in later ages. We report here the longest follow-up study in a population of children presenting with migraine under the age of 6.
Methods: We followed-up 74 children under the age of 6, originally referred for headache to our department between 1997 and 2003 (T0). The study was carried out between October 2016 and March 2018 and consisted of 2 steps: patients' search and clinical interview. Step 1 was achieved through a phone contact directly with the patient or with family doctors to find the subjects of the original cohort and to know basics about the clinical outcome. Then, subjects willing to participate, underwent a clinical interview to evaluate more in detail their actual headache condition (T1). Headache diagnoses were made according to the IHS criteria.
Results: 23/74 patients, 31% of the original cohort, were found at follow-up in a period ranging between 15 to 21 years after the first visit. Seven of them were headache free. The remaining 16 patients had migraine. 13 of these showed persistent migraine disease since T0, while the remaining 3, previously affected by other headaches had changed to migraine. In the migraine group, the localization of pain changed in 75% of the subjects, 11/16 (68.7%) had allodynia and 9/16 (56.25%) had cranial autonomic symptoms
Conclusions: Our results suggest that the onset of migraine at very young age represents a bad prognostic factor for persistence of the disease at later ages. Some clinical features may change during clinical course, and the active persistence of the disorder may lead to an increase in allodynia. Moreover, the occurrence of cranial autonomic symptoms in preschooler migraineurs may be predictive of disease persistence.

Is pediatric headache increasing in emergency department? An Italian experience

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Objective: The aim of this study was to analyze the change in the prevalence of children with headache presenting to the emergency department over a period of ten years.
Methods: The total number of accesses to the emergency department of the Children's Hospital G. Cristina in Palermo was retrospectively analyzed in the two-year period 2009-2010 and in the two-year period 2017-2018 in order to examine the differences over a period of 10 years. The percentage of accesses for headache and the number of specialistic assessments and of imaging procedures (computed tomography) have been analyzed in the two periods examined.
Results: The total accesses to the emergency department have decreased from 55,616 to 50,096 (-10%) between the two-year periods considered while the number of accesses for headache has increased by around 63.56% ($p<0.0001$). The highest increase occurred in the age groups of 7-13 and 14-17 (respectively 69.23% and 52.12%). The increase is mainly due to the entry of probable primary headaches or not classifiable headaches (about 67% of the total increase), especially for the age group 7-13 and for the group 14-17. At the same time the number of child neuropsychiatric assessments and the number of computed tomography have remarkably increased.
Conclusions: The significant increase of accesses for pediatric headaches is probably due to the limited efficacy of the Italian and international guidelines and of the educational strategies, underlying the existing connection difficulties between the primary care network and hospitals. It is also important to reflect on the use of red flags because many of them probably have poor sensitivity and specificity. This results in an avoidable overcrowding of the emergency department for useless accesses, in an increase of unnecessary assessments and procedures and, in the end, in an increase of health costs.

Migraine and insomnia: observational study at the headache ambulatory Cassino/Sora

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Background: Migraine and insomnia are often associated. Some Authors have reported that a percentage varying from 48 to 74% of migraine subjects shows sleep disorders in comorbidity. The literature shows that this comorbidity is bidirectional, hypothesizing common pathogenetic mechanisms between the two disorders. Indeed, sleep loss acts as a trigger factor on migraine attack and vice versa, subjects with migraine refer to insomnia or non-restorative sleep. The aim of our study was to evaluate the presence of sleep disorders in subjects with migraine afferent to the Cassino/Sora Headache Ambulatory.
Materials and method: The subjects at the first visit to the Cassino/Sora Headache Ambulatory from 01.01.2018 to 31.12.2018 were consecutively evaluated, through an interview about sleep. Subjects already in drug treatment were excluded in order to avoid bias due to the therapy itself.
Results: Two hundred and eighteen subjects were recruited, 53 Male and 165 Female, afferent to the Ambulatory as first visit. Between subjects, 142 met the diagnostic criteria for migraine and 76 were suffering from non-migraine headache. In the first group, 42% of subjects reported insomnia, with an average amount of hours of sleep per night equal to 6.3 (ds + 2.1), while among non-migraine sufferers, 31% of subjects reported insomnia, with a statistically significant difference between the two groups ($p<0.003$) and with an average of hours of sleep equal to 7.3 (ds + 1.85). Furthermore, subjects with migraine were divided into subjects with chronic migraine and those with episodic migraine. The evaluation of the presence of sleep disorders among these last two groups did not show statistically significant differences.
Conclusions: In our study, in agreement with the data present in the literature, it emerged that sleep disorders are more frequent in subjects with migraine than in non-migraine subjects. The evaluation of sleep alterations in subjects with migraine is important, since these represent a modifiable trigger factor in migraine attacks and according to some Authors they are involved in the progression of episodic in to chronic migraine.

A prospective study on osmophobia in migraine vs tension-type headache in a large series of attacks

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Background: In literature Osmophobia (Os) is reported as a specific migrainous symptom, with prevalence up to 95%. Despite the International Classification of Headache Disorders 2nd edition proposal of including Os as additional accompanying symptom, it disappeared from the ICHD-3rd edition.
Methods: In order to ascertain Os prevalence and evaluate its diagnostic value in the differential diagnosis among primary headaches, we conducted a prospective study on 193 patients suffering from migraine without aura (MO), migraine with aura (MA), episodic tension-type headache (ETTH) or a combination of them. A total of 512 attacks was studied. We started with a retrospective interview focused on Os and its clinical features; then each patient was asked to describe in detail Os, when present, in the following 4 attacks through a structured questionnaire.
Results: According to prospective data, 45.7% of MO attacks were associated with Os, while no ETTH attack was characterized by intolerance to odours. 67.2% of MO patients (86/128) reported Os in at least 1/4 attacks. Among MO attacks, Os-associated headaches (234/512) showed more typically migrainous features respect to the attacks without Os. An overt stereotypy of the annoying smells (perfumes, cigarette smoke, food in this order) has been found in 71% of cases. Considering the accompanying symptoms composing criterion D of ICHD3, no one keeps an absolute specificity for MO diagnosis, as Os does. In order to evaluate the opportunity of its inclusion among diagnostic criteria, the associations photophobia-Os and phonophobia-Os showed the best available diagnostic accuracy respect to other possible couple of associated symptoms, with good sensibility (74.8% and 74.2% respectively), high specificity (88.6% and 87.1% respectively) and very high positive predictive value (96.5% and 96.0% respectively). Interestingly, Os prevalence increases from 27.9 to 96.9% in parallel with the increase of the number of accompanying symptoms reported in criterion D. In 4.3% of MO attacks (22/512), Os was in association with just one between photophobia and phonophobia; in 4.7% of MO attacks (24/512) it appears with no other accompanying symptoms. With specific attention to these particular cases, the inclusion of Os in the criterion D, would increase diagnostic sensitivity of ICHD3 criteria for migraine of 9.0%.
Conclusions: Osmophobia is a specific clinical marker of migraine, easy to ascertain and able to disentangle the sometimes challenging differential diagnosis between MO and ETTH. We strongly recommend its inclusion among the diagnostic criteria for migraine, as it increases sensitivity, keeping an absolute specificity.

Is pediatric medication overuse headache really due to medication overuse?

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Background: Medication overuse headache (MOH) is a headache occurring on ≥15 days/month in patients with pre-existing primary headache and developing as a consequence of regular overuse of symptomatic medication. Aim of this study was to analyze the clinical features of pediatric MOH, with particular emphasis on the applicability of ICHD-3 criteria.
Method: We retrospectively analyzed clinical data of pediatric patients with MOH; the clinical diagnosis was verified according to ICHD-3 criteria. Although no longer included in the diagnostic criteria, we analyzed how many patients presented a clinical benefit after discontinuation of overused medication.
Results: We identified 42 subjects diagnosed with MOH (31 F, 11 M), aged 8-17 years (mean 13.4 years). They all presented with chronic migraine, 9% fulfilled a diagnosis of migraine with aura. Photo- and photophobia were present in 81% of patients, nausea/vomiting in 30%, dizziness in 18%. ICHD-3 criterion A was fulfilled by 40/42 patients (95%), criterion B by 35/42 (83%), and criterion C by 40/42 (95%). Nineteen patients (45%) did not present an improvement of headache after medication overuse cessation.
Conclusions: The old criteria required a development or marked worsening of the headache during medication overuse, and a resolution within 2 months after medication withdrawal. Both these criteria disappeared in ICHD-3. Our data show that, without the necessity of demonstrating a clear and direct correlation with abuse and discontinuation of symptomatic medications, a definite diagnosis can be achieved in a high rate of patients with a clinical suspicion of MOH. Nearly half of patients with MOH did not improve after medication overuse cessation, thus raising the doubt of a true causal relationship between medication overuse and chronic headache. A high rate of patients with a definite diagnosis of MOH according to new criteria continued to present a high frequency headache despite the withdrawal of overuse.

Cluster-migraine: neither probable cluster headache nor probable migraine

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Background: Cluster headache (CH) is a well definite primary headache. When the attacks fulfil all but one of criteria A-D for CH, established by the International Classification of Headache Disorders, 3rd edition (ICHD-3), probable CH should be diagnosed. The patients with this headache present one of the following conditions: 1) attacks lasting >180 minutes, 2) attacks without local autonomic signs and restlessness, 3) sporadic (less than one every other day) attacks. In the past "cluster-migraine" was considered an atypical variant of CH, but this entity was never categorized, not being sufficiently validated.
Methods: For the last 20 years we have observed 306 patients with CH. Out of these cases, 33 (19 males and 14 females) could not fulfil all criteria for CH. All the patients have been followed-up for at least 5 years.
Results: In this population we could distinguish four different subgroups. Three subgroups could be diagnosed with CH except for: 1) duration >3 hours, ranging 4-8 hours (6 cases), 2) absence of local autonomic signs and restlessness (5 cases), 3) sporadic attacks, with no cluster periodicity (10 cases). We could also identify a fourth subgroup of 12 patients without the typical CH temporal pattern and attacks duration borderline between CH and migraine without aura (MO), usually lasting 3-5 hours. Moreover, the coexistence of MO and CH was noted in 8 cases.
Discussion: The first subgroup overlaps with probable MO. Criteria are not fully met and patients are labelled as probable MO or probable CH, either of which could have features of the other. The second and third subgroups meet criteria for probable CH. The fourth subgroup does not fulfil criteria either for probable CH or probable MO, therefore the old

definition of "cluster-migraine" may be still appropriate, even if this term might be considered a regression to the time when CH was considered a variant of migraine. Interestingly, three patients with "cluster-migraine" evolved into a typical CH over time.
Conclusions: Patients sometimes present with clinical scenarios having characteristics of both MO and CH, but either do not fully meet ICHD-3 criteria for any of the two disorders or have no sufficient symptoms and signs to allow both diagnoses to be present. These occasions provide diagnostic challenges and account for the controversial form of cluster-migraine. Patients with symptoms overlapping CH and MO likely reflect the inherent clinical variability in each of these two disorders, rather than distinct diagnostic entities.

A simply questionnaire to quickly diagnose migraine with aura for non-headache specialists

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Background: Migraine is a primary headache mostly occurring in young women that are also childbearing potential. In particular, migraine with aura has been linked with a higher risk of cardiovascular events, especially if associated with smoke and/or estroprogestinic assumption. Women with a history of migraine with aura may have a wide range of complications during pregnancy and puerperium, like a higher risk of preclampsia, venous tromboembolism, stroke and low birth weight. So, a correct and early diagnosis of migraine is crucial to prevent the above- mentioned events. The aim of this study is to test a simple questionnaire for non-headache specialists for helping them to get a correct diagnosis of migraine with aura.
Methods: A 32-items questionnaire exploring above the gynecologic health status also headache and associates symptoms. A total of 240 patients filled the questionnaire and 176 of them suffered of headache. A total of 100 women with headache were randomly selected by a block randomization list, and, further contacted by phone to perform a free visit to the Headache Center, of these 13 subjects refused to participate.
Results: Migraine with aura was diagnosed in 7/87 (8.0%) of subjects, whilst migraine without aura in 58/87 (66.7%). Migraine with and without aura was complained by 5/87 (5.7%) subjects and other types of headache (mostly tension-type headache) were present in 17/87 (19.5%) subjects. If 2 symptoms of migraine were present, questionnaire's sensitivity was: 85.7% (95% CI 75.3% to 92.9%), specificity was 52.9% (95% CI 27.8% to 77.0%), giving a positive predictive value of 88.2% (95% CI 81.8% to 92.6%). The accuracy was 79.3% (95% CI 69.3% to 87.3%). The presence of 3 migraine symptoms gave a sensitivity of 52.12% (95% CI 39.8% to 64.4%), a specificity of 83.3% (95% CI 58.6% to 96.4%) and a positive predictive value of 92.3% (95% CI 80.7% to 97.2%). The accuracy was 58.6% (47.6% to 69.1%). For the diagnosis of aura, questionnaire gave a sensitivity of 100.0% (95% CI 69.2% to 100.0%), a specificity of 45.5 % (95% CI 16.8% to 76.6%), a positive predictive value of 62.5% (95% CI 49.3% to 74.1%), and a negative predictive value of 100%, and an accuracy of 71.4% (95% CI 47.8% to 88.7%).
Conclusions: The questionnaire seems to be useful for an early diagnose of migraine with aura and for helping a non-headache specialists to prevent the associated complications.

A 1-year epidemiological survey on headache patients with Alice in Wonderland Syndrome: prevalence, comorbidities and clinical profile

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Background: Alice in Wonderland Syndrome (AIWS) is a complex disorder of sensory misperception, mostly involving visual and somatosensory integration. AIWS has been associated with several medical conditions, although migraine is the most common cause in adults. However, the reason behind this association is not yet clear. As the first step to better defining this association, we performed an epidemiological survey with a longitudinal follow-up to understand epidemiological and clinical overlap between the two conditions.
Material and methods: Over the course of 1 year, all the first-visit outpatients of our Tertiary Headache Centre were consecutively screened for AIWS symptoms by means of a custom-made questionnaire. Patients answering positively to the questionnaire were double-checked with medical interview by headache specialist physicians trained in AIWS. Medical investigations and migraine acute and preventive therapy were chosen according to migraine history (regardless AIWS). Headache patients who also had AIWS were clinically followed up for other 12 months.
Results: During 1 year, 31 (18%) patients were confirmed to have experienced at least a lifetime AIWS episode. All AIWS patients were diagnosed with migraine with aura (according to ICHD-3) all but 4 had an episodic form. Mean age was 40.9 years and the female/male proportion was 26/5; 23 (74%) patients presented only visual disturbances as AIWS symptoms, while eight (26%) had visual-somatosensory AIWS symptoms. No patient in our sample had only somatosensory AIWS symptoms. In all but 2 patients AIWS symptoms occurred only during migraine with aura attacks.
During the follow-up, 9 patients dropped out. In 16 out of the 22 left, we prescribed preventive treatments for migraine (e.g antiepileptics, β-blockers and tricyclic antidepressants): half of these patients reported no new episode of AIWS, while the others referred at least a decrease in frequency. In the 6 patients in whom we did not introduce preventive therapy due to a low frequency of attacks, 4 were still experiencing AIWS symptoms.
Conclusions: In migraine, AIWS prevalence seems to be higher than expected. Moreover, AIWS is strongly associated to migraine with aura, mostly during the migraine with aura attack itself, suggesting that AIWS seems to depend somehow on aura mechanisms. For this reason, it is not surprising that, contrary to literature data showing the existence of AIWS symptoms involving only somatosensory functions, migraine patients had also disturbances of visual cortices, where cortical spreading depression principally occurs. Due to this association, it seems sound that preventive therapy for migraine also reduced AIWS symptoms.

Qualitative and quantitative relationships between right-to-left shunt and white matter brain hyperintensities in patients with migraine

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Background: Migraine is associated with a higher prevalence of right-to-left shunt (RLS) and white matter brain MRI hyperintensities (WMHs) compared with the general population. However, the relationship between

the two conditions and the modifying effect of aura, age, and migraine frequency are unclear. We aimed to assess the qualitative and quantitative relationships between RLS and WMHs in a group of subjects with episodic (EM) or chronic migraine (CM), with (MA) or without aura (MO).
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 3 Tesla brain MRI scan and a transcranial Doppler ultrasonogram to detect RLS, quantified as mild, moderate, or severe. WMH burden was quantified by lesion counting and by the Fazekas score. We performed the chi squared or Spearman's correlation tests.
Results: We included 77 subjects, 85.7% female, with a mean age of 43.4 ±9.3 years and a mean age at migraine onset of 20.7±8.8 years. Thirty-five (45.5%) patients had RLS, 23 (65.7%) in basal conditions and 12 (23.3%) only after the Valsalva maneuver, while 27 (35.1%) had WMHs. We found no association between the presence of RLS and that of WMHs (P=0.657); this result was similar within patients with EM and CM, MA and MO. We found a negative correlation between age at migraine onset and basal RLS severity in patients with EM (Rho= -0.540; P=0.031) and in those with MA (Rho= -0.714, P=0.019) but not in those with CM or MO. We also found a positive correlation between age and the number of WMHs (Rho=0.380; P=0.001) or the Fazekas' score (Rho=0.297; P=0.009), while no quantitative correlation was found between RLS severity and the number of WMHs or the Fazekas' score. The positive correlation between age and the number of WMHs regarded CM (Rho=0.380, P=0.038), EM (Rho=0.328, P=0.039), MA (Rho=0.548, P=0.019), and MO (Rho=0.360, P=0.009). Migraine frequency was positively correlated with RLS after the Valsalva maneuver only in patients with MO (Rho=0.448; P=0.032).
Conclusions: According to our data, RLS and WMHs, both highly prevalent in patients with migraine but are not associated. Patients with higher RLS severity had an earlier onset of EM or MA and an increased frequency of MO, while WMH burden increased with age.

Aeroplane travel trigeminal neuralgia. Description of a case

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Background: Headache attributed to aeroplane travel (HAAT) is a recently identified headache occurring during and caused by aeroplane travel. It is characterized by severe, unilateral, orbitofrontal pain, of jabbing or stabbing quality, occurring predominantly during the descent phase of a plane and promptly remitting after landing. It is generally believed to be caused by an imbalance between intrasinus and external air pressures. Here we describe a HAAT with clinical features indistinguishable from those of idiopathic trigeminal neuralgia (TN).
Case report: During the descent phase of a flight a 18-year-old female complained of a very severe (10 on a 1-10 scale) tightening pain in the right zygomatic and maxillary regions. No accompanying symptoms were noted. The pressing pain lasted about 10 minutes, ceasing after landing, but recurrent brief electric shock-like pains in the same region started immediately afterwards. Pain lasted 2-3 minutes and was extremely severe, recurring every few minutes. No neurovegetative symptoms were present. The attacks were always spontaneous and could not be precipitated by innocuous stimuli. A low-grade, pressing pain persisted in between pain paroxysms. Naproxen sodium 550 mg and paracetamol 1,000 mg were only modestly effective in reducing, but not abolishing, painful paroxysms for a couple of hours. After 2 days the attacks resolved spontaneously. Neurological examination was normal as well as 3-T brain MRI and paranasal sinus CT. A second episode with similar characteristics occurred during another flight, beginning just before landing and continuing for three days afterwards.
Conclusions: HAAT typically begins during the descent phase of a flight and lasts less than 30 minutes. In few cases, headache persisted for days or even for two weeks, but it was described as a continuous mild pain, pressing in nature. To our knowledge, this is the first case of HAAT with clinical features closely resembling those of TN. Apart from its clinical interest, it may open new vistas about the pathophysiology of this rare type of headache.

Chronic daily headache in children and adolescents: retrospective study in a tertiary Pediatric Headache Centre

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Background: Chronic Daily Headache (CDH) is defined as headache occurring at least 4 hours per day, 15 days or more a month, for longer than 3 months (ICHD III). New daily-persistent headache (NDPH), a variety of CDH, is daily unremitting headache essentially since onset, in patients without significant prior history of headache. There are few studies about CDH in the pediatric age; the reported prevalence ranged from 0.9% to 7.8%, and it is higher in girls than boys. The pathogenesis of CDH in children is multifactorial and involves genetic, familial, cultural and environmental factors. The aim of this study was to describe epidemiological features of a pediatric population with CDH.
Methods: All the patients referred as first visit to the Pediatric Headache Centre (PHC) of the Regina Margherita Children's Hospital of Turin, Italy, between January 2015 and October 2017 were retrospectively reviewed. We screened the medical record databases of our PHC. Descriptive analysis is provided.
Results: Seven hundred and nineteen patients had their first visit in our PHC during the study period (median age: 11 years, range 2-18; females: 51%). Overall, the diagnoses were migraine (55.0%), not classified (13.6%), mixed headache (13.5%), tension-type headache (9.1%) and CHD (8.2%). The mean age of children with CDH was 11 years (range 5-18); 38 were females (16 of them had already had menarche) and 21 males. The subtypes of CDH were: NPDH (56.0%), chronic migraine (16.9%), mixed forms (10.0%), chronic tension-type headache (8.5%), not classified (5.0%). Most children (91.0%) with CDH had familiar history for headache; 44.0% had sleep disorders. Almost all patients with CDH needed prophylactic treatment: 20% with benefit, 10% not improved, 70% were missed at follow-up; 44% were referred to a neuropsychiatrician and 69.2% of them continued this follow-up.
Conclusions: CDH is not rare in the pediatric age; in our population, its prevalence was similar to previous reports and the most frequent subtypes was NPDH. The treatment required multimodal approach including both pharmacological and non-pharmacological therapies and collaboration with neuropsychiatric specialists.

Epidemiology, clinical features and family history for major cardiovascular events in children with migraine: a 12-year retrospective study

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Background: We report a study that analyze epidemiology, clinical features and family history for cardiovascular events in children with migraine.
Methods: A retrospective study was performed over 12 years. The hospital record databases were screened for migraine with (MA) or without aura (MO), based on ICHD-II (until 2013) and III beta criteria. Descriptive and multivariate analysis is provided; significance at $p<0.05$.
Results: Migraine was diagnosed in 851 children (25.3% MA, 74.7% MO), mainly between 9 and 14 years. Children with MA were significantly older than those with MO (mean (SD) age: 12.0 (2.3) and 9.8 (2.4) years, respectively) ($p<0.001$). After stratification into 5 age-groups, we observed that females with MA prevailed significantly in the group 12-14 years ($p=0.003$), while males with MO prevailed significantly in the group 9-11 years ($p=0.005$). In both groups, the attacks were usually severe, infrequent (≤3/month), and lasting <2 hours; nausea/vomiting, photophobia, and phonophobia were more frequent in MO. Visual auras were the most common occurrence (87.4%). Family history of headache was reported in 91.5% children with MA and 95.2% with MO. Family history for cerebral ischemic events <50 years was significantly more reported by children with MA (12.9%) than with MO (5.0%) ($p<0.001$) and the control group of healthy children (6.3%) ($p=0.012$). The prevalence of family history for deep venous thrombosis (DVT) was significantly higher in children with MA (4.5%) than in those with MO (1.8%) ($p=0.038$).
Comparing family history for stroke and transitory ischemic attack, we observed moderately increased risk in MA vs MO (Odds Ratio: 2.8; confidence interval: 1.62-4.8) and vs control group (Odds Ratio: 3.3; confidence interval: 1.6-6.5). Moreover, comparing family history for DVT we observed moderately increased risk for MA (Odds Ratio: 2.5 confidence interval: 1.02-6.13).
Conclusions: We describe the characteristics of pediatric migraine, showing a likely significant loss of diagnoses using ICHD-III beta criteria, due to duration limits. Children with MA are older and more frequently female than those with MO. Anyway, MO occurs more commonly and shows more frequent attacks and a higher prevalence of associated symptoms. Migraine may be a risk factor to develop ischemic stroke in young adults. In our study, we observed that family history for cerebral ischemic events ≤50 years leads to significantly increased risk of developing MA. Further studies are needed to explore the mechanism underneath this association.

Gender differences in the clinical features of cluster headache: results from a single-center study

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Background: Cluster headache (CH) is the most severe primary headache disorder. The disease has a prevalence of around 0.1% of the general population, and its onset can occur at almost any age. CH was historically considered to have a male preponderance, with a high male-to-female ratio. However, recent studies observed that there is a downward trend in male preponderance. Clinical features are generally reported to be similar in both genders. The aim of our study was to review our large single-center series of CH patients that were followed in a period of about 10 years in our Neurology Department, in order to analyse demographic, epidemiological and clinical features of the disease.
Methods: One hundred and ninety-seven patients with cluster headache (155 males and 42 females, mean age± SD: 43.8±12.1 years) were recruited for the study at the Department of Neuroscience, University of Torino, Italy. CH diagnosis was performed according to the ICHD-III criteria. Demographic factors, clinical characteristics, comorbid medical conditions, family history, triggers, and smoking history were collected according to a standardized questionnaire.
Results: In our sample, the male-to-female ratio was 3.7. No difference in smoking history was found between females and males. Age at onset of CH did not differ from females and males (27.4±12.05 yrs vs 25.0±9.55 yrs, $p=0.19$). Woman cluster headache sufferers had a lower number of attacks a day in respect to men ($p=0.03$), and less nocturnal attacks ($p=0.04$). Circadian periodicity for CH is less present in females in respect to males ($p=0.01$). Interestingly, women were significantly more likely to experience during a CH attack concomitant symptoms not included in the diagnostic criteria for CH, as nausea ($p=0.001$) and photo/phonophobia ($p=0.02$). For acute treatment, no significant gender differences were observed. Among the comorbid conditions, female CH sufferers were significantly more likely to experience depression and insomnia than males ($p=0.02$ and $p=0.03$, respectively).
Conclusions: This study confirms the presence of gender-related differences in the clinical characteristics of CH. Notably, women were significantly more likely to experience also nausea and photo/phonophobia during a CH attack. Thence, CH could be under and misdiagnosed in women also for the presence of concomitant symptoms not included in the diagnostic criteria for CH, that could resemble migraine. Neurobiology mechanisms involved in these gender-related differences of CH characteristics need further studies.

Occupational risk factors and impact on job performance of primary headache among staff of a Roman Hospital: a case-control study

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Background: Primary headaches account for 90% of all the forms of headache. The disease is characterized by high occurrence in the working-age population and by significant impact in countries with high economic and social development. In an occupational setting, several physical, psycho-social or organizational circumstances are known to cause the onset of attacks in workers who already suffer from primary headache. To date, epidemiological data on the prevalence of headache in hospital workers in Rome are lacking. We therefore performed a study to assess the prevalence of primary headache, and the occupational factors associated with a headache attack among medical and paramedical staff of the Policlinico Tor Vergata in Rome. In addition, we evaluated the impact of loss of performance due to absenteeism and presenteeism caused by headache disorders.
Methods: Four hundred and seven patients were consecutively interviewed from the Headache Center and Department of Occupational Medicine of the Policlinico Tor Vergata. Participants filled out a structured questionnaire to gather demographic and socioeconomic data, headache characteristics over the previous year, and occupation-related factors. The demographic and headache profile sections of the questionnaire were the same items as used in other epidemiological studies and were validated for headache assessment and diagnosis in the general population. Data were processed and analysed using MATLAB software. Multivariate logistic regression was applied to identify odd ratios with 95% confidence intervals for different types of headache, according to social-demographic characteristics. Statistical significance was set at $p < 0.05$.
Results: The form of primary headache with higher prevalence was represented by migraine without aura (51.5% of all headache workers)

followed by tension-type headache (42.5%) and by migraine with aura (6%). A positive family history was found in 60% of patients and many of them had a disease duration longer than 5 years. Multivariate analysis showed that female sex, smoking, prolonged use of display screen and acoustic discomfort were a statistically significant risk factor for migraine; job satisfaction seemed to have a protective role. The probability of having a severe impact of the headache on daily life was associated with the increase of frequency attack and pain intensity, correlating with reduced work performance and more absenteeism.

Conclusions: Primary headache is very common but generally neglected disorder. It is a remarkably disabling condition and occupational factors may play an important role. Awareness and avoidance of trigger factors can not only decrease the frequency of headache but also reduce the possibility of chronic headache and medication overuse, guaranteeing the working health of workers and thus improve their output.

Allopregnanolone serum levels in female migraineurs

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Background: Migraine and epilepsy are similar brain disorders in many aspects and for both, a neuronal hyperexcitability has been hypothesized. Cyclic changes in ovarian hormones are involved in exacerbating both migraine and epilepsy during perimenstrual period, leading to menstrually-related migraine and catamenial epilepsy, respectively. Ovarian hormones and derived neurosteroids can regulate important functions in neurons and glial cells in the brain; in particular, progesterone reduces seizure susceptibility partly through its conversion to allopregnanolone, a potent positive allosteric modulator of the GABA-A receptor [1]. In spite of their neuroprotective potential [2], the role of neurosteroids in migraine has not been thoroughly investigated. Therefore, we determined serum levels of testosterone, progesterone and allopregnanolone in three groups: women suffering from menstrually-related migraine (n=30), post-menopausal women suffering from migraine without aura (n=30) and non-headache control females (n=20).

Methods: The enrolled migraineurs were patients afferent to the Headache Centre of Modena University Hospital; the control females were friends or relatives of the above patients. All women gave their written consent and the Ethical Committee of the Province of Modena approved the study. The fasting blood specimens were processed and then analyzed by HPLC-ESI-MS/MS.

Results: Testosterone and progesterone levels were significantly higher in both non-headache control females and women suffering from menstrually-related migraine compared to post-menopausal women suffering from migraine without aura ($P<0.005$, t-test). Conversely, serum allopregnanolone levels were significantly lower in both women suffering from menstrually-related migraine (0.051 ng/mL; SD: 0.018) and post-menopausal women suffering from migraine without aura (0.025 ng/mL; SD: 0.013), compared to non-headache control females (0.078 ng/mL; SD 0.036, $P<0.005$, t-test).

Conclusions: Women suffering from migraine presented low serum levels of allopregnanolone, a neurosteroid that modulates GABAergic inhibition. Consequently, the reduced GABAergic inhibition could inadequately protect women suffering from migraine against inflammatory and algogenic stimuli. In particular, it could contribute to the severity and poor response to treatments of migraine attacks. According to our preliminary results, a raise in the GABAergic transmission achieved by drugs increasing the biosynthetic pathway of inhibitory neurosteroids or the use of synthetic analogs could represent a possible novel therapeutic strategy for migraine management.

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Sporadic hemiplegic migraine with PPRT2 variant of uncertain significance responsive to lamotrigine

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Background: Hemiplegic migraine (HM) is a form of migraine with aura, in which attacks are associated with both typical aura and fully reversible motor weakness. In the sporadic hemiplegic migraine (SHM) no first- or second-degree relative is affected by migraine with motor aura. HM is genetically heterogeneous. Mutations in three ion transportation genes (i.e. CACNA1A, ATP1A2, SCN1A) can all cause the familial phenotype, but more, so far unknown, genes are implicated. Among putative genes for HM there is PRRT2 (i.e. proline rich transmembrane domain protein 2) that can also be involved with paroxysmal movement disorders. Nearly 200 patients affected by SHM have been described, although worldwide epidemiological studies on HM have never been performed. The therapeutic management of HM is empirical, relying on the general principles of treatment of migraine and on evidence mainly coming from reports of patients affected.

Case report: A 21-years-old woman was evaluated for attacks that consisted of severe pulsating left-sided headache, nausea, dizziness and motor weakness of upper and lower limbs associated with a combination of confusion, widespread paresthesia, and visual aura. Typical aura symptoms generally resolved within 4 hours, while motor impairment lasted up to a maximum of 7 days. At the moment of the first evaluation, the patient referred she had suffered of 15 attacks of migraine without aura and 2 attacks of HM per month in the previous 3 months. No family history of HM was reported. Brain and spinal cord MRI and electroencephalography were normal. Laboratory investigations and a full thrombotic risk evaluation showed no evidence of a genetic or acquired coagulation disorders. The sole relevant abnormality was the increase of antiphospholipids IgM (15.3 MPL-UI/mL). Genetic testing for CACNA1A, ATP1A2 and SCN1A mutations were negative. However, a heterozygous variant of uncertain significance of PRRT2, inherited from the mother, was detected. The patient had been treated with several migraine prophylactic drugs over the years with limited to no benefit. A preventive therapy with lamotrigine, titrated to 100 mg daily, was prescribed. A 9-month treatment reduced the number of both migraine without aura and HM attacks by 50%, with no side effects.

Conclusions: This case supports efficacy of lamotrigine in the prophylactic treatment of SHM. The detection of a variant of uncertain significance in a gene involved in synaptic glutamate release suggests that other unknown genetic alterations or environmental factors may play a role in SHM expression.

Proteomic serum profile of female migraineurs

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Background: Migraine is considered a complex disease, a variable disorder of nervous system function that has a genetic background, yet the final phenotypic outcome largely depends on the individual's environment and lifestyle. In particular, there is a clear relationship between menstruation cycle and the onset of migraine. In fact, over 50% of migraine women suffer from perimenstrual attacks, that are more serious, lasting and resistant to the treatment than non-menstrual migraine attacks [1]. We hypothesized that serum proteome analysis could help to identify potential biomarkers of menstrually-related migraine (MM) and post-menopausal migraine (PMM).
Methods: We analyzed and compared the serum proteomic profile of three groups: women suffering from MM (n=15), post-menopausal women suffering from migraine without aura (n=15) and non-headache control females (n=14). The enrolled migraineurs were patients afferent to the Headache Centre of Modena University Hospital; the control females were friends or relatives of the above patients. All women gave their written consent and the Ethical Committee of Modena approved the study. Serum samples obtained from each study participant were subjected to bi-dimensional gel electrophoresis (2-DE) coupled to mass spectrometry (MS) analysis for protein identification. The 2D-gel maps were examined by the PDQuest software, to detect the differentially expressed protein spots between the different groups [2].
Results: A total of 13 significantly different protein spots were revealed in migraine women compared to controls. Of these proteins, most (n=10) resulted increased in migraineurs *vs* controls, while only 3 proteins were decreased. Specifically, the greater expression differences involved the up-regulation of transthyretin in PMM and the down-regulation of apolipoprotein A1 in MM. Other proteins, such as prothrombin, serum amyloid P-component and Ig-k-chain C region, were found significantly over-expressed in migraine sufferers in comparison to controls, while one spot, recognized as serum amyloid A-4 protein, resulted decreased.
Conclusions: The serum proteome of migraine women showed proteins characteristic of cell damage, oxidative stress and lipoperoxidation, as well as acute phase proteins and inflammation markers. This pilot study demonstrates the ability of proteomics to reveal differences in protein expression between women suffering from MM and post-menopausal women suffering from migraine without aura against non-headache women. Further analysis will be carried out to expand and confirm these preliminary results.
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Proposal of a randomized trial for a new surgical treatment of Chronic Cluster Headache: endoscopic endonasal Vidian neurectomy vs transcranial extradural GSPN neurectomy

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Background: Chronic Cluster Headache is a neurovascular disorder caused by an hyperactivation of a trigeminal autonomic reflex, involving parasympathetic system. The management of this pathology represents a real challenging because of poor response to medical therapy. Different surgical procedures were proposed, as stimulation or block/ablation of sphenopalatine ganglion, but complication rate is significant, as dry eye syndrome or cheek and gum paraesthesia.
Methods: We proposed to realize a randomized trial with two patient groups: the first group underwent endoscopic endonasal Vidian nerve (VN) Neurectomy (with ablation of parasympathetic and sympathetic pathway) and the second group transcranial subtemporal extradural great superficial petrous nerve (GSPN) Neurectomy. Patient selection considered the International Classification of Headache Disorders second edition criteria, evaluating history, duration and attack frequency in preoperative and postoperative period.
Results In a recent prospective study exclusive vidian neurectomy permitted reduction of frequency, duration and intensity of attacks in over half of the patients, however complication rate remained high.
Conclusions: Vidian nerve origins from anastomosis between GSPN (parasympathetic pathway) and deep petrous nerve (DPN – sympathetic pathway). VN section provides a block of both systems. We hypothesize that the exclusive interruption of GSPN/parasympathetic pathway improves chronic cluster headache without appearance of complications.

Unusual QEEG analysis during aura migrainous attack: a case report

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Introduction: In migraine, EEG abnormalities have been reported by several authors. However, evidence of definitely abnormal EEG rhythms have not been consistent. During visual aura, either slow waves, depression of background activity amplitude or normal EEG have been reported. Intercritical EEG between episodes of headache showed changes in EEG rhythms. During hemiplegic migraine or during attacks of migraine with disturbed consciousness unilateral or bilateral delta activity has been found. In recent years, new EEG recording methods, employing EEG frequency analysis, topographic brain mapping and quantitative EEG (qEEG) has been helpful in this field. Main results were or increased focal slowing waves or abnormalities in power spectral values due to an increasing of slow activity or decreased alpha activity in the posterior leads or in all cortical regions. Unlike Walker found an excess of high frequency beta activity [1].
However most of these studies are based on the observation of EEG activity during the post-ictal period of migraine attack. Here we report EEG signal during the painful attack in a patient suffering of migraine with aura.
Case report: A 15-year old girl was admitted to our neurological consult, because, a few hours before, she had complained the start of visual and subsequently sensory aura followed by severe unilateral pulsating pain. At the time of the consult, after initially performing an EEG, she complained only moderate pain when she began to experience the same symptoms that had just preceded the onset of the aura. Immediately another EEG exams was performed during the aura until its conclusion. Subsequently the patient was hospitalized and underwent several investigations without significant anomalies. A quantitative EEG analysis was applied to two performed EEG. Recorded trace was cut in time blocks of 20 seconds each one during the aura and the pain phase.

Results: Data were analysed considering the delta, theta and alpha activities. QEEG show a decrease of slow rhythms during the aura in the posterior leads and a subsequent immediate increase in the subsequent pain phase. Fast rhythms were equally represented in both phases.
Conclusions: The EEG patterns observed in our migraine patient seem to suggest the possible changes in cortical EEG rhythms between the two main phases of migraine attacks (aura and pain phases), to support the physiological connection between migraine and brain activity and may shed new light on migraine pathophysiology.
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The role of mental pain and psychosomatic factors in migraine: results of the PAINMIG study

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Background: Migraine is a disabling primary headache disorder which may interfere with patients' psychological status, quality of life, and functioning. Nevertheless, migraine evaluation according to psychosomatic principles, including psycho-social factors which might affect its course has been poorly performed. The present study was aimed at evaluating psychosomatic, psychosocial, and psychological variables as potential risk factors for migraine.
Methods: A cohort study design was applied. Two-hundred subjects were enrolled at the Headache Center of the Careggi University Hospital (Florence, Italy): 100 subjects had a diagnosis of chronic migraine (CM) and 100 had a diagnosis of episodic migraine (EM). One-hundred healthy subjects (HS) were also enrolled form the general population of Central Italy as healthy controls (ratio case: control = 2:1). Participants completed a clinical assessment including: Structured Clinical Interview for DSM-5 (SCID-5); Clinical Interview for Depression (CID); Diagnostic Criteria for Psychosomatic Research-Revised - Semi-Structured Interview (DCPR-R SSI); Psychosocial Index (PSI); Mental Pain Questionnaire (MPQ); Euthymia Scale (ES).
Results: The most frequent DSM-5 diagnosis were Agoraphobia (CM = 7; EM = 8; HS = 2; χ^2(df) = 3.87(2); p = 0.145), Panic Disorder (CM = 6; EM = 5; HS = 9; χ^2(df) = 1.39(2); p = 0.498), Major Depressive Disorder (CM = 10; EM = 6; HS = 2; χ^2(df) = 5.67(2); p = 0.059).
The most frequent DCPR-R diagnosis were Allostatic Overload (CM = 31; EM = 24; HS = 14; χ^2(df) = 8.24(2); p = 0.016); Type A Behavior (CM = 8; EM = 13; HS = 8; χ^2(df) = 7.14(2); p = 0.028), Irritable Mood (CM = 13; EM = 4; HS = 10; χ^2(df) = 5.13(2); p = 0.077) and Alexithymia (CM= 5; EM = 10; HS = 12; χ^2(df) = 3.18(2); p = 0.204).
Among the variables taken into account, higher levels of mental pain (OR = 1.26; 95% CI = 1.04-1.53) or more severe depressive symptoms were found as risk factors for CM as compared to healthy subjects; mental pain (OR = 1.33; 95% CI = 1.10-1.62) was higher in CM as compared to EM. No risk factors were found for EM towards healthy subjects.
Conclusions: CM patients exhibit a significantly higher risk than healthy subjects and EM patients with regard to series of psychosomatic variables (i.e., mental pain and depressive symptoms), whereas there was no difference between EM patients and healthy controls. Thus, mental pain and depressive symptoms are psychosomatic variables deserving attention in migraine patients.

Anxiety sensitivity and headache triggers

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Objectives: To assess relation between anxiety sensitivity and headache trigger susceptibility.
Background: Individual with recurrent headache exhibit fear of pain and avoidance of behaviors or stimuli that may instigate or perpetuate their headache pain. Fear of pain recently has been shown to be strongly predicted by anxiety sensitivity, or the fear of benign bodily sensations stemming from the belief that these sensations have harmful consequences. However, studies have not explored relations between anxiety sensitivity and susceptibility to headache triggers, a needed area of research given centrality of avoidances models of chronic pain and potential implications for intervention.
Methods: One hundred and sixty-nine headache sufferers retrospective chart review 1/10/2018 – 2/2/2019 (57% females 33% men, age 18-75 yrs mean 37.2, primarily episodic migraine and ETTH) completed battery of measures including the Hamilton Anxiety and questions about headache triggers; associations were quantified between the three subscales of ASI – 3 (concerns cognitive, physical, social) and trigger variables using generalized.
Results: Anxiety sensitivity was strongly and positively associated with the total number of endorsed triggers (ps<0.001) estimates of how often important trigger was encountered (ps<0.001), and the perceived potency of an important trigger (p<0.0001). Physical concerns were associated with all three aspects of these trigger perceptions, while cognitive concerns were related to the number of triggers and frequency of encounter only. Social concerns were uniquely associated with sensitivity to exercise and alcohol as triggers.
Conclusions: Headache sufferers with high anxiety sensitivity perceive themselves to have more headache triggers, more frequent exposure to triggers, and higher potency of triggers (probability of headache following exposure) than individuals lower on anxiety sensitivity. Anxiety sensitivity may function as a previously unknown but important factor and target of behavorial therapy for triggers management.

Everyday life social cognition in chronic migraine

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Objective: The ability to attribute mental states to oneself and others is an important aspect of social cognition, also known as Theory of Mind (ToM). The ability to make social cognitive inferences is indeed crucial for successful social behaviours because they mediate an understanding of the intentions and dispositions of others and lead to the correct prediction of behaviour. Previous evidences have shown an association between ToM and Alexithymia (A), which refers to the inability to identify and express emotions, as well as pathological scores in these aspects in chronic migraine. Given the relevance of Theory of Mind in social interactions, it is important to assess it by using tests approximating the demands of everyday life social cognition, which is lacking in previous studies. The present study is aimed to evaluate whether chronic migraine is associated to deficit in ToM and in other aspects of social functioning, by using a video-based instrument, the Movie for the Assessment of Social Cognition (MASC), requiring subjects to make inferences about video characters' mental states.

Methods: 40 patients suffering from chronic migraine (CM) (79.5% female, Age: 47.3±11.1) and 37 patients suffering from episodic migraine (EM) (83.8% female; Age: 41.0±11.4) were evaluated using a battery of ToM tasks comprising the MASC and the Reading the Mind in the Eyes Test (RMET), as well as questionnaires on their social functioning. Chronic migraine diagnosis was operationally defined according to ICHD-IIIβ. Data were analyzed with analysis of variance.
Results: Compared with EM, CM patients had significantly lower scores in the MASC (CM=17.7±14.7, EM =22.9±14.0, $p<.05$), and these differences resulted also when distinguishing between cognitive (CM=9.9±9.4, EM =14.6±9.1, $p< .05$) and affective (CM=5.8±5.5, EM =8.3±5.2, $p<.05$) components. EM also had higher scores in the RMET (CM=21.7±3.1, EM =24.4±3.8, $p<.005$), and believed to be abler to understand ones and others' feelings in comparison to chronic migraineurs.
Conclusions: Our results indicate that CM patients have more difficulties in understanding others' mental states than EM, which is highlighted also by tasks reflecting everyday life competences. This evidence suggests the existence of a link between this chronic condition and social competent behaviours and abilities.

Efficacy of fremanezumab in patients with chronic migraine and comorbid moderate to moderately severe depression

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Background: Depression is common in CM and contributes to the already substantial burden of disease. Fremanezumab (TEV-48125), a fully humanized monoclonal antibody targeting calcitonin gene-related peptide (CGRP), has demonstrated efficacy in migraine prevention.
Methods: In this Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, eligible patients aged 18–70, with prospectively confirmed CM (≥15 headache days and ≥8 migraine days per month) were randomized 1:1:1 to receive subcutaneous injections of fremanezumab quarterly (675 mg at baseline; placebo at Weeks 4 and 8), fremanezumab monthly (675 mg at baseline; 225 mg at Weeks 4 and 8), or matching placebo over a 12-week treatment period. Post hoc analyses evaluated changes in headache and migraine frequency and depression in patients with moderate to moderately severe depression (score of 10–19 on the 9-item Patient Health Questionnaire [PHQ-9]) at baseline.
Results: Almost 20% (219/1130) of randomized patients had moderate to moderately severe depression at baseline (quarterly, n=74; monthly, n=88; placebo, n=57). As in the overall study population, fremanezumab-treated patients in this subgroup had significant reductions from baseline in the mean number of monthly headache days of at least moderate severity (quarterly: −5.4 ±0.79; monthly: −5.6±0.75) versus those who received placebo (−2.2±0.84) during the 12-week treatment period (both, P<0.001), with effects observed as early as Week 4 (P<0.0001). Similar treatment differences were observed for change in the mean number of migraine days (P<0.001). Fremanezumab also reduced the mean PHQ-9 score from baseline to Week 12 (quarterly: −10.5±0.68; monthly: −9.5±0.63) versus placebo (−8.7 ±0.71); the quarterly group reached significance (P<0.05).
Conclusions: Fremanezumab demonstrated efficacy in preventive treatment of CM in patients with comorbid moderate to moderately severe depression, reducing migraine and headache frequency and improving depression.

Role of maternal stress and alexithymia in children's migraine severity and psychological profile

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Objective: A growing body of literature explored the role of mother-child interaction in children's migraine severity. Recent studies showed that patients' attachment style and maternal alexithymia traits may impact on psychological profile and pain expression in children/adolescents suffering from migraine. Very few studies focused on the relationship between maternal stress, their children's psychological profile and migraine severity. Aims of our study were to explore the role of maternal parenting stress and alexithymia on: 1) their children's headache severity (frequency); 2) maternal perception of children's psychological conditions and 3) children's psychological profile.
Methods: We studied 51 migraineurs (mean age 11.6 ± 2.1 years; 22 M and 29 F). Patients were divided in two groups according to headache attack frequency: 1) high frequency (from weekly to daily episodes) and 2) low frequency patients (≤3 episodes per month). Maternal stress and alexithymia levels were evaluated respectively by PSI-SF and TAS-20 questionnaire. SAFA "Anxiety" and "Depression" scales were used to explore children's psychological profile. To evaluate maternal perception of children's psychological conditions CBCL 6/18 was employed.
Results: We found a correlation between maternal stress and CBCL Internalizing (p=0.00), Externalizing (p=0.00) and Total scales (p=0.00). A positive correlation has been identified between mothers' PSI Total score and SAFA-D Total score (p=0.03). In particular, a positive correlation was found between "Parental distress" and children's SAFA-D "Feeling of guilt" subscales (p=0.04). Maternal stress and alexithymia did not show significant differences among the two migraine frequency groups (p>0.05). However, in the high frequency group, PSI Total score showed a positive correlation with Internalizing scale (p=0.00). No relationships were found between TAS-20, CBCL, SAFA and migraine frequency.
Conclusions: Maternal stress has no relationship with children's migraine frequency. However, it shows a relationship with maternal perception of children's psychological profile and patients' depressive symptoms, which in turn may impact on migraine severity.

Coping strategies in migraine without aura: a cross-sectional study

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Background: In the context of causal relationship between stress and migraine, coping strategies aim to manage stressful life events and reduce the distressing emotions connected to them.
Methods: Fifty-two consecutive patients with migraine without aura (MwoA) and fifty-two healthy controls (HC) completed three self-

report questionnaires assessing a broad range of coping (cognitive and behavioural) strategies: the Coping Orientation to Problems Experienced (COPE), the Coping Inventory for Stressful Situation (CISS) and the Proactive Coping Inventory (PCI). Moreover, the Perceived Stress Scale (PSS), a scale measuring self-perception of stress, global cognitive functioning, depressive symptoms, apathy, state and trait anxiety was administered to all participants.
Results: No significant difference was found on the scales and subscales of PCI and CISS as well as in the PSS between MwoA patients and HC. However, the two groups showed different scores in the subscale "turning to religion" of COPE (21.58 ± 5.30 in migraineurs vs 23.70 ± 4.60 in HC, p=0.003). A significant negative correlation of turning to religion score with HIT-6 score was found.
Conclusions: The present study revealed that MwoA patients show a significantly reduced use of the "turning to religion" approach, an emotion-focused coping strategy. Although migraine patients appeared to be less oriented to transcendent (that means a reduced utilization of an adaptive coping strategy) they did not perceive daily living more stressful than HC. Finally, the reduced utilization of the "turning to religion" coping strategy is associated with a great impact of migraine on ability to function on the job or at school, at home and in social situations in migraine patients.

A subjective cognitive impairments scale for migraine attacks: validation of the Italian version of the MIG-SCOG

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Background: The MIG-SCOG is a questionnaire to assess self-reported subjective cognitive symptoms during migraine attacks, consisting of 9 items related to executive functions and language. The aim of this study was to evaluate the psychometric properties of the Italian version of the MIG-SCOG (I-MIG-SCOG) in patients with migraine without aura (MwoA).
Methods: The MIG-SCOG was translated into Italian. The first draft of the questionnaire was administered to 20 Italian healthy subjects to assess its comprehensibility. Then, the final I-MIG-SCOG was completed by 125 MwoA patients. To assess divergent validity, MwoA patients underwent Montreal Cognitive Assessment, Beck Depression Inventory and Apathy Evaluation Scale.
Results: The final I-MIG-SCOG was easily comprehensible. There were no missing data, no floor and ceiling effects; mean I-MIG-SCOG score was 7.24±3.78; Cronbach's alpha was 0.814. The I-MIG-SCOG showed good divergent validity (i.e. poor correlation between I-MIG-SCOG and MoCA, BDI and AES).
Conclusions: The MIG SCOG is confirmed to be a reliable patient-centered and disease-related instrument to identify cognitive symptoms during migraine attacks also in Italian patients. The I-MIG SCOG should be used in the clinical practice as well as in the research scenario to evaluate the contribution of cognitive symptoms on migraine burden and to monitor the divergent effects of symptomatic treatments on cognitive functions in migraine patients.

Neuropsychological disorders in migraineur children

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Background: Among the comorbidities of the migraineur children and adolescents there are some neuropsychological disorders. Many authors have demonstrated this relationship, although not uniquely. This research aims to evaluate this comorbidity depending on the diagnosis of the migraine type.
Methods: One hundred and six children, aged 4-17 years, 62 F and 44 M form the sample. The patients were recruited consecutively during 2018 at the Abruzzo Regional Headache Center, Childhood Age-Dep. Child Neuropsychiatry-Hospital San Salvatore L'Aquila. The sample was divided according to ICDH-III criteria into 2 groups: Migraine with Aura (MwA) and Migraine without Aura (MwoA). We used the following tests: "Leiter-R" for sustained attention and "Corsi test" for spatial-visual short memory; the "CBCL 6/18" for emotional-behavioral disorders. Statistical analysis was done with Fisher test.
Results: Seventy-six children suffering from MwoA and 30 from MwA. They had a mean age of 13 years and the mean age of onset of headache was 9 years. Twelve children with MwoA had an attention deficit and 2 mnesic deficits, the remaining sample did not seem to show such alterations. Twenty-four children showed positivity for internalizing disorders and 3 for externalizing disorders. Eight children with MA had an attention deficit and 2 had a mnesic deficits. Twenty children had positivity for internalizing disorders and 2 externalizing disorders. Therefore comparing the two groups, MwA had a higher degree of disability in sustained attention and psychopathology for internalizing disorders. Comparing the percentages, children suffering from migraine with aura (MwA 36% Vs MwoA 28%) report greater impairment of attentive skills and more comorbidity with internalizing disorders (MwA 66% Vs MwoA 56%). The statistical analysis of the data did not show statistically significant results, therefore we can only support a qualitative observation of the data found.
Conclusions: Mood disorders can play an important role in neuropsychological performances. Neuropsychological disorders seem to be influenced by the presence of anxiety.
Suggested reading
Chiappedi M, Mensi M, Antonaci E et al (2018) Intellectual Profile of Adolescents with Headache: A Case-Control Study Using the WISC-IV. Front Neurol 9:128. doi: 10.3389/fneur.2018.00128

Therapeutic innovation

Migraine and Vitamin D serum level

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Introduction: Vitamin D is very important in mineral homeostasis but is also an anti-inflammatory hormone and has a negative effect on proliferation of mast cells and can stimulate nitric oxide (NO) [1]. Therefore vitamin D has an important role in cardiovascular disease [2]. Recently growing but conflicting evidence has shown a possible relationship between vitamin D and chronic or recurrent painful conditions such as migraine [3].
Objective: Our aim was to determine 25(OH)D level in our migraineurs patients and correlate them to age and headache duration.
Material and methods: We collected, in a small preliminary analysis, 25(OH)D level in 50 consecutive migraineurs patients belonging to our headache centre, in San Luca Hospital, Vallo Della Lucania. 25-Hydroxy vitamin D [25(OH)D] plasma levels were measured by MicroVue 25-OH Vitamin D EIA. 40 patients were women, 10 were male; 44 were

diagnosed with migraine without aura, 6 had fulfilled criteria for migraine with aura; mean age was 39.9±12.7 years; mean disease duration was 10.4±10.3 years.

Results: Mean vitamin D serum level was 18.7±5.3 ng/ml, denoting a state of insufficiency. Among our 50 patients, only 6 have serum level above 30 ng/ml (sufficiency); most patients (40 out of 50) showed serum level among 10 and 30 ng/ml, while in 4 patients serum level was less than 10 ng/ml. All these last three patients were diagnosed with migraine without aura.

Conclusions: Vitamin D insufficiency is a frequent finding in our migraineurs patients, but we cannot postulate a definite relationship between vitamin D deficiency and migraine. We suggest that this conclusion needs to be supported with randomised clinical studies containing a larger number of samples and controls. Moreover, intervention studies are required to find out if supplementation of vitamin D and calcium is effective in patients with migraine.

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Increased neural connectivity between the hypothalamus and cortical resting state functional networks in chronic migraine

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Background: Resting-state functional MRI studies suggest that abnormal functional integration between interconnected cortical networks characterizes the brain of migraineurs. The aim of this study is to investigate the functional connectivity between the hypothalamus, the brainstem –the supposed generators of migraine–, and the areas that encompass the following networks involved in the pathophysiology of migraine: the default mode network (DMN) and the dorsal attention system (DAS).

Methods: Twenty patients with chronic migraine (CM) without medication overuse and 20 healthy subjects (HS) were prospectively recruited. All study participants underwent 3T MRI scans using a 7.5-minute resting state protocol. Using a seed-based approach, we performed a ROI to ROI analysis choosing hypothalamus as seed and areas belonging to the DMN and the DAS, and brainstem as target region of interests.

Results: Compared to HS, CM patients showed significant increased neural connectivity between the hypothalamus and brain areas belonging to DMN and DAS. We haven't detected any connection abnormalities between the hypothalamus and the brainstem. The correlation analysis showed that the severity of migraine headache correlates positively with the connectivity strength of the hypothalamus and negatively with the connectivity strength of the middle prefrontal cortex, which belongs to the DMN.

Conclusions: These data provide evidence for hypothalamic involvement in large-scale reorganization at the level of the functional networks during chronic migraine and in proportion with the severity of perceived migraine pain.

Chronic migraine patients show a different profile of the white matter fiber bundles compared to healthy subjects

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Background: In recent years, several studies have shown that the migraine brain is characterized by an alteration of the intrinsic functional connectivity of different cortical networks. Little is known about the microstructural integrity of the fiber bundles that interconnect them. Here, we have investigated intracerebral fiber bundles through the most modern techniques of diffusion tensor imaging (DTI) analysis.

Methods: For this study, we prospectively enrolled 19 episodic migraineurs (EM) between attacks, 18 chronic migraineurs (CM) without overuse of symptomatic drugs and 18 healthy subjects (HS). All subjects underwent diffusion tensor imaging (DTI) scans using 3T MRI. We investigated the microstructure of white matter using tract-based spatial statistics (TBSS) analysis to calculate diffusion metrics, including fractional anisotropy (FA), axial (AD), radial diffusion (RD) and mean diffusion (MD). All analysis was corrected for age and gender.

Results: TBSS showed no significant differences between MO patients and HC for FA, MD, RD and AD maps. In comparison to HS, CM exhibited widespread increased RD (bilateral superior, anterior and posterior corona radiata [CR], right splenium of corpus callosum [CC]; bilateral genu of CC, right anterior and posterior limb of internal capsule [IC], bilateral retrolenticular part of IC, bilateral external capsule, bilateral posterior thalamic radiation [include optic radiation], bilateral sagittal stratum [include inferior longitudinal fasciculus [LF] and inferior fronto-occipital fasciculus], bilateral fornix [cres]/stria terminalis) and MD values (left superior and posterior CR, left superior LF, left splenium of CC). In comparison to MO, CM patients showed decreased FA (bilateral superior and posterior CR, bilateral body of CC, bilateral superior LF, bilateral posterior thalamic radiation [include optic radiation], left sagittal stratum [include inferior LF and inferior fronto-occipital fasciculus], bilateral retrolenticular part of internal capsule) and increased MD values (bilateral superior and posterior CR, bilateral body of CC, left superior LF, bilateral splenium of CC, left posterior limb of IC).

Conclusions: Our results provide evidence for microstructural alterations in brain white matter fiber bundles in CM patients that could be the underlining cause of the abnormalities previously observed in large-scale organization of the resting-state cortical functional networks.

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 not to 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.
Conclusions: 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.

Advanced visual network and cerebellar hyperresponsiveness to trigeminal nociception in migraine with aura

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Background: Despite the growing body of advanced studies investigating the neuronal correlates of pain processing in patients with migraine without aura (MwoA), only few similar studies have been conducted in patients with migraine with aura (MwA). Therefore, we aimed to explore the functional brain response to trigeminal noxious heat stimulation in patients with MwA.
Methods: Seventeen patients with MwA and fifteen age- and sex-matched healthy controls (HC) underwent whole-brain blood oxygen level–dependent (BOLD) fMRI during trigeminal noxious heat stimulation. To examine the specificity of any observed differences between patients with MwA and HC, the functional response of neural pathways to trigeminal noxious heat stimulation in patients with MwA was compared with eighteen patients with MwoA. Secondary analyses investigated the correlations between BOLD signal changes and clinical parameters of migraine severity.
Results: We observed a robust cortical and subcortical pattern of BOLD response to trigeminal noxious heat stimulation across all participants. Patients with MwA showed a significantly increased activity in higher cortical areas known to be part of a distributed network involved in advanced visual processing, including lingual gyrus, inferior parietal lobule, inferior frontal gyrus and medial frontal gyrus. Moreover, a significantly greater cerebellar activation was observed in patients with MwA when compared with both patients with MwA and HC. Interestingly, no correlations were found between migraine severity parameters and magnitude of BOLD response in patients with MwA.
Conclusions: Our findings, characterized by abnormal visual pathway response to trigeminal noxious heat stimulation, support the role of a functional integration between visual and trigeminal pain networks in the pathophysiological mechanisms underlying migraine with aura. Moreover, they expand the concept of "neurolimbic-pain network" as a model of MwoA including both limbic dysfunction and cortical dys-excitability. Indeed, we suggest a model of "neurolimbic-visual-pain network" in MwA patients, characterized by dysfunctional correlations between pain-modulating circuits not only with the cortical limbic areas but with advanced visual areas as well. Furthermore, the abnormal cerebellar response to trigeminal noxious heat stimulation may suggest a dysfunctional cerebellar inhibitory control on thalamic sensory gating, impinging on the advanced visual processing cortical areas in patients with MwA.

Default mode networks abnormalities predict the cutaneous allodynia in patients with episodic migraine without aura

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Background: Approximately two-thirds of patients with migraine without aura (MwoA) complain of cephalic or even extracephalic cutaneous allodynia (CA) during migraine attacks. CA is a clinical sign of central nociceptive pathway sensitization and independent predictor for migraine chronification. This article aims to investigate if abnormalities of default mode network (DMN) functional connectivity could predict the development of cutaneous allodynia in patients with MwoA.
Methods: Thirty-seven patients with MwoA were recruited between 2009 and 2015 and underwent whole-brain blood oxygen level–dependent (BOLD) fMRI. All these patients have been followed over a three years period and then divided into 2 groups based on whether or not cutaneous allodynia was developed. Then, we compared functional connectivity within the DMN in 20 patients with MwoA who have developed CA versus 17 patients with MwoA who have not developed CA and 19 sex- and age-matched healthy controls (HC). Furthermore, we assessed the correlation between functional connectivity within DMN and all clinical parameters of disease severity.
Results: We observed a significantly lower functional connectivity within posterior cingulate cortex (PPC)/precuneus in patients with MwoA who have developed CA when compared to patients with MwoA who have not developed CA and HC.
Discussion: PCC is known as a key hub of DMN with a prominent antinociceptive functions, deactivated by experimental pain in HC but not in patients with chronic pain condition which show a reduced brain posterior cingulate cortex volume. Interestingly, an increased functional connectivity between the precuneus and the posterior cingulate cortex regions of the DMN has been observed in patients with MwoA. We suggest that DMN abnormal functional connectivity could represent a prognostic imaging biomarker for the incipient development of CA in patients with episodic MwoA.

Safety and efficacy of erenumab for the preventive treatment of migraine: a real-world, prospective, observational study from a Headache Center

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Background: Clinical trials have shown the efficacy and safety of monoclonal antibodies targeting the calcitonin gene-related peptide or its receptor for migraine prevention. We aimed to evaluate the safety and efficacy of erenumab in routine clinical use in a sample of patients with high frequency episodic (EM) and chronic migraine (CM).
Methods: We included consecutive patients with EM (≥ 4 monthly migraine days, MMD) or CM aged ≥18 years admitted to our Regional Headache Referral Center from January to April 2019 and treated with erenumab monthly injections. We recorded baseline characteristics including headache features, headache frequency and duration, drug abuse, and prior preventive treatment failure. We evaluated change in mean MMD, number of acute medication use, and pain intensity according to the Visual Analog Scale (VAS) from baseline to week 8.
Results: We included 25 subjects (22 women; mean age±SD, 46.89±11.20 years); 1 had EM and 24 CM (72% with medication overuse). All patients received erenumab 70 mg at the first injection, and 2 patients received erenumab 140 mg at the second injection. Seven (28.0%) patients failed 1, and 18 (72%) failed 2 or more prior preventive treatments; 13 patients with CM (54.2%) had failure of onabotulinumtoxinA. In 10 patients erenumab was started as an add-on treatment. Compared to baseline, change in MMD was -2.23±2.79 days at week 1 (P=0.003), -8.41±8.62 days at week 4 (P<0.001), and -13.00±6.91 days at week 8 (P<0.001); change in acute medication use was -2.20±2.67 days at week 1 (P<0.001), -8.88±10.01 days at week 4 (P=0.002), and -14.22±8.83 days at week 8 (P=0.001); change in pain intensity was -1.31±1.55 VAS points at week 1 (P=0.010), -1.25±1.77 points at week 4 (P=0.013), and -1.67 ±1.50 at week 8 (P=0.010). Significant improvements in MMD, acute medication use, and pain intensity were observed also considering the 15 patients who stopped the other preventive treatments after starting erenumab. Six (24.0%) patients reported 8 adverse events, including pruritus (4.0%), wheal at injection site (4.0%), constipation (12.0%), aerophagia (4.0%), fatigue (4.0%), and flu-like syndrome (4.0%); none reported adverse events that led to treatment discontinuation.
Conclusions: In the real-life setting the benefits of erenumab appeared better than expected by the results of clinical trials. Possible explanations may rely on the different characteristics of patients but possibly also on the placebo effect. Moreover, our findings confirm the rapid onset of efficacy of erenumab and the lack of necessity of detoxification before treatment of patients with medication overuse.

The behaviour of Intrinsic Connectivity Networks in episodic and chronic migraine

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Background: Changes in the basal behavior of intrinsic connectivity networks, including the Default Mode Network (DMN) and the Salience Network (SN) may be associated with the occurrence of Episodic Migraine (EM) and the process of transformation toward a chronic form. The aim of the present study is to investigate functional connectivity (FC) within the SN and the DMN in EM and chronic migraine (CM), in order to identify any functional brain connectivity changes associated with chronification.
Methods: Patients consecutively referring to the Regional Headache Centre of L'Aquila with a diagnosis of migraine were screened for the inclusion in the study. The diagnosis of EM or CM was made according to the criteria of the International Classification of Headache Disorders (ICHD-III beta version). Thirty-five women with EM (mean age 44.6 ±9.1), 32 women with CM (mean age 44.9±9.4) and 28 healthy women (mean age 44.2±10.3) were included. All subjects underwent a neuroradiological assessment through a 3 Tesla Magnetic resonance Imaging (MRI) scanner (Discovery MR750w). Resting-State fMRI data were analysed by means of a seed-based approach, using four and six different seeds, sampling the main hubs of the DMN and SN respectively.
Results: SN in CM patients was characterized by a reduced FC between left supramarginal gyrus and cerebellar tonsils, compared to HC (p=0.001), and between the left anterior insula and the midcingulate cortex, compared to EM patients (p=0.0007). EM patients showed extensive alterations in the DMN compared to HC, mainly due to reduced FC of the frontal DMN hub with the precuneus (p=2·10-5) and the right lower parietal (p=5·10-5) cortex.
Conclusions: A reduced FC among crucial hubs of the SN, which is responsible for switching between the DMN and the central executive network through the selection of internal and extrapersonal stimuli, may be associated with the process of migraine chronification. On the other hand, changes in the DMN, which mediates self-reference and own emotional states, may be a neural marker of earlier EM.

Visual cortical excitability in fibromyalgic and migraine patients: a study with sound induced flash illusion

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Background and aims: Excitability of pain-processing areas and response to incoming somatosensory stimuli are abnormally enhanced in Fibromyalgia (FM) and in migraine. To explore if such facilitation represents a more general sensorial activation not strictly related to pain, we evaluated excitability of visual cortex, an area not directly involved in pain processing, through Sound-Induced Flash Illusion (SIFI). SIFI are cross-modal illusions, strictly dependent upon visual excitability, where visual perception is influenced by auditory input. When a single flash is accompanied by multiple beeps, it is perceived as multiple flashes (fission illusion), conversely when one flash is accompanied by more beeps, more flashes are seen (fusion illusion). SIFI are reduced when visual cortical excitability increases.
Methods: We performed SIFI in five FM patients, five migraine with aura (MWA) patients and five without aura (MWoA) patients and 5 healthy controls (HC). Throughout the test, 0 -four flash were presented on a monitor together with 0-4 beeps delivered by loudspeakers, in different combinations. The observer's task was to judge the number of flashes seen.
Results: Data do not show a significant reduction in fission illusions in the comparison between MWoA and HC (p>0.05). A significant reduction is seen when FM patients are compared to HC and MWoA patients (particularly when one flash is accompanied by two, three, or four beeps,

p<0.01), but also to MWA (when one flash is accompanied by three or four beeps, p<0.05). MWA patients have a significant reduction compared to HC and MWoA (when one flash is accompanied by two, three or four beeps, p<0.05)
Conclusions: Our results suggest an increased visual excitability especially in FM patients even greater from that observed in MWA patients. No significant results were shown for MWoA patients in comparison to HC. This could shed more light on pathophysiological mechanisms of these diseases and the relations between pain and cortical connectivity likely opening also new ways for treatment. SIFI represent an easy and effective tool to explore cross-modal audio-visual perception and visual cortical excitability in FM and MWA patients.

The study of sensorimotor integration in migraine reveals basal ganglia disfunction related to consumption of medications taken for acute headache attack

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Objectives: Neurophysiological and neuroimaging studies have shown dysfunctions of brain areas responsible for multisensory integration in migraine. Among these areas, the basal ganglia, the thalamus, and the primary somatosensory area (S1) play a major role in sensorimotor integration. One of the experimental approaches to assess mechanisms of sensorimotor integration and sensory gating is to measure the somatosensory temporal discrimination threshold (STDT)- i.e. the shortest interval at which an individual recognizes two stimuli as separate in time- at rest and during movement execution. STDT involves the activation of the subcortical network signalling salient events and S1. Testing STDT during movement execution (sensory gating) involves basal ganglia/thalamus interplay. Here we investigated STDT tested at rest and during index finger abductions in patients with migraine without aura during and outside the attacks.
Methods: We tested STDT in 24 migraine without aura patients, 16 in between attacks (MO) and 9 during an attack (MI). The patients were compared with a group of 30 healthy volunteers (HVs). STDT was tested at rest and during index finger abductions (at movement onset and 100, 200, and 500 milliseconds afterwards).
Results: Compared to HV, basal STDT values and those obtained 500 ms after movement onset (when movement is already ceased) were significantly reduced in MI patients (p=0.013), with MO patients falling in between HV and MI. When data of MO and MI patients were combined, Pearson's test disclosed that STDT value tested at rest and that obtained 500ms after movement onset correlated negatively with monthly number of medications taken for acute headache attack. No significant differences or correlations were instead observed in STDT values tested during movement executions.
Conclusions: Here we have reported reduced STDT values in patients with migraine during an attack. In addition, we have observed a close relationship between electrophysiological abnormalities and the number of acute medications consumed monthly. Further studies are needed to understand whether these changes suggest an abnormally hyperactive subcortical network signalling salient events during migraine attack, which would send excessive information to S1, or to medication-induced neural adaptation promoted by changes in basal ganglia neurotransmission.

DNA methylation analysis of calcitonin gene–related peptide gene in patients with migraine

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Background: For complex disorders such as migraine, both genetic and environmental components play an important role in disease pathogenesis. Epigenetic markers are heritable changes in phenotype or gene expression in the absence of changes in DNA sequence. DNA methylation is the most common type of epigenetic modification, and plays a key role in several disorders as cancer and neurodegenerative disorders. Changes in global DNA methylation have been associated with environmental factors. To date, little is known about DNA methylation in migraine. Several studies have shown that the neuropeptide calcitonin gene–related peptide (CGRP), encoded by *CALCA* gene, has a key role in migraine pathogenesis, and successful new drugs for migraine prophylaxis target CGRP. The aim of the study was to evaluate DNA methylation of *CALCA* gene in patients with migraine.
Methods: Twenty-two patients with episodic migraine (15 females, 7 males; mean age± SD: 39.7±13.4 years) and 20 controls (12 females, 8 males; mean age± SD: 40.5±14.8 years) were recruited for the study at the Department of Neuroscience, University of Torino, Italy. The diagnosis of migraine was made according to ICHD-III criteria. All samples were studied by direct bisulfite sequencing. Cytosine-to-thymine conversion by sodium bisulfite was performed using EZ DNA Methylation™ Kit.
Results: DNA methylation in both patients and controls was more pronounced at 5' flanking region. No overall difference was found in the global methylation of *CALCA* in patients with migraine and controls. Interestingly, stratification analysis showed that in migraineurs the methylation level was significantly lower in 2 out of the 6 analysed CpG islands (CpG -302, p=0.04; and -256, p=0.04, respectively). Finally, CpG unit at -302 correlates with age at onset of migraine (p=0.038).
Conclusions: This study provides the first evidence that DNA methylation of *CALCA* gene promoter could play a role in migraine. Global DNA methylation of *CALCA* gene in migraineurs does not differ from controls. However, DNA methylation profile in two CpG units (-302 and -256) of the promoter region is lower in migraineurs in respect to controls. Importantly, the -256 unit is located into a 7 nucleotides region containing a cAMP responsive element which binds CREB, a cellular transcription factor. Further studies with larger sample size are needed to confirm these preliminary results and to evaluate the potential role of methylation in the clinical response of migraine therapy.

The role of osteopathic complementary treatment in high frequency paediatric headache: a randomised controlled study

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Background: The pathogenesis of high frequency headache in children is multifactorial and often needs a multidisciplinary approach that includes both pharmacologic and non-pharmacologic therapies, such as

biobehavioural management, agopuncture, osteopathic treatment. Osteopathic treatment results effective in some paediatric conditions, but in primary headache the possible efficacy is still unknown.
The aim of this study is to evaluate the effectiveness of osteopathic manipulative therapy in supporting prophylactic medications in paediatric patients with high frequency headache.
Methods: This is a randomized controlled double blind study in collaboration with "Scuola Superiore di Osteopatia Italiana" and is still ongoing. We recruited patients who referred to the Headache Centre of Regina Margherita Hospital in Turin, aged 8-18 years, with high-frequency headache, in which prophylactic medication for at least two months had failed. Patients were randomised into two groups: the Osteopathic Manipulative Therapy (OMTh) group and the Light Touch Therapy (LTTh) group. The LTTh retained the same areas used for osteopathic approach but avoided prolonged touch in any area of the body by moving the hands every few seconds and by flattening and softening the surface of the hands in order to minimize focal areas of force. Both treatment groups received 5 therapies: the first at baseline, the second after 1 week, the third after 3 weeks, and then 2 more treatments on a monthly basis. The outcome measures were: reduction on frequency of headache episodes (primary outcome), reduction of analgesic use, improvement of quality of life and adverse events caused by OMTh (secondary outcomes). These data were evaluated by headache diary and a quality of life questionnaire at baseline (T0), after 4 weeks (T1), at the last Osteopathic Manipulative Therapy or Light Touch Therapy (T2), at 3 months from baseline (T3).
Results: The study started in April 2018 and we recruited eighteen patients, 15 females and 3 males (mean age: 12.9 years, range 8-17). Seven of these had already completed the study with the last evaluation at T3; for 8 patients the treatments are ongoing and 3 patients interrupted the study due to poor compliance.
Conclusions: Several studies have demonstrated the effectiveness of OMTh in high frequency tension-type headache on adults but its role in paediatric headache is unknown. This is the first study conducted in paediatric age that evaluates the possible efficacy of OMTh on high frequency headache. The results are still partial and we need to recruit more patients to have a statistical significance.

Use of the ultrasound-guided occipital nerve block in the treatment of post-herpetic neuralgia: case report

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Background: Post-herpetic neuralgia is difficult to treat and over 50% of patients fail to achieve satisfactory relief from pain, despite the application of the most effective methods of care available. Current guidelines recommend the use of anticonvulsant drugs, antidepressants, topical treatments and opioid drugs, administered individually and in resistant cases in combination. Our clinical case reports the result of the combination of pharmacological and infiltrative therapy in the treatment of post-herpetic neuralgia.
Case reports:A 60-year old male appeared complaining of severe pain (RSV 8) in the left occiput-parietal-frontal region which had been occurring for about 5 months. Morning pain of moderate intensity (RSV 5) was accentuated during the day until it became severe in the evening and did not regress with the administration of NSAIDs and opiates (Tramadol) taken at high doses.
Speaking with the patient about his clinical history a herpetic-type rash emerged in the same area about 3 years earlier. It was decided to start therapy with Pregabalin 75 mg 2 times/day for 15 days and then 150 mg 2 times/day for 1 month without significant improvement in symptoms (RSV 7).
After 2 months of oral drug treatment, it was decided to associate Pregabalin therapy with 1 cycle of 3 ultrasound guided infiltrations (large occipital nerve block) with administration of Lidocaine (80 mg) and dexamethasone (4 mg) spaced 7 days before the first two and 15 days the second from the third.
Results: The patient reported temporary improvement (3 days) after the first 2 infiltrations with gradual recovery of painful symptoms. At follow-up performed after 1 month from the last infiltration the patient reported discreet control of the symptoms (RSV 3-4), this improvement persisted at 3 months from the infiltration despite the reduction of the oral medication (Pregabalin reduced to 75 mg 2 times/day)
Conclusions: In our opinion, infiltrative therapy with ultrasound-guided nerve blocks is a valid support in the treatment of pain caused by post-herpetic neuralgia, where medical therapy alone does not allow optimal control of symptoms. Discordant results on the efficacy of infiltrative therapy are reported in the literature and standardized infiltration timings have not been proposed; in our opinion the frequency used in this case, 3 infiltrations in 1 month spaced 7 and 15 days respectively, could be applicable in the majority of patients.

The use of a phytotherapic compound containing Tanacetum Parthenium and Andrographis, in combination with CoQ10 and Riboflavin, for migraine prophylaxis: a randomized double blind versus placebo clinical trial

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Background and objectives: Most migraineurs patients need prophylactic treatments to reduce the burden of disease in terms of attacks, days with headache, and symptomatic drugs consumption because their headache is characterized by a middle to high frequency of migraine attacks. So far, pharmacologic prophylactic treatments are characterized by a suboptimal efficacy due to the high number of patients that do not respond to the treatments, and the elevated incidence of side effects. To match the patient needs, waiting for the next generation treatments, the use of herbal medicine is very common among the migraine population. In the last years, phytoextracts of feverfew (tanacetum parthenium) were studied and adopted to treat migraineurs. In particular, there is a fixed combination of Tanacetum Parthenium, Andrographis, Coenzyme Q10, and Riboflavin, that is widely used in Italy. In order to verify the efficacy of that association, we designed a randomized double blind versus placebo clinical trial.
Methods: Forty patients were enrolled and randomly assigned to receive the verum or the placebo treatment for 3 months. Each treatment kit, blinded by a unique code that was coupled to each patient, was composed by 120 pills, enough for 3 months: (1 pill b.i.d. in the first month, 1 per day in the second and third month).
Results: When the blind was broken, 21 patients resulted to be assigned to verum group, 19 to placebo. Eight patients out of 21 assigned to the verum arm of the study improved their headache frequency at least 50% (responder rate of 38.1%). On the contrary, only 2/19 patients that received the placebo treatment improved their headache frequency at least 50% (responder rate of 10.52%). No major side effects were reported.
Conclusions: The traditional use of herbal medicine is as old as the history of medicine and that ancient practice is present in almost all cultures. Our results show that the examined combination is effective in the migraine prophylaxis if compared to placebo and safe if compared with data about synthetic drugs, as they are reported in literature.

A particular case of facial paraesthesias due to a meningioma

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Background: Meningiomas are the most frequently diagnosed primary brain tumors (about 30% of all primary brain and central nervous system tumors). Although most are benign, their intracranial location may lead to severe and even potentially lethal consequences. Most meningiomas are asymptomatic, some may cause seizures and others may lead to focal signs. Here, we aim to show a particular case of facial paraesthesias due to the uncommon cause of a meningioma.
Methods: A 63-year-old woman came to our outpatient neurological clinic for the gradual onset of paraesthesias to the left half of the superior lip in three months. Her complaint started as a tingling sensation and became progressively more and more intense until turning into a burning and swelling sensation. The sensations were constant, worsened by speaking and reduced during the night. We first prescribed a medical therapy (pregabalin and a supplement drug containing vitamins B1, B6, E and α-lipoic acid). After, the patient underwent a massive facial MR and, later, a brain contrast enhanced (CE) MR. Finally, she underwent a neurosurgical and a radiotherapy consultation and cyberknife intervention.
Results: Neurological examination was irrelevant, symptoms decreased just a little after medical therapy. The basic massive facial MR showed only an intrasellar arachnoidocele. The following brain CEMR showed an extracranial vascularised formation at the level of left cerebellopontine angle (coronal diameter 13x12mm, axial one 16.7x16.4mm), with marked dural contrast enhancement and associated to compression of the origin of left trigeminal nerve and Gasser's ganglion. Such formation was referable to a meningioma. Neurosurgeon suggested to consult a radiotherapist, who set two options: watchful waiting or performing cyberknife intervention; our patient chose the latter option (25Gy in 5 fractions) with a reduction of symptoms (no more swelling sensation and no speech worsening), but persistence of paraesthesias.
Conclusions: Cerebellopontine angle tumors may cause trigeminal neuralgia, but such painful condition is usually brief, intense and electric shock-like. In our case, the meningioma is probably the cause of such particular clinical presentation and cyberknife intervention may have reduced tumor dimensions, soothing symptoms. Since the patient did not recover fully, other approaches are still needed.

The prevention of migraine without aura with KUZIK®. An open-label observational trial

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Background: Kudzu (*pueraria lobata*) is a wild climbing plant native to Central Asia belonging to the Fabaceae family, with a root having a high content of isoflavones. This open-label observational study evaluated the efficacy and tolerability of kudzu (K) developed with an innovative programmed release technology (Kuzik® by GAM FARMA) in a sample of 60 consecutive patients with migraine without aura (MWOA), who needed prophylaxis treatment (diagnosis and prophylaxis according to ICDH-II)
Methods: Sixty patients (F/M = 13/47, age: 37.9±11.4) with MWOA received K at a dose of 1 cps UID for 120 days. The efficacy of the treatment was evaluated considering the days of headache per month (primary endpoint), pain intensity according to the NRS scale and NSAID consumption per month (secondary endpoints), at T0, T1 and T2 (after 60 and 120 days of therapy), with the help of the patient's headache diary.
Results: *Frequency:* At T0, was 10.1±3.2. At T1, the average frequency was 6.8±3.2 (min: 0 max: 15) resulting in a statistically significant mean reduction of 3.3 attacks (I.C. 95%: 2.6 - 3.9; p<0.001). At T2 the value was 5.7 ± 2.8 with an average reduction, compared to T0, of 4.4 (95% CI: 3.6 - 5.2; p<0.001). The percentage of patients who observed a reduction equal to or greater than 50% in the frequency was 16.7% at T1 and 31.7% at T2. *NRS:* The mean value on NRS on T0 was 8.3±3.2. At T1, a statistically significant reduction of 2.0 points was observed (I.C. 95% 1.5 - 2.5%, p<0.001). At T2, the mean reduction from baseline was 2.7 points (I.C. 95% 2.0 - 3.4%, p<0.001). *NSAID Consumption:* At T0 the average consumption of NSAID was 9.5±4.7 units. At T1 the consumption was reduced by 3.6 units (95% CI: 2.5 - 4.7, p<0.001), this reduction was substantially confirmed at T2 (4.5, 95% CI: 3.2 -5.7, p<0.001) with NSAID consumption 5.0±3.1 units.
Conclusions: The prophylactic use of Kudzu resulted in a reduction equal to or greater than 50% of the frequency in 31.7% of patients, a significant reduction in the average consumption of NSAID and in the NRS score. No side effects were reported during therapy. These data demonstrate the efficacy of Kudzu as prophylaxis treatment for migraine without aura, associated with good tolerability.

Efficacy of fremanezumab in patients with chronic migraine with or without concomitant use of preventive medication

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Background: Some patients with CM may take more than one preventive medication. Fremanezumab (TEV-48125), a fully humanized monoclonal antibody targeting calcitonin gene-related peptide (CGRP), has demonstrated efficacy in migraine prevention.
Methods: In this Phase III, randomized, double-blind, placebo-controlled, parallel-group study, eligible patients with prospectively confirmed CM (≥15 headache days and ≥8 migraine days per month) were randomized 1:1:1 to receive subcutaneous injections of fremanezumab quarterly (675 mg at baseline; placebo at Weeks 4 and 8), fremanezumab monthly (675 mg at baseline; 225 mg at Weeks 4 and 8) or placebo at each time point over a 12-week treatment period. Changes from baseline were assessed in the monthly average number of headache days of at least moderate severity, and in migraine days in patients with or without concomitant preventive medication.
Results: Analyses included 239 patients receiving one concomitant preventive medication (quarterly, N=77; monthly, N=85; placebo, N=77) and 882 patients receiving none (quarterly, N=298; monthly, N=290; placebo, N=294). During the 12-week treatment period, fremanezumab reduced from baseline the mean number of monthly headache days of at least moderate severity versus placebo in patients receiving concomitant preventive medication (quarterly: −3.8±0.61; monthly: −4.5±0.57; placebo: −2.5±0.61), reaching significance with monthly dosing (P=0.003). Reductions were also significant for fremanezumab quarterly and monthly in those not receiving concomitant preventive medication (quarterly: −4.6±0.33; monthly: −4.9±0.33; placebo: −2.7±0.33; both, P<0.0001). These reductions were observed as early as 4 weeks after initiation of fremanezumab monthly in patients receiving concomitant preventive

medication (P=0.028); similarly early reductions occurred with fremanezumab monthly and quarterly in patients not receiving concomitant preventive medication (P<0.0001). There were also fewer migraine days with both fremanezumab regimens.
Conclusions: Fremanezumab demonstrated efficacy in patients with CM, regardless of concomitant preventive medication use.

Long-term impact of fremanezumab on response rates, acute headache medication use, and disability in patients with episodic migraine: interim results of a 1-year study

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Background: Migraine preventive treatment is intended to reduce the frequency, severity, and disability associated with migraine attacks. Fremanezumab, a fully humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), is approved for the preventive treatment of migraine.
Methods: In this 52-week, multicenter, randomized, double-blind, parallel-group study, patients with EM (rolled over from a placebo-controlled study and new patients) received either subcutaneous fremanezumab quarterly (675 mg every 3 months) or monthly (225 mg every month). The percentage of patients achieving ≥50% reduction in monthly average number of migraine days or headache days of at least moderate severity, the mean change from baseline in the monthly number of days of use of any acute headache medications, and the mean change from baseline in Migraine Disability Assessment (MIDAS) scores were assessed.
Results: This study enrolled 780 patients (119 new, 661 rollover). The proportion achieving ≥50% reduction in migraine days at Month 12 was 66% with quarterly dosing and 68% with monthly dosing. Similar response rates were observed for headache days of at least moderate severity (quarterly 68%, monthly 66%). The mean change in monthly number of days of use of any acute headache medications from baseline to Month 12 in patients with EM was –4.6 days in the quarterly group and –4.4 days in the monthly group. The change from baseline in the MIDAS disability score in patients with EM was similar in both treatment groups at Month 12; disability scores decreased by 26.0 and 27.4, respectively, in the quarterly and monthly groups.
Conclusions: Efficacy, reduced acute medication use, and improvements in disability were maintained through 12 months of treatment with fremanezumab in patients with EM.

High frequency migraine with aura: efficacy of combination of tanacetum parthenium, 5-HTP and Mg+ (Aurastop©) in the reduction of the frequency of the aura attacks

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Background: Each component of the novel phytotherapic combination of Tanacetum Parthenium (150 mg), 5-hydroxy tryptophan (20 mg) and magnesium (185 mg) (Aurastop©) acts on a different target among the main mechanisms involved in the pathophysiology of migraine and of the aura itself: sensitization of the trigeminal vascular system, central sensitization and activation of the "migraine generator" located in the brainstem, through glutammate and kynurenine pathways and the cortical spreading depression. Aim of this study was to test the effectiveness of Aurastop© in the prophylaxis of migraine with aura with high frequency
Methods: Thirty patients (F: n=18, M: n=12, mean age: 32) presenting with an ICHD-3 beta diagnosis of migraine with aura (MWA) but with a frequency of more than 5 attacks of migraine with aura per month for at least 6 months, (High frequency MWA) were enrolled in the survey and treated with Aurastop© twice a day for a period of 3 months. Diary cards were filled in during a 3-months period prior the beginning of the survey and during the 3-months duration of the study. The reduction of MWA attacks per month was assessed as the primary end-point; the reduction of the duration and disability of the aura and of the intensity of the headache were considered as secondary end-points.
Results: A statistically significant reduction of MWA attacks/month was observed: more than 90% of the patients referred a reduction >60% of the frequency. Moreover, a sensible reduction of the duration and disability of the aura phenomena was reported by more than 80% of the patients and, in 55% of the patients also a reduction of the intensity of the headache. No side effects were reported. The efficacy started to appear during the first month of intake and was maintained during the three months of therapy .
Conclusions: In this observational open study, Aurastop© appears to be effective and safe as a preventive treatment of MWA in the patients with a high frequency of attacks.

Comparison of the effect of tanacetum parthenium, 5-hydroxy tryptophan and Mg+ (Aurastop) versus magnesium alone on aura phenomenon and its evolution

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Background: None of the clinical trials on migraine conducted thus far have focused on the possibility to modulate the phenomenon of aura and result in a better control of the headache phase.
Methods: In the setting of a single-center, pilot clinical trial we aimed at comparing the effects of Aurastop (a combination of tanacetum parthenium [150 mg extracted at 0.8%=1.2 mg di of active partenolide], griffonia simpliciofila [20 mg of 5-hydroxy tryptophan], and magnesium [185 mg of magnesium pidolatum]) with those of magnesium alone (2.25 grams/tablet, corresponding to 184 mg of Mg ++) in the treatment of acute attacks of migraine with aura. Between June 2017 and June 2018, 50 consecutive patients (27/23 male/female; mean age, 31 years [18–57]) with at least 3 episodes of aura per year were included (t0). Participants were instructed to keep track of the following 4 episodes of migraine with aura (t1), and invited to assume 1) a tablet of Aurastop at the beginning of the following 2 episodes of aura, and 2) a magnesium tablet alone at the occurrence of the third and fourth aura attacks.
Results: Forty-eight (96.0%) had >50% reduction in aura duration when treated with Aurastop vs 7 (14.0%) when treated with magnesium alone (p<0.001), 48 (96.0%) had >50% reduction of aura-related disability when receiving Aurastop vs 5 (10.0%) patients when treated with magnesium alone (p<0.001), while patients receiving Aurastop did not need to take pain killers in 35% of aura attacks vs 3% when assuming magnesium (p<0.001).
Conclusions: These results support the hypothesis that Aurastop might be effective in interfering with the phenomenon of aura and provide evidence that the clinical benefit attributable to this combination of

molecules might be greater than that obtained with single compounds of proven effect on the biology of migraine.

One-year treatment with galcanezumab in patients with chronic migraine: results from the open-label phase of the REGAIN study

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Background: Chronic migraine is a neurological condition with a high disease burden and unmet clinical need. The objective was to assess long-term efficacy and safety of galcanezumab, a humanized monoclonal antibody that selectively binds to calcitonin gene-related peptide, in adult patients with chronic migraine.
Methods: This was a phase 3, double-blind (DB), randomized, placebo-controlled, 3-month study with a 9-month open-label extension (OLE). Eligible patients with chronic migraine were randomized 2:1:1 to subcutaneous injections of placebo (N=558), galcanezumab 120mg with a 240 mg loading dose (N=278), or galcanezumab 240 mg (N=277), given once monthly for 3 months. Patients entering the OLE received a 240-mg loading dose of galcanezumab, followed by a maintenance dose of 120mg/month at the next month, with flexible dosing thereafter (120 or 240 mg/month). Efficacy measures included number of monthly migraine headache days (MHD), ≥50% reduction in monthly MHD, and Migraine-Specific Quality of Life Questionnaire Role Function-Restrictive (MSQ-RFR) domain score. Change from baseline in continuous and categorical measures over 12 months was analyzed using mixed model repeated measures analysis and generalized linear mixed models (GLIMMIX), respectively. OLE results are reported by prior DB treatment assignment.
Results: Of 1,037 patients who completed DB treatment, 1,022 subsequently entered the OLE, with 825 completing. Patients previously treated with placebo showed a rapid mean reduction in monthly MHDs after the first open-label dose and maintained this improvement over time, whereas the previous 120 and 240mg galcanezumab groups generally maintained or improved upon gains from the DB treatment phase (month 12: placebo, -8.41; galcanezumab 120mg, -8.89; galcanezumab 240mg, -7.99 from a baseline of 19.4 MHDs). The mean percentage of patients with ≥50% reduction from baseline ranged 44.5-45.6% at month 6 and 53.3-56.9% at month 12. Mean improvement from baseline on MSQ RFR ranged 26.5-30.2 points at month 6 and 29.0-32.9 points at month 12 on the 100-point scale. The most common (≥5%) treatment-emergent adverse events were nasopharyngitis (9.6%), upper respiratory tract infection (6.2%), and injection-site reaction (5.9%). 4.5% of patients discontinued due to an adverse event, and 4 patients (0.4%) discontinued due to an injection-site–related adverse event. There were no clinically meaningful changes in any of the safety measures.
Conclusions: Final OLE results support the observation that galcanezumab appears effective, safe, and well tolerated for the preventive treatment of chronic migraine. Galcanezumab had a favorable safety profile after 1 year of treatment at doses of 120 or 240mg/month. No new safety findings were identified.

Shift from chronic migraine to episodic migraine status in a long-term phase 3 study of galcanezumab

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Background: Relative to episodic migraine, chronic migraine is associated with substantially greater disease-state burden due to higher rates of disability, comorbid conditions, acute medication use and healthcare resource utilization. Galcanezumab is approved for prevention of chronic and episodic migraine. Results from a long-term Phase 3 study in patients with chronic migraine are reported. The objective was to assess proportions of patients with chronic migraine who shift to episodic migraine status during treatment with galcanezumab or placebo.
Methods: REGAIN included patients aged 18–65 years with an ICHD-3β diagnosis of chronic migraine who met chronic criteria during a 1-month prospective baseline period (i.e. ≥15 headache days/month, of which at least 8 are migraine headache days [MHDs]). Patients were randomized 2:1:1 to receive subcutaneous monthly injections of placebo, galcanezumab 120 mg (with a loading dose of 240 mg) or galcanezumab 240 mg for up to 3 months of double-blind treatment. Patients who completed the double-blind period could enter a 9-month open-label extension (120 or 240 mg/mo galcanezumab). Results from patients who received galcanezumab during the double-blind and/or open-label periods are reported. Achieving episodic migraine status was defined as <8 MHDs or <15 headache days/month for ≥3 consecutive months. In addition, we evaluated the proportions of patients who shifted to <8 MHDs/month (low frequency) and <4 MHDs/month (very low frequency).
Results: In REGAIN, at baseline, mean (SD) number of MHDs/month was 19.4 (4.5) and mean (SD) number of headache days/month was 21.4 (4.1). At the end of double-blind treatment period (Month 3), a greater proportion of galcanezumab-treated patients shifted to episodic status (30.9%) than did placebo-treated patients (19.7%). Among galcanezumab-treated patients across the entire 12-month trial, 65.1% shifted from chronic migraine to episodic status, 44.2% shifted to low frequency and 21.5% shifted to very low frequency for ≥3 consecutive months. Proportions of patients shifting from chronic migraine to episodic status for ≥3 consecutive months and until last patient visit were: shift to episodic status: 55.0%; shift to low frequency: 33.4%; shift to very low frequency: 13.9%.
Conclusions: Treatment with galcanezumab led to a majority of patients with chronic migraine shifting to episodic migraine status. These results suggest that long-term treatment with galcanezumab may lead to substantial reductions in the disability and economic burden associated with chronic migraine.

Patient gains in daily functioning and reductions in disability with galcanezumab among patients with episodic and chronic migraine

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Background: The Migraine Disability Assessment (MIDAS) and the Migraine-Specific Quality of Life Questionnaire v.2.1 (MSQ) are patient-reported outcome instruments that assess patients' migraine-related disability and functional impairment. The objective of this study was to evaluate categorical shifts in patients' migraine-related disability and functioning after treatment with galcanezumab.
Methods: The MIDAS and MSQ were performed during three double-blind clinical studies, including two 6-month studies that enrolled patients with episodic migraine (EVOLVE-1 and EVOLVE-2, N=1,773) and one 3-month study of patients with chronic migraine (REGAIN, N=1,113). Based on MIDAS scores, patients were grouped into 5 disability grades, from "little/no disability" up to "very severe disability." Categorical shifts in MIDAS disability grade from baseline to endpoint were compared between galcanezumab and placebo groups. Individual improvements

in the 7 items of the MSQ Role Function-Restrictive domain (MSQ-RR) were also evaluated.
Results: Among patients who had "moderate to very severe disability" at baseline in EVOLVE-1&2 (pooled), 44.0% of galcanezumab patients shifted to "little/no disability" at the end of 6 months, compared to 26.5% of placebo patients. Among patients with "very severe disability" at baseline in REGAIN, 49.5% of galcanezumab patients had shifted to lower grade levels at the end of 3 months, compared to 39.9% of placebo patients. Patients using galcanezumab improved their MIDAS disability grade by one or more grades at study completion at significantly ($p<0.01$) higher rates than were seen with placebo (73.0% vs 57.5% for episodic and 48.6% vs 40.3% for chronic). Significantly ($p<0.001$) greater percentages of patients showed improvements in each MSQ-RR item for EVOLVE-1&2 when treated with galcanezumab (range: 73.1% to 80.3%) compared to placebo (range: 60.4% to 66.1%); REGAIN results were also significant for most items.
Conclusions: Patients treated with galcanezumab for the prevention of episodic or chronic migraine showed lower levels of migraine-related disability and greater improvements in daily functioning compared to placebo.

Rapid onset of effect of galcanezumab for the prevention of episodic migraine: post-hoc analyses of two phase 3 studies

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Background: The humanized monoclonal antibody galcanezumab (LY2951742), which binds to calcitonin gene-related peptide, has been evaluated for migraine prevention. The aim of these post-hoc analyses is to describe the onset of effect of galcanezumab for prevention of episodic migraine based on data from the Phase 3 clinical program.
Methods: These analyses were derived from patients who participated in the randomized, double-blind, placebo-controlled Phase 3 studies (EVOLVE-1 [NCT02614183] and EVOLVE-2 [NCT02614196]) that included patients aged 18-65 years with a diagnosis of episodic migraine and a history of migraine headaches for ≥1 year. A total of 1,773 (858 EVOLVE-1, 915 EVOLVE-2) patients were randomized and received either 120 mg or 240 mg galcanezumab (n=879) or placebo (n=894). Study drug was administered subcutaneously once per month for 6 months. The patient population was predominately female (83.7% EVOLVE-1, 85.4% EVOLVE-2) and white (80.4% EVOLVE-1, 70.3% EVOLVE-2) with a mean age of approximately 41 years (40.7 years EVOLVE-1, 41.9 years EVOLVE-2). On average, patients had been diagnosed with migraine approximately 20 years prior to study entry (20.1 years EVOLVE-1, 20.6 years EVOLVE-2), most patients experienced severe disability (Migraine Disability Assessment total score: 33.2 EVOLVE-1, 33.0 EVOLVE-2); the approximate mean number of baseline monthly migraine headache days (MHDs) was 9 (9.1 days EVOLVE-1 9.1 days EVOLVE-2). Patients in the 120-mg group received a 240-mg loading dose for the first month. Onset-of-effect analyses therefore evaluated the pooled galcanezumab-treated patients vs placebo as both galcanezumab groups received 240 mg in the first month. The number of weekly MHDs was modeled using a repeated measures ordinal logistic regression, and the odds ratios of having fewer MHDs for the galcanezumab group compared with the placebo group were evaluated for each week in Month 1. Onset of effect was defined as the earliest week in which a statistically significant separation between galcanezumab and placebo was observed and maintained for all remaining weeks in Month 1.
Results: For both studies, change from baseline in MHD showed a statistically significant separation of galcanezumab from placebo at Month 1 and for all subsequent months (each $p<0.001$). The weekly MHD analyses showed that onset of effect occurred at Week 1. The odds ratio of having fewer weekly MHDs with galcanezumab vs placebo was statistically significant at Week 1 for each study and maintained for Weeks 2-4 ($p\leq0.004$).
Conclusions: This rapid onset of effect of galcanezumab makes it a promising medication for prevention of migraine.

Reversion of patients with chronic migraine to an episodic migraine classification with fremanezumab treatment

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Background: CM and EM are clinically, functionally, and anatomically differentiated, with evidence suggesting that they may be separate conditions. Furthermore, patients with CM usually have more comorbid conditions and more-frequent medication overuse, which complicates their clinical management. Fremanezumab (TEV-48125), a fully humanized monoclonal antibody targeting calcitonin gene-related peptide (CGRP), has demonstrated efficacy in migraine prevention.
Methods: In this Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, adults with prospectively confirmed CM (≥15 headache days and ≥8 migraine days per month) were randomized 1:1:1 to subcutaneous injections of fremanezumab quarterly (675 mg at baseline; placebo at Weeks 4 and 8), fremanezumab monthly (675 mg at baseline; 225 mg at Weeks 4 and 8), or matching placebo over a 12-week treatment period. Post hoc analyses evaluated the proportion of patients who reverted from CM to EM, defined as patients who had ≥15 headache days per month at baseline (28-day pre-treatment period) and then had <15 headache days per month in all 3 months of the treatment period.
Results: In an analysis of the 1130 CM patients randomized in this trial (quarterly, N=376; monthly, N=379; placebo, N=375), significantly more fremanezumab-treated patients reverted from having ≥15 headache days per month at baseline to <15 headache days per month in Months 1, 2, and 3 (quarterly: 121 patients [32%]; monthly: 133 patients [35%]) than those who received placebo (86 patients [23%]; both, $P\leq0.002$). On average, these fremanezumab-treated patients had 18–19 headache days per month at baseline and showed reductions to 6–9 headache days during any month in the treatment period, representing up to an approximately 70% reduction in headache days.
Conclusions: Along with its efficacy as a migraine preventive treatment, fremanezumab demonstrated the potential benefit for reversion from CM to EM.

The impact of fremanezumab on headache-related disability in patients with chronic migraine using the Headache Impact Test (HIT-6)

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Background: Fremanezumab is a fully-humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), has been shown in clinical trials to reduce the frequency, severity, and duration of headaches in patients with chronic migraine (CM). However,

the full impact of a treatment cannot be fully evaluated from headache frequency alone. Accordingly, the 6-item Headache Impact Test (HIT-6) has been developed to assess headache-related disability.
Methods: Study TV48125-CNS-30049 was a 12-week multicenter, double-blind study of the efficacy, safety, and tolerability of fremanezumab in treatment of CM. Eligible patients were randomly assigned 1:1:1 to quarterly dosing (fremanezumab 675 mg s.c. at baseline, placebo at Weeks 4 and 8), monthly dosing (fremanezumab 675 mg at baseline, 225 mg at Weeks 4 and 8), or placebo at each time point. As a secondary endpoint, HIT-6 scores were evaluated from baseline to 4 weeks after the last dose. Efficacy analyses were performed in the full analysis set (FAS; all randomized patients receiving ≥1 dose and having ≥10 days of post-baseline primary endpoint assessments, N=1121), and repeated for the per-protocol analysis set (PPS; all patients completing the study without violation of eligibility criteria or omission of drug administration, N=959).
Results: Treatment with both fremanezumab regimens led to significant and large reductions in HIT-6 scores from baseline to endpoint. In the FAS, least-squares mean changes (± standard error) were −6.4±0.5 for quarterly dosing (n=375), −6.8±0.4 for monthly dosing (n=375), and −4.5 ±0. 5 for placebo (n=371), leading to significant treatment differences (quarterly: −1.9±0.5; monthly: −2.4±0.5; both P<.001). Similar treatment differences were observed in the PPS (quarterly: −2.1±0.5; monthly: −2.3 ±0.5; both P<.001).
Conclusions: In this Phase 3 study, fremanezumab treatment was associated with significant improvement in headache-related disability in patients with CM.

The impact of fremanezumab on headache-related disability in patients with episodic migraine using the Migraine Disability Assessment

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Background: Episodic migraine(EM), attacks on ≤15 days per month, has a risk for progression to chronic migraine and affects daily functioning. In clinical trials, fremanezumab, a fully-humanized monoclonal antibody (IgG2Δa), selectively targets calcitonin gene-related peptide ligand, reduced headache frequency in EM patients. The impact of migraine is evaluated utilizing the Migraine Disability Assessment (MIDAS), a validated questionnaire, to assess disability in migraine patients.
Methods: 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adults with EM(TV48125-CNS-30050), randomized 1:1:1 ratio to 1 of 3 treatment groups: (1)monthly dosing: 225 mg fremanezumab at months 1, 2 and 3, (2)quarterly dosing: 675 mg fremanezumab at month 1, followed by placebo injections at months 2 and 3, and (3)monthly administration of matching placebo. As a secondary endpoint, changes in MIDAS scores were evaluated from baseline to 4 weeks after last dose. Efficacy analyses were performed in the full analysis set (FAS; all randomized patients receiving ≥1 dose and having ≥10 days of post-baseline primary endpoint assessments, N= 865), and repeated for the per-protocol analysis set (PPS; all patients completing the study without violation of eligibility criteria or omission of drug administration, N=847).
Results: A total of 875 patients were randomly assigned to fremanezumab quarterly (n=291), fremanezumab monthly (n=290), or placebo (n=294). Least square mean (± standard error) changes from baseline in MIDAS score were larger for fremanezumab (quarterly:−23.0±1.6; monthly: −24.6±1.6) than for placebo (−17.5±1.6), resulting in significant treatment differences (quarterly: −5.4±1.8, P=.002; monthly: −7.0±1.8, P<.001) versus placebo. Similar treatment differences versus placebo were observed in the PPS (quarterly: −5.5±1.9, P=.003; monthly: −7.3±1.8 points, P<.001).
Conclusions: In this Phase 3 study, fremanezumab treatment demonstrated a significant improvement in headache-related disability in patients with EM.

The impact of fremanezumab on medication overuse in patients with chronic migraine

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Background: Overuse of acute or symptomatic headache medications, such as triptans, ergot derivatives, opioids, and combination analgesics, can cause medication overuse headache (MOH). CM is often accompanied by MOH. Fremanezumab, a fully humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), is efficacious in preventing CM.
Methods: In this Phase 3, multicenter, randomized, double-blind, placebo-controlled study, CM patients were randomized 1:1:1 to receive subcutaneous fremanezumab quarterly (675 mg at baseline, and placebo at Weeks 4 and 8), fremanezumab monthly (675 mg at baseline, and 225 mg at Weeks 4 and 8), or placebo (at baseline, Weeks 4 and 8). We assessed the proportion of patients who reverted from overusing medications at baseline to not overusing medications during the 12-week treatment period, and the change from baseline in the number of days of acute headache medication use.
Results: Among patients with medication overuse at baseline (quarterly n=201; monthly n=198; placebo n=188), more patients treated with fremanezumab reported no medication overuse during the treatment period (quarterly: 55%, P=0.0389; monthly: 61%, P=0.0024) than those who received placebo (46%). Response to treatment was seen by Week 4 (quarterly: 51%, P=0.0091; monthly: 54%, P=0.0014; vs placebo: 39%). Among the patients who responded to treatment, the baseline number of days with medication overuse was similar across treatment groups (quarterly [mean]: 16.6 days; monthly: 16.7 days; placebo: 16.6). Within this population, fremanezumab treatment significantly reduced the days of acute headache medication use (quarterly: –9.0 days, P=0.0017; monthly: –8.9 days, P=0.0040) compared with those who received placebo (–7.1 days).
Conclusions: Fremanezumab treatment was associated with a reduction in overuse of acute medications and a corresponding decrease in days using acute medications.

Long-term impact of fremanezumab on response rates, acute headache medication use, and disability in patients with chronic migraine: Results of a one-year study

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Background: Migraine preventive treatment is intended to reduce the frequency, severity, and disability of migraine attacks. Fremanezumab, a fully humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), is approved in the US for the preventive treatment of migraine.

Methods: In this 52-week, multicenter, randomized, double-blind, parallel-group study, patients with CM received either subcutaneous fremanezumab monthly (225 mg every month with a starting dose of 675 mg) or quarterly (675 mg every 3 months). The percentage of patients achieving ≥50% reduction in monthly average number of headache days of at least moderate severity or migraine days, the mean change from baseline in the monthly number of days of use of any acute headache medications, and the mean change from baseline in Headache Impact Test (HIT-6) score (assessing disability) were assessed.
Results: This study enrolled 1110 patients with CM. The proportion achieving ≥50% reduction in monthly average number of headache days of at least moderate severity at Month 12 was 54% with quarterly dosing and 59% with monthly dosing. The proportion achieving ≥50% reduction in monthly average number of migraine days at Month 12 was 53% with quarterly dosing and 57% with monthly dosing. The mean change in monthly number of days of use of any acute headache medications from baseline to Month 12 was –6.0 days in the quarterly group and –6.2 days in the monthly treatment group. HIT-6 scores decreased by 8.4 and 7.7 at the end of treatment for the monthly and quarterly groups, respectively, meeting the minimally important difference.
Conclusions: Efficacy, decreased acute medication use, and improvements in disability were maintained through 12 months of treatment with fremanezumab in patients with CM.

Reduction in acute headache medication use among episodic migraine patients in the HALO fremanezumab trial

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Background: Overuse of acute headache medications in people with EM can lead to worsening of headaches or transformation to chronic migraine. Fremanezumab (TEV-48125), a fully humanized monoclonal antibody targeting calcitonin gene-related peptide (CGRP), has proven efficacy in migraine prevention.
Methods: In this Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, eligible adult patients with prospectively confirmed EM (6–14 headache days and ≥4 migraine days per month) were randomized 1:1:1 to receive subcutaneous injections of fremanezumab monthly (225 mg at baseline, Weeks 4 and 8), fremanezumab quarterly (675 mg at baseline, and placebo at Weeks 4 and 8), or placebo at each time point over a 12-week treatment period. The monthly numbers of days on which patients used either acute headache medications of any type or those specific to migraine (triptans and ergots) were evaluated as secondary and exploratory endpoints.
Results: 875 patients were randomized (monthly, N=290; quarterly, N=291; placebo, N=294). Both fremanezumab regimens significantly reduced the monthly number of days with use of any acute medication (monthly: −3.0±0.22 days; quarterly: −2.9±0.22 days;) versus placebo (−1.6±0.21 days) during the 12-week treatment period (both, P<0.0001), with significant reductions observed as early as Week 4 (monthly: −2.9±0.24 days; quarterly: −2.8±0.24 days; placebo: −1.1±0.24 days) and at each time point thereafter (all, P<0.01). Similarly, fremanezumab significantly reduced migraine-specific acute headache medication use (monthly: −3.1 ±0.26 days; quarterly: −3.1±0.26 days) versus placebo (−0.9 ±0.27 days) over the 12-week period (both, P<0.0001).
Conclusions: Fremanezumab reduces the need for acute headache and migraine-specific medication use in patients with EM.

Alcohol evokes periorbital allodynia via acetaldehyde and TRPA1 in mice

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Background: Alcoholic beverages cause in susceptible individuals headaches associated with flushing and hangover and provoke migraine attacks in a relevant proportion of migraineurs. A typical feature of alcohol-evoked headaches is a delayed onset that markedly outlasts the presence of ethanol in blood and tissues. The transient receptor potential vanilloid 1 (TRPV1) that belongs to the TRP family of ion channels, is selectively gated by 1-3% concentrations of ethanol, that by this mechanism signals pain and inflammation. Another TRP channel, the ankyrin 1 (TRPA1) subtype, highly sensitive to the redox state of the milieu, is gated by an unprecedented series of reactive oxygen (ROS), nitrogen (RNS) and carbonyl (RCS) species and unsaturated and saturate aldehydes, including the ethanol metabolite, acetaldehyde. The present study explored the role of TRP channels in mediating prolonged responses that may be relevant for the delayed ethanol-evoked headaches in patients.
Methods: Ethanol and acetaldehyde were administered by local injection in the periorbital area of C57BL/6, and TRPA1 and TRPV1 wild type and knock out mice. Spontaneous nociception was assessed by measuring the time (seconds) that the animal spent face rubbing the injected area with its paws. Periorbital mechanical allodynia was evaluated by applying the von Frey filaments to the periorbital region over the rostral portion of the eye before and after (1-24 h) ethanol or acetaldehyde.
Antagonists were administered by local and systemic injections.
Results: Local injection of ethanol in the periorbital skin caused two sensory responses, which are temporally and mechanistically distinct: a short-lived nociceptive response that was absent and a delayed and prolonged mechanical allodynia that was maintained in TRPV1-deleted mice. Allodynia was prevented by pretreatment with an alcohol dehydrogenase inhibitor, thus supporting the view that acetaldehyde, derived from ethanol metabolism, mediates the prolonged allodynic effect of ethanol. In addition, genetic deletion of TRPA1 prevented ethanol- and acetaldehyde-evoked allodynia underling that the aldehyde and not its precursor gates TRPA1 and plays a major role in the ethanol-evoked allodynia.
Conclusions: The present study confirms that exposure to ethanol causes an acute nociceptive response that is mediated by TRPV1 and reveals that the prolonged mechanical allodynia is due to TRPA1 activation by the alcohol metabolite, acetaldehyde. Results underline that TRPA1 may be an effective molecular target for an effective treatment for pain caused by alcohol ingestion.

Ethanol ingestion causes prolonged pain in mice via Schwann Cells and TRPA1

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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, a sensor for oxidative and carbonyl stress, 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 (intragastric administration) 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: Both acute and chronic ethanol ingestion caused delayed periorbital mechanical allodynia in mice. Inhibition of ADH or deletion of TRPA1prevented allodynia. Acetaldehyde generated by ADH in both liver and Schwann cells surrounding nociceptors was required for TRPA1-induced allodynia. 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.
Conclusions: 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 alcohol-evoked mechanical allodynia. These findings suggest that antagonists of TRPA1 might represent a therapeutic options for ethanol-evoked pain in humans.

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 signalling 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 their paws after local administration of prostaglandin E_2 (PGE_2), prostacyclin (PGI_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) 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 PGE_2, PGI_2, $PGF_{2\alpha}$, but not histamine evoked spontaneous nociception. Histamine, PGE_2 and PGI_2, but not $PGF_{2\alpha}$ evoked a dose-dependent periorbital mechanical allodynia. The painful responses were attenuated by systemic or local (periorbital) administration of selective antagonists of the histamine (H_1), PGE_2 (EP_4), and PGI_2 (IP) receptors, respectively.
Conclusions: The ability of histamine, PGE_2, PGI_2 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 $PGF_{2\alpha}$ to elicit PMA in mice is consistent with the observation that such prostanoid does not provoke migraine-like attacks in humans.

Cannabis for the treatment of refractory headaches: a case-series of 18 patients

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Introduction: Cannabinoids are emerging as promising therapies for chronic pain conditions. In Italy, cannabinoids have been recently approved for the treatment of chronic neuropathic pain of moderate or severe intensity (NRS>=7). Since 2017 even general practitioners can prescribe cannabis preparations to their patients. So that, the availability of these drugs has dramatically increased. However, limited evidence exists regarding the use of cannabinoids in chronic migraine. The aim of this study was to assess the possible benefits of its use on chronic migraineurs.
Methods: Clinical status of patients receiving cannabis oil formulation named "FM2" (titrated at the 5-8% of delta-9-tetrahydrocannabinol and at 7-12% of cannabidiol) was retrospectively analyzed, to check out variations in headache index, analgesic consumption and medium numeric rating scale (NRS) score. Statistical calculation were made with STATA Ic13 software.
Results: Globally, 18 patients were analyzed. Medium age was 53±6. The mean number of headache days over 30 days in the last three months before starting medical cannabis was 0.86 [95% CI, 0.75÷0.96] and after that was 0.75 [95%CI, 0.6÷0.89] (ttest P-value=0.2039). Before starting cannabis the mean analgesic consumption was 1.83 [95% CI, 0.58÷3.07] and after 3 month was improved [0.85; 95% CI, 0.5÷1.19], even if not significantly (ttest p-value=0.11889). Finally, mean NRS score passed from 0.83 [95% CI, 0.78÷0.89] to 0.64 [95% CI, 0.55÷0.74], stating a significant reduction (ttest P-value=0.0013). The most frequent complained adverse events were drowsiness and short attention.
Conclusions: Cannabinoid oral formulation can be a safe and effective therapeutic weapon to reduce, at least, pain intensity in chronic refractory headache- helping patients to improve their almost low quality of life.

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.
Conclusions: 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.

Prophylactic effect of ultramicronized N-Palmitoyl Ethanol Amide (PEA) on pediatric migraine

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Background: Palmitoyl ethanolamide (PEA) is an amide of endogenous fatty acids widely distributed in different tissues, including nervous tissues. PEA is emerging as a new therapeutic approach in pain and inflammatory conditions and it has been evaluated in studies on various painful diseases. However, to date no studies have been conducted to evaluate the role of PEA in the management of migraine in pediatric patients. The aim of this open-label study was to evaluate the efficacy of ultramicronized PEA (um-PEA) in the prophylactic treatment of migraine.
Methods: The study included 53 patients with mean age of 10.67± .1 (24.5% M and 75.5% F). All patients had a diagnosis of migraine without aura (ICHD 3 criteria) and received umPEA (600 mg/day orally) for three months. We compared the attack frequency (AF) and attack intensity at baseline and after three months. Patients were asked to classify the intensity of the attack with a value ranging from 1 to 3 where 1 means mild attack, 2 moderate and 3 severe attack.
Results: After 3 months of treatment with um-PEA, the headache frequency was reduced by >50% per month in 56.6% patients. Three patients discontinued treatment too early (less than a month) and were not considered in the results. After three months of treatment the number of monthly attacks decreased significantly compared to the start of therapy (from 13.89±7.6 SD to 6.43±5.1 SD; $p<0.05$). The intensity of the attacks went from 1.70±0.6 (pre-PEA) to 1.19±0.5 (post-PEA).
Discussion: Our preliminary data show that um-PEA administered for three month reduces pain intensity and the number of attacks per month in pediatric patients with migraine. Although the small number of patients and the lack of a control group do not allow us to consider these initial results as definitely reliable, they encourage us to expand the sample.

Comparative assessment of efficacy of physical therapy and onabolulinumtoxin A on headache parameters and pressure pain threshold in chronic migraine

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Objectives: The first aim consists to compare Onabotulinum toxin A (BoNT-A) and Physical Therapy (PT) in Chronic Migraine (CM) concerning headache parameters, such as, frequency of migraine, duration of attacks and intensity of pain.
The second one of evaluating central sensitization with the instrumental assessment of Pressure Pain Threshold (PPT) in 5 muscles of trigeminal area, 1 far from this area.
Methods: Patients suffering from Chronic Migraine (ICHD-3 beta criteria) were enrolled in the Headache Centre of Trieste (T0). Patients were not taking prophylaxis in the three months prior to their enrolment. A three-month baseline period was registered with an ad hoc diary (T1). The PPT was assessed with algometry Somedic in 5 muscles of trigeminal area (trapezius, levator scapula, temporalis, suboccipitalis, middle scalene right and left) and 1 far from this area (tensor fascia lata right and left). The patients followed a randomization scheme 1:1:1 and were included in the 3 treatment groups, respectively (T2): Onabotulinum toxin A (BoNT-A), Onabotulinum toxin A + Physiotherapy (BoNT-A+ PT), Physiotherapy (PT). Finally, after three months of treatment, the final visit was performed (T3) with analysis of the parameters reported in the diary and of the PPT with algometry. Concerning BoNT-A we used a specific protocol PREEMPT approved by FAD, while PT protocol was an integrated type treatment of manual therapy, active exercises and patient education.
Data was analysed with Wilcoxon test of the sample pair to compare initial and final evaluations, and Kruskal-Wallis test for the comparison of the two final evaluations. The statistical significance level was 95% (0.05).
Results: Six BoNT-A, 10 BoNT-A+PT, 10 PT patients were enrolled. At the final assessment frequency improved statistically significant in all groups (PT p=0.002; BoNT-A+PT p=0.01; BoNT-A p=0.03) and also duration of attacks (PT p=0.009; BoNT-A+PT p=0.002; BoNT-A p=0.03); while pain intensity decreased statistically significant only in BoNT-A (p=0.03) and BoNT-A+PT (p=0.003).
Conceming PPT in BoNT-A+PT increased in all muscles and statistically significant in 5 of 12 sites (levator scapula left p=0.02; suboccipitalis left 0.03; middle scalene right p=0.03 and left p=0.01; tensor fascia lata left p=0.01); while in PT in 2 sites (suboccipitalis right p=0.003; tensor fascia lata right 0.04) and in BoNT-A only in one site (suboccipitalis right p=0.03).
Conclusions: PT in combination with BoNT-A could be an effective option offered in patients with CM. The combined treatment is more effective in central sensitization than monotherapy treatment with BoNT-A or PT alone.

URB937 as a potential lead for the treatment of chronic migraine? A study in an animal model

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Background: The modulation of the endocannabinoid system may theoretically counteract peripheral and central sensitization, the main pathophysiological mechanisms underlying chronic migraine. This can be achieved using blockers of the degradation of endocannabinoids. The aim of this study was to investigate the effects of chronic maintenance of peripheral anandamide (AEA) in an animal model of chronic migraine, by evaluation of mediators involved in trigeminal hyperalgesia.
Methods: We investigated the modulatory effect of chronic URB937, a peripheral fatty-acid amide hydrolase (FAAH) inhibitor, the enzyme that degrades anandamide, in the animal model of chronic migraine obtained via repeated and intermittent nitroglycerin (NTG) administration (5 mg/kg, i.p.) every 2 days over a 9-day period. Animals received URB937 or vehicle daily and, 24 hours after the last injection of NTG or vehicle, underwent orofacial formalin test. mRNA expression of Calcitonin Gene Related Peptide (CGRP), substance P (SP) and mir-155 was evaluated in the trigeminal ganglion (TG) ipsilateral to formalin injection.
Results: NTG-treated rats developed orofacial hyperalgesia and showed a significant increase in the expression of neuropeptide genes together with mir-155 upregulation in the TG. URB937 treatment prevented NTG-induced hyperalgesia and inhibited the increase in CGRP and SP mRNA levels and mir-155 expression in the area evaluated.
Conclusions: URB937 modulates NTG-induced trigeminal hyperalgesia via the reduction of neuropeptides mRNA levels and mir-155 expression in the TG.

TRPA1 antagonism in a pre-clinical model of migraine: modulation of the inflammatory pathway

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Background: Pre-clinical data point to the contribution of the transient receptor potential ankyrin 1 (TRPA1) channels in the complex mechanisms of migraine pain. Activation of these channels causes the release of calcitonin gene-related peptide and elicits pain, whereas their pharmacological blockade counteracts hyperalgesia and allodynia in animal models of migraine. TRPA1 channels are expressed not only in primary sensory neurons, but also in non-neuronal cells such as glial cells and monocytes and they can be activated/sensitized by inflammatory mediators.
The aim of this study was to investigate the relationship between TRPA1 channels and inflammation in migraine pain using a pre-clinical animal model of migraine based on nitroglycerin administration.
Methods: The effects of the TRPA1 antagonist ADM_12 on nitroglycerin-induced hyperalgesia at the trigeminal level were investigated in male rats using the orofacial formalin test. mRNA expression of cytokines was quantified in peripheral (trigeminal ganglia) and central (medulla, cervical spinal cord) areas relevant for migraine pain using RT-PCR. Glial activation (microglia and astroglia/satellite cells) was evaluated in the trigeminal nucleus caudalis (TNC) and trigeminal ganglia (TG) using immunohistochemistry.
Results: In nitroglycerin-treated rats ADM_12 showed an anti-hyperalgesic effect in the second phase of the orofacial formalin test. TRPA1 antagonism was also able to reduce nitroglycerin-induced increase in the mRNA of cytokines (TNF-alpha, IL-6, IL-1beta) in all the evaluated areas ipsilaterally to formalin injection. This effect was paralleled by a significant reduction of nitroglycerin-induced increase in the activation state and number of CD11b+ microglial cells and GFAP+ astrocytes in the TNC, and of GFAP+ satellite glial cells in the TG.
Conclusions: The anti-hyperalgesic effect of TRPA1 antagonism is associated with reduced cytokine expression and glial (both microglia and astroglia/satellite cells) activation in specific areas involved in trigeminal pain, suggesting a strong relationship between TRPA1 channels and inflammation in the generation of trigeminal hyperalgesia in a model of migraine pain.

High-dose intravenous methylprednisolone for treatment of cluster headache in two pediatric patients.

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Background and objectives: Cluster headache (CH) is a trigeminal autonomic headache characterized by severe, unilateral headache attacks of orbital, supraorbital or temporal pain accompanied by ipsilateral autonomic symptoms and signs. The mean age of onset of cluster headache (CH) is in the late third decade. Only few cases of childhood-onset (<14 years) CH have been reported in the literature. We report two cases of CH with onset at childhood, treated with high dose of intravenous (i.v.) methylprednisolone with benefit.
Case reports: The first case is a 15-year-old girl (onset at 12 years), with unilateral pain localized in the orbital region associated with conjunctival injection, ipsilateral nasal obstruction and hyperemia of the left face. She was previously treated with Verapamil and after with Carbolithium with little benefit. Subsequently she underwent blockage of the sphenopalatine ganglion, without benefit. For recrudescence of symptoms, she was treated with methylprednisolone i.v. (20 mg/kg) for 5 days, with improvement of symptoms.
The second case is a 14-years-old boy (onset at 12 years), with episodes characterized by severe intensity pain located in the frontal and temporal region with conjunctival injection. Verapamil was started with partial response, interrupted for atrioventricular block. He was treated with methylprednisolone i.v. (20 mg/kg) for 5 days, with control of the attacks.
Conclusions: According to the criteria of the International Classification of Headache Disorders (ICHD-3), our patients should be considered as having chronic CH, with a drug-resistence form. Throughout the past 50 years, many investigators have reported beneficial effects of oral or parenteral corticosteroid regimens in the treatment of CH. In the absence of definitive trial data, the choice of corticosteroid regimen for CH can be extrapolated from the limited published reports only. In summary, the quality of the evidence in support of the use of corticosteroids for CH is quite low, especially in the pediatric age; however, on the whole, the evidence provides a clear signal of therapeutic benefit for corticosteroids in pediatric CH.

Regulatory issues and health system

Cost of migraine in Italy: real world data from a tertiary level headache centre

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Objective: The objective of the study consists in the realization of a model of Economic Burden of Disease in Italy based on real world data.
Methods: We retrospectively reviewed the medical records of 548 patients with episodic migraine and chronic migraine (female 85.4%, mean age 52 years) referring to the Regional Referral Headache Centre of the Sant'Andrea Hospital in Rome. All patients were under continuous care in the 2 years before 31 January 2019 (data collection date) in order to guarantee the same observation period for each enrolled person.
Information regarding the number of accesses in the Emergency Room, access to day hospital, specialist visits, specialist diagnostics, use of medicines (reimbursed and not reimbursed by the National Health System - NHS) was collected. The consumption of drugs was quantified considering the number of days of treatment and the daily dosage.
Results: The expense charged to the NHS relating to hospital management of the patient in terms of first aid and day care, amounts to € 7.250 in two years, corresponding to an average expenditure per patient of about € 13.The recourse to at least one diagnostic test involved 57 patients (12.2%), and the most frequent examinations were brain MRI (59% of the total exams carried out) and carotid doppler (11% of the total). Specialist assistance and check-ups involved a charge of € 78.652 in two years, equal to about € 144 per patient. The expense paid by the NHS for pharmacological treatment was € 1.23 million over 2 years. It follows that the treatment of a single patient with migraine, involved an annual expense for the NHS equal to € 1.126. Out-of-pocket expenditure amounts to over € 174.000 in 2 years of observation, corresponding to an annual patient expense of € 159.
The total expenditure charged to the NHS for the analyzed sample exceeds € 1.32 million in 2 years and, assuming that the individual cost items analyzed are constant during the follow-up, an annual expenditure of approximately € 660.000 could be estimated. Considering also the expense to the patient, the economic impact of migraine in terms of direct health costs amount to € 747.000 a year corresponding to an average annual expense per patient of € 1.364.
Discussion: In an Italian tertiary level headache centre 93.5% of the annual economic burden of a migraine patient is related to pharmacological treatments and only 0.5% is related to accesses in the Emergency Room.

Chronic neurological pain management in the Territory: results and perspectives

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Background: In the Campania region, the Territorial Neurology, through specifically outpatient dedicated structures, provides for chronic neurological pain management in the absence of institutional codified paths.
Methods: Three headache centers located in main areas of the province of Salerno (Agro nocerino-sarnese, Eboli and Vallo della Lucania) were involved in the study of management of chronic headaches. Patients were administered two different questionnaires: the first included general data (first visit, number of accesses to the Emergency Department (ED), etc.) referring to the period from January 2018 to March 2019; a second questionnaire regarded the clinical features of the headache, the treatments performed, the number of symptomatic drugs taken, in reference to a continuous period covering the last three months. For disability, MIDAS and HIT 6 were performed. Direct access was provided for patients coming from the Emergency Department (ED) and discharged with a diagnosis of primary or unspecified headache, and for patients sent by the General Practitioner (GP) with a diagnosis of chronic headache or being chronic. These patients were admitted and evaluated within 6±2 days.
Results: Of the 1,685 patients evaluated, 12% suffered from chronic headache, mainly migraine type or drug overuse. 35% referred chronic pain for not less than 2 years. 29% had at least one access to the ED. In addition, 75% of patients performed at a minimum one instrumental neuroimaging investigation (CT or MRI). 62% of them reported the assumption of a prophylaxis therapy; 76% practiced OTC products while resulted very low the number of those practicing detoxication therapy (21%). Only 24% used triptans. All patients showed a significant impairment of their personal, social and working life. At the end of the study the early and specific treatment resulted in a significant reduction in disability (average values of MIDAS from 69.98 to 49.58).
Conclusions: The analysis of the data showed the need to redefine appropriateness in management of chronic headache patient. In the absence of specific PTDs, a network including primary care physician, headache expert Territorial neurologist, and close relationship with Emergency Department, can guarantee efficient results. Of primary importance should be considered the improvement of access to the competent healthcare facilities as well as the support of information and training programs in the field of diagnosis and treatment, aimed at both patients and the various medical professionals involved in headache field.

Strengths and limits in a 5 years' use of a digital platform in headache training

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Objective: The increasing development of social networks and in general of digital instruments led us to implement our project of a digital platform only focused on headaches, started in 2014. The aim of this study was to analyze *strengths and weaknesses* in a 5 year period.
Methods: Our platform is totally free. It is possible to access using website or smartphone app. It has been divided into a section for pediatric headaches and a section for adult headaches and contains more than 270 resources concerning headache. Each member can download or upload contents and discuss clinical cases. We alert members about new contributions via email and WhatsApp group. Administrators can follow the members' activity (number of access, trend topics, uploaded/downloaded resources, discussions, average download for user). We monitored the evolution of the platform's activities over time and compared our experience with other digital platforms.
Results: To this day the section dedicated to adult headaches includes 60 members with 14 downloads on average each. The section dedicated to pediatric headaches includes 67 members with an average of 19 downloads. We highlighted a progressive increase in the number of users since the start of our project and an increase in the number of downloads

simultaneously with upload of new resources. The items that most capture the attention are PowerPoint presentations and resources closely related to common clinical cases or with short reading time. In each year the activity of the members during the summer appeared to be considerably reduced in number of downloads, uploads and new contributions.
Conclusions: The increase in subscriptions shows that our social network dedicated to headaches is appreciated by the scientific community. Nevertheless, the activity does not appear equally increased and a considerable number of members very rarely access the platform. Furthermore, on average the number of uploads is remarkably lower than downloads, indicating a passive use of the platform. On the other platforms, discussions and downloads are considerably less than the number of subscribers, similarly to the activity of our platform. These results confirm the potential but also the limits of digital instruments in the training for specialists, both in headaches and in other disorders.

Headache know-how, headache centers organization ad clinical activity: results from a national survey

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Objective: To evaluate the "state of the art" of headache know-how between Members of the Italian Society for the Study of Headaches (SISC) and organization in SISC headache centers.
Methods: We send a codified email link to an official mailing list of SISC Members, to answer a web-based, anonymized survey; it was possible to complete the survey in different times from 01.09.2014 for 48 days; there were mandatory questions and optional questions; multiple choice answers.
Results: Four hundred and fifty-five questionnaires were sent, 188 were answered (41%), among these 155 were assessable (34%); 74 responses from women (47.7%), 81 from men (52.3%), average age 50.3 ±11.3. Most participating regions were: Lazio (22 questionnaires), Sicilia (16), Lombardia (14), Veneto (13); same percentage of participation among those working in university and non-university centers.
Sixty percent of responders refers to be experienced with lessons about headaches during the course of studies, mainly with a duration of weeks (67%) and only theoretical (55%); among those who had taken lessons ("educated") the same were considered adequate (58%) to acquire competence to dedicate themselves to headaches; among "educated" the average SISC membership was 9.4 years and average working time 16.4 years, while, among the "uneducated", average SISC membership were 12.4 years and average working time 26.7; 92% of respondents had attended in the last 2 years congresses on headaches; the percentage of doctors dedicated to headaches in the total of the unit is generally less than 30%. About daily clinical activity: 60% use paper schedule and 66% use a semi-structured questionnaire; 56% use ICHD III beta; 86% adopted SISC guidelines; 99% use headache diary which, in 66%, is self-made; off-label prescriptions are "a limit" for 10% of university center doctors and 13% of non-university doctors, a "second choice" for 48% of university and 59% for non-university, "no limit" for 42% of university and 28% for non-university.
Conclusions: This survey was appreciated: 41% answered; there was a heterogeneously participation among regions; basic knowhow about headaches is present, brief, but is considered quite formative; we observed a good update about headaches between SISC Members; headache specialists are not so widespread in teams; until today the digital gap is too elevated (only 40% use digital schedule); ICHD-III beta is used in more 50%; 86% of SISC members use Society guidelines; furthermore there's a tendency to off-label prescription (especially in university centers).

ALCMEONE App: a new tool for supporting the empowerment and self-management of headache patients

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Background: The industrial research and development project "ALCMEONE" (Italian Ministry of Economic Development funds, 2018-2021) aims at providing an innovative organizational model and an advanced technological platform of services for supporting the integrated clinical management of headache patients. One of the main features of the project concerns the integration of patient-centered healthcare pathways, by involving and supporting the same patient in the self-management of the disease. To this end, the "ALCMEONE App" is currently under development and testing.
Methods: The "ALCMEONE App" is based on a state-of-the-art software artefact allowing to realize a suitable environment that envelops and sustains the headache patient for the self-management of the disease. In order to design and develop the system, the main issues concern the definition of a user-friendly interface, which allows an immediate and intuitive interaction with the end-user, and an efficient data collection and communication infrastructure, which guarantees a seamless and interoperable integration with the different healthcare informative systems. The proposed technological approaches exploit the most innovative solutions of the "man-machine interaction" domain.
Results: The "ALCMEONE App" supports patients in the management of health conditions, providing the "headache diary", services for the control of the therapy compliance, questionnaires for monitoring the life style and detect the current status of the disease. All the collected data and information are made available, with the appropriate access rights and by assuring the relevant privacy policy, to all the relevant healthcare operators.
Conclusions: Following a patient centered perspective, "ALCMEONE App" is adaptable (different languages, gender and age tailored), is integrable (electronic health record, different healthcare information systems, medical devices and sensors, environmental sensors), compatible with the most recent technological standard, also enabling participation of patients and relatives in care processes. "ALCMEONE App and Platform" jointly provide an effective collaboration tool involving patients and health care professionals.

A decision support system for headache diagnosis based on ICHD-3

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Background: Automatic or semi-automatic software tools have proven to be successful at assisting practitioners in the diagnosis of pathologies. The headaches domain is challenging due to the high amount of possible diagnosis and diagnostic criteria. The International Classification of Headache Disorders 3rd edition (ICHD-3), is considered by the World Health Organization as the official classification of headaches. ICHD-3 provides specific diagnostic criteria for diagnosing known headaches. The possible diagnoses are organized in a hierarchical structure that expresses the existing relationships between them. ICHD-3 guidelines are

written in natural language and are intended to be read and understood by practitioners, while machines are not capable of automatically reading and understanding them.
Methods: We adopt Artificial Intelligence techniques in the field of Knowledge Representation and Reasoning in order to formally represent the knowledge present in the ICHD-3 guidelines. On top of such formal representation we build a decision support system for the diagnosis of headaches. From a technological perspective, we adopt standard Web development frameworks for implementing distributed applications so to make the resulting system easily accessible by practitioners and platform independent.
Results: We transformed the ICHD-3 guidelines into a formal representation based on known formalisms for Knowledge Representation and Reasoning. Headaches have been formally encoded into a hierarchical structure known as taxonomy and diagnostic criteria have been encoded in terms of logical rules. The resulting representation is precise and captures the knowledge present into ICHD-3. By leveraging on the formal representation, we devised a web platform that assists practitioners during their diagnosing process. The system implements a multiple step process and at each step recommends, relevant questions to ask the patient and exploits the answers to narrow down the diagnosis, visually presenting the practitioner the advancement in the diagnosis in terms of confirmed, excluded and not-yet determined diagnosis. At each step, the next question to be asked is determined automatically by selecting the question that maximizes the number of diagnosis that become determined.
Conclusions: We developed a web application that helps practitioners in the diagnosis of headaches as specified in the ICHD-3 guidelines. By using state-of-the-art techniques for Knowledge Representation and Reasoning, the system fully captures the knowledge present in ICHD-3 and is thus precise in the classification. The systems architecture is general purpose and it is designed to be easily adaptable to new versions of the guidelines.

Digital health and clinical decision support: project Alcmeone and the Calabria Headache network

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Objectives: Good clinical governance of headache implies efficient and accessible diagnostic and therapeutic pathways involving different levels of health care
Background: Information and communication technology can play a key role improving access to treatment and, from the clinical management perspective, in increasing the levels of quality, efficiency and prevention. The Alcmeone project is a networking and interoperability technology platform, designed to assist healthcare decision making and improve access to care at appropriate levels
Methods: Between December 2014- and June 2015 primary care general practitioners in Catanzaro, three secondary care neurologists, and one multidisciplinary tertiary care team from the headache center Pugliese-Ciaccio hospital in Catanzaro, used the pilot client software and accessed the health Soaf platform.
Results: In the period considered GP recruited 197 patients with headache diagnoses made with the support of a technological platform: 19 (9.64%) had a suspected diagnosis of secondary headache and were referred to the emergency room; 74 (37.56%) were diagnosed with episodic primary headache and managed exclusively by GP at primary headache level; 36 (18.27%), also with episodic primary headache, were managed by both GP and outpatient neurologists, again in the primary setting; 68 (34.52%) were sent to the reference headache centre. The date from the pilot study, showing an approximately 50% reduction in inappropriate referrals to the hospital reference centre (15.42% vs 7.35%) indicate enhanced diagnostic accuracy and appropriateness of referrals within the codest diagnostic, therapeutic and care pathways.
Conclusions: The use of ICT support in clinical decision making and management processes is a valuable aid in clinical practice.

Headache fast track from the Emergency Room

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Background: Primary headaches are a problem in every age group, weighing significantly for costs both in national welfare budgets and as a factor of reduced productivity. In our hospital a preferential fast track for patients coming from the Emergency Room has been established and evaluation is guaranteed within 48 hours of discharge from the ER. In a retrospective study through the electronic medical record, we analyzed the caseloads related to access to estimate the clinical benefits of this approach on the population affected by primary headaches.
Methods: We evaluated 102 patients, 66 women (mean age 34.5 years) and 36 men (mean age 37.5 years) sent for evaluation from ER. Twenty-four did not show up at the visit, while 1 woman and 1 man were diagnosed with secondary headache. Women presented the following distribution by diagnosis: 54 high frequency episodic migraine (disease duration: 227.77 months), 20 of which had correct diagnosis before access to ER, 10 in prophylaxis therapy; 6 chronic migraine (disease duration: 198 months), 6 of which correctly diagnosed, 0 in prophylaxis therapy; 6 cluster headache (disease duration: 120 months), 6 correctly diagnosed, 4 in prophylaxis therapy. The men presented the following distribution by diagnosis: 27 high frequency episodic migraine (disease duration: 37.5 months), 18 correctly diagnosed, 6 in prophylaxis therapy; 6 chronic migraine (disease duration: 200 months), 4 correctly diagnosed, 2 in prophylaxis therapy; 3 cluster headache (disease duration 480 months), 3 correctly diagnosed, 2 in prophylaxis therapy.
Results: All patients evaluated in our center received a prophylaxis therapy according to the EHF guidelines. At six months control, the average monthly frequency differences for headache showed significant improvement for all groups. Days of headache per month, women first visit 12.5 to check 2.33 while men went from first visit 9 to control 3.
Conclusions: Data analysis showed a delay in the initiation of prophylaxis therapy, even in those patients who showed a long clinical history, laying the foundations for an excess of request for emergency assessments. Nonetheless, the inclusion of appropriate prophylaxis, even in patients undergoing chronic conditions, allows significant clinical improvement.

Facial muscles activity and cervical spine mobility in female patients with migraine

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Background: The scientific literature has investigated the presence of cervical/mandibular sensory nerves irritation and muscle pain of the facial and neck regions in patients affected by migraine. Based on these

researches, the aim of this study was to assess the cervical range of motion and the activity of facial muscles in female individuals with migraine.
Methods: Twenty-nine female participants affected by migraine (mean age: 35.97±11.26 years) were recruited for the study and performed a cervical range of motion (ROM) evaluation, using a wireless inertial motion sensor (Moover®; Sensor Medica®; Guidonia Montecelio, Roma, Italia), and a surface electromyography (EMG) of masseter and temporal muscles, via a Bluetooth surface electromyograph (Teethan®, Teethan S.p.A., Garbagnate Milanese, Milano, Italia). For the cervical ROM measurement, each participant performed three maximal tests that included: left and right rotation (R), left and right lateral flexion (LF), flexion-extension (FE) with the inertial motion sensor positioned medially of the frontal bone of the skull. Each test was performed for three times and the mean value was used for statistical analysis. For the EMG of the masseter and temporal muscles, each participant performed a calibration test, *i.e.* a 5-s maximum voluntary clench with two 1-cm-thick cotton rolls positioned between the arches, and an acquisition test, *i.e.* a 5-s maximum voluntary clench in intercuspal position. The EMG potentials recorded during the acquisition tests were expressed as per cent of the mean potential recorded during the calibration test. Mean values and standard deviations were carried out using Statistica Software 12 (StatSoft®, TIBCO® Software Inc, Palo Alto, CA, USA). Pearson's correlation coefficient was calculated between EMG an ROM parameters with the alpha level set at <0.05.
Results: Regarding the EMG, our results showed muscular asymmetry between paired muscles (left and right masseters: 81.79%; left and right temporalis: 79.62%) compared with the percentage overlapping coefficient (POC) in which the perfect symmetry is at 100%. Moreover, we found a lower masseter muscles activity (left *vs.* right: 23.24% *vs.* 23.66%) respect to temporal muscles activity (left *vs.* right: 25.79% *vs.* 27.31%). In respect to the cervical ROM, we found lower mean value of the maximal LF (36.32±8.15 *vs.* 35.42±8.41, left *vs.* right respectively) compared to normal values. No correlation was found between EMG an ROM parameters.
Conclusions: Our results suggest that the activity of neck muscles in patients with migraine influence the cervical spine lateral flexion mobility and, moreover, these subjects may show mandibular muscles unbalance.

The role of brain MRI in patients with chronic headache who have normal neurological examinations

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Background and objectives: There is a low likelihood of discovering significant disease in evaluating chronic headache patients with normal neurological examinations by magnetic resonance imaging (MRI) because previous studies considered silent brain infarct an insignificant lesion. We investigated the incidence of abnormal findings including silent brain infarct in MRI of the brain for the patients who have normal neurological examinations.
Methods: We retrospectively reviewed the medical records and MR images of 825 patients chronic headache between January 2014 – December 2018. Only 312 patients with normal neurological examinations were included in this study
Results: The patients were diagnosed has having tension-type headache chronic (26.7%), migraine chronic (67.8%), and atypical type headache (5.4%). Clinical significant abnormalities on MRI were found in 56 patients (13.8%) which were silent infarct, tumor, MAV, and aneurysm. The most common abnormality on MRI was Silent brain infarct (65.5%).We found that SBI in chronic headache with normal neurological examinations were related not only to hypertension and heart disease, but also to the type of headache.
Conclusions: These results indicate that brain MRI in chronic headache is a useful tool for detecting SBI, which may be an independent risk factor for symptomatic brain infarcts.

Zonulin, a possible driver of gut-brain axis in migraine

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Introduction: Migraine is regarded as a multifactorial disorder that recognizes several triggers and aggravating factors. Among them an important but not yet very well studied feature is the integrity of gastrointestinal system since gut symptoms (as constipation, inflammatory and irritable bowel disorders) are very frequent among migraineurs. Aim of this study is to analyze the link between zonulin serum concentration (a marker of gut barrier integrity) and type and frequency of headache in a population of patients with different gastrointestinal disorders.
Methods: A group of patients who self-referred to a gastroenterologist for various disorders, were asked to undergo a neurological evaluation to receive a headache diagnosis. We divided 78 patients into 3 groups. *Group 1*: 20 no headache suffering. *Group 2*: 25 tension-type headache patients. *Group 3*: 33 migraine patients. We compared among the groups the zonulin serum concentration and analyzed its correlation with the frequency of headache
Results: Differences in terms of zonulin serum concentration emerged among Group 1 and 3 ($p=0.003$). Further, we observed a positive correlation between zonulin serum levels and the frequency of migraine attacks ($R=0.572$, $p=0.001$). There was no significant correlation between zonulin serum levels and tension-type-headache attacks.
Discussion: The observed links between zonulin and migraine could be explained by the role of zonulin as a marker of gut inflammation. Intracellular zonulin signaling may likely play a key role in the tight-junction regulation in the intestinal epithelial barrier. Inflammatory alterations of this pathway have been associated with the leaky gut phenomenon, which could lead to the passage of potentially systemic pro-inflammatory substances in the blood circulation, as observed in previous studies. One of these is the lipopolysaccharide that was observed to trigger, in an experimental migraine model, an intense TNFα release leading to central sensitization and trigeminal inflammation. Further prospective studies on migraine patients should confirm our early observations and clarify the actual mechanism of action underpinning this link.

Impact of medical care on symptomatic drug consumption and quality of life in headache: A one year population study

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Background: Headache is one of the most common painful syndrome and can be responsible for high disability. It is a widespread disorder both in episodic and chronic form. Chronic headache often leads to a high use/overuse of symptomatic drugs [1]; indeed, medication overuse headache

(MOH) occurs in over half of chronic headache patients [2], with significant management difficulties.
Objective: To provide data about symptomatic drug (NSAIDs and triptans) consumption in an outpatient population of the Health District of Pavia, and describe how the clinical picture may change after being taken over by headache experts.
Materials and methods: Two hundred and seventy-six patients using symptomatic drug for headache were recruited in 32 pharmacies. A telephonic interview was carried out in 199 of them. Data collection included sociodemographic characteristics and features of headache and drug consumption/abuse. Patients underwent 4 visits: a baseline visit (T0) and 3 follow-up visits performed by a neurologist at 3, 6 and 12 months (T3, T6 and T12, respectively). During each visit, patients underwent a complete neurological assessment and received therapeutic adjustments aimed at obtaining a proper management of headache.
Results: Patients with chronic migraine or MOH were 16% and 12%, respectively, at the telephonic interview. After 12 months of follow-up, we observed a significant decrease in the frequency of attacks (T0: 9±9/month vs T12: 2±2/month; $p<0.001$), in the days/month of headache (T0: 11±9 vs T12: 4±4; $p<0.001$), and in the duration of the single attack (T0: 34±30 hrs vs T12: 10±19 hrs; $p<0.001$). The improvement of headache management resulted in both a significant decrease in the analgesic consumption per month (T0: 12±16 vs T12: 4±6 doses/month; $p=0.014$), and an increase in the quality of life, scored by MIDAS and HURT ($p<0.001$).
Conclusions: This study showed that a proper medical management is more effective than self-treatment of headache, resulting in lower disability and improved quality of life within a few months from taking-over by headache specialists.
RC MINSAL 2013-2015 IRCCS MONDINO
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Cyclic vomiting syndrome and benign paroxysmal torticollis are associated with a high risk of developing primary headache: a longitudinal study

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Background: Periodic migraine variants are a group of disorders affecting patients with migraine or with an increased risk of presenting it, and likely represents an early life expression of migraine. Cyclic vomiting syndrome (CVS) and benign paroxysmal torticollis (BPT) are well characterized and represent a frequent cause of request for specialistic consultations. Aim of this study was to longitudinally assess the rate of headache in patients presenting with CVS and BPT during infancy, and to define the main clinical features of the disorder.
Methods: We administered a questionnaire to the parents of all our pediatric patients with previous diagnosis of CVS and/or BPT according to ICHD-3; questions were focused on the main clinical features of the disorder as well as the prognosis, with particular emphasis on the development of headache.
Results: For the final analysis we considered 82 patients with CVS and 33 with BPT. Seventy-nine percent of patients with CVS presented with headache during the follow-up, with a mean age at onset of 6 years; 67% of patients with BPT suffered from headache during the follow-up, with a mean age at onset of 5 years.
Conclusions: CVS and BPT are associated with a very high risk of developing headache, mostly migraine, later in life. In both groups of patients, the vast majority presented with different periodic migraine variants at different ages, thus suggesting an age dependent evolution of migraine-like symptoms before the onset of clear migrainous headache.

The usefulness of red flags in prescholar headaches: a study in pediatric emergency department

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Objective: The aim of this study was to evaluate red flags' specificity and correlation with neuroimaging abnormalities in preschool children admitted in our Emergency Department for headaches. In literature we currently found no evidence regarding preschool children evaluated in Emergency Department, however several works suggest an increased in incidence of dangerous headaches in this population.
Method: We collected 377 clinical cases (168 Males – 209 Females) of children from 1 to 7 years old, suffering from headache, admitted in the Emergency Department of our Hospital (Ospedale dei Bambini, Palermo), from October 2015 to December 2018. Our sample represents 22.9% of total access for headache.
Results: We found that 56.23% of them (212 children) had one or more red flags from the list and 125 children between them (58.96%) underwent CT. We found several different outcomes: 103 children showed benign abnormalities (cerebellar tonsils ptosis, inflammatory processes of paranasal sinuses or nonspecific abnormalities) certainly not related with clinical presentation, 22 children showed no abnormalities, and only 3 children (0.8%) showed major abnormalities (2 tumors and 1 hemorrhage).
Conclusions: Our study, according to other studies, highlights that headache in preschool age is less infrequent than expected. We showed that several children (more than 50%) presented at least one red flag. The correlation between red flags and dangerous abnormalities in neuroimaging is not so direct; in addition, in this age the red flags do not increase the recognition of dangerous headaches. In conclusion, in presence of normal neurological evaluation we can decide to avoid or postpone neuroimaging examination.

Prophylactic drug treatment of pediatric migraine: What is new?

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Background: Migraine is a frequent and very disabling disease in the pediatric age. Despite this, there is a lack of controlled studies on the pharmacological treatment of primary migraine in the developmental age. Despite the recent advent of calcitonin gene-related peptide (CGRP) receptor antagonist, there is still no drug with exclusive indication for migraine treatment in pediatric age. This involves numerous limitations in terms of adherence and effectiveness of the therapy.
Methods: We reviewed the real evidence on the prophylactic therapy of pediatric migraine through the review of clinical studies published between 2010-2019.

Results: Sixty-four articles concerning preventive treatment of migraine in children were included in our study. Among them, there were 40 reviews (Rs) of the literature concerning the prophylactic treatment of pediatric migraine, 21 clinical trials (CTs), and 3 retrospective studies (RSs). As for the CTs, 15 were randomized control trials (RCTs) and one was an open label study (OL). All the included studies were published from 2010 to the present.
Discussion: To date, some efficacy data in controlled studies are present for topiramate, amitriptyline, flunarizine and valproate. However, the main novelty is given by the CHAMP study. This study showed that the efficacy of pharmacological treatments such as amitriptyline and topiramate give the same results of placebo. This study therefore raises two problems that remain current in the study of pediatric headaches. The first is the impact of the placebo effect in pediatric age, the second connected to the first is the question on which approach to use for migraine therapy in children should be more appropriate. We have no conclusive data on nutraceuticals and non-famracological therapies.

Prophylactic treatment with Tanacetum Parthenium, 5-Hydrossitriptophan (5-Http) and Magnesium (AURASTOP®) in children with episodic migraine without aura: an observational study

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Background: The synergistic effects of Tanacetum parthenium, Griffonia simplicifolia and Magnesium (Aurastop®) have been retrospectively analyzed. Until now, the nutraceutical preparations have been given to adults with migraine with aura as symptomatic treatment and as prophylactic treatment in those with episodic migraine without aura, with several benefits. In this study we prospectively evaluated the efficacy of prophylactic administration of Aurastop ® in terms of reduction of intensity, duration, frequency and analgesics use in children with episodic migraine without aura.
Materials and methods: In this open prospective study, we selected 36 children suffering from episodic migraine without aura for at least 6 months followed at the Headache Centre of the Regina Margherita Children's Hospital of Turin, Italy. The diagnosis of migraine without aura was done using the IHS criteria (ICH III) and the recruitment was voluntary. Informed consent was obtained by the parents of the patients before their inclusion. The study protocol was approved by our Ethical Committee. Clinical information about duration, intensity, frequency of the episodes and need of analgesics (number of medication) was recorded for each patient in a personal headache diary before the treatment and three months later. In 7 cases the follow-up was stopped after one month and in 3 cases after two months because of insufficient compliance.
Results: Of the 36 patients (mean age: 13 years, range 6-16; 12 males and 24 females), 15 (40.5%) showed a reduction in frequency and 4 (11.1%) in duration of migraine episodes. A decrease in intensity was detected in 22 patients (61.1%). In 14 (38.9%) cases, lower use of analgesics was reported. Only 4 patients (11.1%) did not obtain any benefit and in reverse 2 children (5.6%) showed improvements in all the variables; both of them had been under Aurastop® for at least three months.
Conclusions: Our observational study suggested that the treatment with Tanacetum Parthenium, 5-Hydrossitriptophan (5-Http) and Magnesium (Aurastop®) could represent an efficient prophylactic therapy also for children with episodic migraine without aura. However, a large randomised control trial should be designed to confirm the efficacy of this treatment.

To Scan or not to scan: a case of migrainous infarction in elderly

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Background: Migraine infarction (MI) is a rare form of ischemic stroke occurring during a typical migraine attack with aura (MA) with permanent symptoms and an appropriate lesion for neuroimaging. The incidence of MI is lower than 1% of all ischemic strokes, but it may represent up to 20% of all ischemic strokes in younger patients. The diagnosis of MI is very difficult in older subjects in whom ischemic stroke is commonly related to typical cardiovascular risk factors frequently present in elderly. We present a rare case of migraine infarction in an elderly patient.
Case report: A 67-year-old woman, non-smoker, suffered from migraine headaches, frequently with a visual aura, since she was 15. The visual aura was characterized by scintillating scotomas, blurred vision, and partial right hemianopia. She had 1-2 attacks per month. Since menopause, at the age of 50, she had no more migraine attacks. She had no vascular risk factors or neuropsychiatric disorders.
She went to the emergency room of our hospital for pulsating frontal headache accompanied by nausea with photo- and phonophobia and a persistent visual aura, occurred an hour after she woke up in the morning.
Results: Neurological examination showed right hemianopia. Brain MRI showed an acute ischemic lesion in the right occipital lobe. The patient underwent a thorough etiological investigation: laboratory blood tests and analysis of cerebrospinal fluid that showed no alterations; an ECG, transthoracic and transoesophageal echocardiography, Holter ECG, duplex extracranial ultrasound and standard electroencephalogram were normal. We prescribed aspirin 100 mg/die for secondary stroke prevention. The headache resolved about 48 hours after admission, while the visual field defect partially improved in the following days.
Conclusions: Although MI is prevalent among young people, it should be considered as a cause of stroke even in the elderly. According to the AAN guidelines, the routine use of neuroimaging is not justified in a patient presenting MA attacks matching the ICHD-3 diagnostic criteria. However, symptoms similar to a well-known previous aura attack may actually be due to an ischemic stroke. This case highlights how there could be exceptions to the diagnostic workup indicated in the guidelines. Furthermore, a previous MA diagnosis might delay access to the emergency room because the patient and the doctor could presume that the neurological symptoms are transitory as in the previous attacks. These factors might delay the diagnosis of stroke and reduce the chances of successful treatment with reperfusion therapy.

OnabotulinumtoxinA affects visual cortical excitability in chronic migraineurs: 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 onabotulinumtoxinA.
Methods: We enrolled 15 chronic migraine patients without aura (mean age 53 yo +13; 14 females) for onabotulinumtoxinA therapy (395UI in 39 sites) and 12 control subjects (10 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: a first time comparing healthy controls and baseline migraineurs, then baseline migraineurs VS the ones three months after first treatment. 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=0.011), while the second analysis did not show significant changes in such scores before and after 3 months from the treatment (p=0.194), but post-hoc analysis showed a significant augmentation of scores between 1F4B tests (p=0.010).
Conclusions: Data obtained suggest that chronic migraineurs manifest less fission illusions than healthy controls, consistently with previous studies. Furthermore onabotulinumtoxinA restores, though partially, fission illusions and, consecutively, normalizes visual cortical excitability.

Sustained efficacy and safety of ONABOTULINUM TOXIN TYPE A in chronic migraine patients: a multicentric prospective real-life study

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Background: Onabotulinum toxin type A (OnaBoT-A) is approved for the prophylactic treatment of chronic migraine (CM). OnaBoT-A is given every 12 weeks, following the standard 1-year protocol and dosage PREEMPT treatment. This multicentric prospective study aimed to give answers to several real-life questions: long-term efficacy and safety is one of the most relevant.
Methods: This prospective observational open-label study is divided into 2 phases: during the *Phase 1*, patients with CM who are eligible for OnaBoT-A underwent 5 cycles of therapy (155-195U), one every 3 months (1-year of treatment), recording headache characteristics and any adverse events on a daily basis in a diary. Then, patients are divided into 3 groups: responders (R; reduction in the number of headache days per month ≥50%), partially responder (PR; reduction <50%, but ≥30%) and non-responder (NR; reduction <30%). NR patients left the study, while PR and R patients were offered another 4 treatment cycles (1 further year, *Phase 2* of the study).
Results: Overall, 195 patients were included (female 82.05%). At the end of the *Phase 1* there were 52.3% (F/M: 89/13; mean age 47.82±14.16) of R patients, 17.9% (F/M:21/14; mean age 46.96±11.95) of PR patients, 15.4% (F/M24/6; mean age 45.40±13.66) of NR patients and 14.4% (F/M:26/2; mean age 49.48±9.70) of drop-outs. There were no statistically significant differences between the types of abused drug (paracetamol/NSAID, triptan/ergotamine, analgesics in combination, combination of analgesics) among the 4 groups, as well as in the demographic characteristics. During the second year of treatment, R patients presented a confirmation of the improvement achieved during the first year of treatment (from 24.24±5.57 headache days/month before the start of the *Phase 1*, to 6.96±4.27 $p<0.001$, after the first year of treatment, to 6.94±5.13 p=ns); PR patients presented a trend of further improvement, although not statistically significant, during the second year of treatment(from 23.77 ±5.77 headache days/month before the start of the *Phase 1*, to 17.37 ±5.25 $p<0.001$, after the first year of treatment, to 15.31±5.77 p=ns). No serious adverse events were reported among the *Phases* of the study.
Conclusions: This real-life multicenter study showed how the long-term efficacy and safety of OnaBoT-A treatment in CM patients were sustained over two years of treatment. Thus, these results suggest that, although the pivotal trials have tested OnaBonT-A up to a year of treatment, the real-life experience demonstrates an efficacy and safety even in prolonged prophylaxis.

Effects of OnabotulinumtoxinA on headache disability and comorbid depression in chronic migraine patients

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Background: Chronic migraine (CM) results in a serious limitation of life activities and it is frequently associated (more often than episodic migraine) to psychiatric comorbidity, particularly to depression. OnabotulinumtoxinA is an approved treatment for CM patients, so we aim to evaluate positive effects of such therapy on migraine disability and concomitant depressive symptoms.
Methods: We enrolled 12 women (mean age 49.91 years old ±11.00) suffering from chronic refractory migraine who started treatment with OnabotulinumtoxinA (195 UI divided among 39 sites every 90 days). We asked patients to fill in a headache diary and two questionnaires: Migraine Disability Assessment (MIDAS) and Beck Depression Inventory II (BDI-II). The evaluations were administered at baseline, at three and six months after OnabotulinumtoxinA injections.
Results: The number of headache days reduced significantly during the six months since first administration of therapy (p=0.00493). Similar reductions, even if slightly less statistically significant, were observed on MIDAS (p=0.01177) and BDI-II scores (p=0.3196). Moreover, it is worth to note that significant therapeutic effects were already observed at three months after first drug administration.
Conclusions: OnabotulinumtoxinA is an effective treatment for patients suffering from chronic migraine and such effect is not only important for a reduction of headache days (as already showed by literature), but even for an improvement of disability, as well as depressive symptoms associated to migraine.