
CONGRESSO VIRTUALE
TORINO
23-26 SETTEMBRE 2020
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CONGRESSO NAZIONALE
DELLA SOCIETÀ ITALIANA
PER LO STUDIO DELLE CEFALEE
CEFALEE 2020: LA NUOVA ERA
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ABSTRACTS

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ORAL COMUNICATIONS

Efficacy of galcanezumab in high-frequency episodic/chronic migraine and ≥3 previous preventive treatment failures: subgroup analysis from CONQUER

Mark Weatherall[1], Manjit Matharu[2], Andrew Pain[3], Antje Tockhorn-Heidenreich[3], Marie-Ange Paget[3], Grazia Dell'Agnello[3], Giorgio Lambru (Presenter)[4]

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Background: Is galcanezumab efficacious in patients with high-frequency episodic migraine (HFEM) or chronic migraine (CM), and a prior history of failure with ≥3 preventive treatments?

Methods: CONQUER (Phase 3, multicentre, randomised-controlled trial) assessed the efficacy and safety/tolerability of galcanezumab in treatment-resistant migraine. Patients (18-75 years) with 2-4 migraine prevention medication category failures in the past 10 years were randomised 1:1 to placebo and galcanezumab 120 mg/month (240 mg loading dose). We evaluated a subgroup of patients with HFEM (<15 headache days/30-day period, 8-14 are migraine headache) or CM (≥15 headache days/30-day period, migraine headache: ≥8), and ≥3 prior preventive medication category failures. Evaluated endpoints included change in monthly migraine headache days and proportion of patients achieving ≥50% and ≥75% reduction in monthly migraine headache days across the 3-month double-blind period. Migraine-Specific Quality of Life (MSQ) Role Function-Restrictive (RF-R) and Migraine Disability Assessment (MIDAS) were assessed at Month 3.

Results: 166 patients (36% of CONQUER patients; HFEM=80, CM=86) were included in baseline analyses. Baseline characteristics were not statistically different between treatment groups. Following treatment, there were statistically significant differences between placebo and galcanezumab in mean change from baseline in monthly migraine headache days (placebo vs galcanezumab: baseline mean [SD]: 15.38[5.61] vs 14.66[5.23]; least squares [LS] mean change [SE] from baseline: -1.54[0.75] vs -5.85[0.68]; LS mean change difference [SE] vs placebo: -4.31[0.78]; p<0.01), ≥50% response (estimated rate [SE]: 11.3% [3.0] vs 39.4% [4.2]; odds ratio (95% CI) vs placebo: 5.07 [2.55, 10.10]; p<0.01), ≥75% response (estimated rate [SE]: 3.9% [1.9] vs 17.1% [3.3]; odds ratio (95% CI) vs placebo: 5.05 [1.69, 15.06]; p<0.01), MSQ RF-R score (baseline mean [SD]: 41.56[20.48] vs 44.05[17.73]; least squares [LS] mean change [SE] from baseline: -10.14[2.84] vs 26.46[2.60]; LS mean change difference [SE] vs placebo: 16.32[3.12]; p<0.01) and MIDAS score (baseline mean [SD]: 60.77[57.29] vs 53.23[49.47]; least squares [LS] mean change [SE] from baseline: -2.09[6.77] vs -27.43[6.30]; LS mean change difference [SE] vs placebo: 25.34; p<0.01).

Conclusion: Galcanezumab significantly improved key efficacy endpoints versus placebo in patients with HFEM or CM who had previously failed ≥3 preventive treatment categories.

Erenumab treatment in chronic migraine with/without medication overuse headache: real life experience in a tertiary Headache Center

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Background: Migraine is a primary, highly prevalent, headache disorder determining great impact in personal and socio-economics settings. Indeed, Chronic Migraine (CM) has recently reached the status of social disease in Italy. In recent years anti-CGRP receptor monoclonal antibodies were developed for migraine prevention.

Aim: To present real-life long-term clinical data on effectiveness and tolerability of erenumab in subjects with chronic migraine (CM) with/without medication overuse.

Methods: Erenumab (70 or 140 mg dose) was administered monthly to 82 patients (F59, M23, mean age: 49.5±9.9SD) who had already failed at least two preventive therapies. Changes in monthly migraine days and acute medication intake were collected from a daily diary; standardized questionnaires were completed to detect disability (MIDAS), headache life impact (HIT-6), global health status (EQ-5D-5L), allodynia (ASC-12 scale) at baseline and every three months. Here are summarized the data regarding the first 9 months of treatment. Statistical analysis was conducted using ANOVA for repeated measures and subsequent post-hoc tests.

Results: A significant improvement ($p<0.001$) was detected already at month 1 (T1) for all the evaluated parameters: monthly migraine days (baseline: 22.1±5.8, T1: 12.2±8.5), monthly acute medication doses (baseline: 34.9±30.9; T1: 14.2±18.3) and days of drug intake (baseline: 19.1±8.1; T1:9.1±7.4). During treatment the effectiveness tended to become more marked: at T9 the number of migraine days decreased to 9.04±7.9. Measures of disability and health status improved accordingly ($p<0.001$ for all questionnaires at all time points). Patients who manifested a pattern reversal from chronic to episodic migraine were 50% at T1, 61% at T3, 65% at T6, 72% at T9. Erenumab was well tolerated, patients only detected mild side effects, mainly worsening or new onset of constipation, tolerable and transient local skin reactions and asthenia.

Conclusion: Clinical improvement was detected early after one month of treatment with erenumab and it was maintained over the long-term observation period. The treatment was well tolerated over time without drop out because of side-effects. Therefore, erenumab exhibited improvement in multiple indicators of effectiveness - which is maintained over time - and a good tolerability profile.

Disclosures: GV,GF,RDI,EG,SB,VB, and MA, have no conflicts of interest. CT and GS received honoraria for participation in advisory boards or oral presentations from: Allergan, Electrocore, Eli-Lilly, Novartis and Teva and from Eli-Lilly and Novartis, respectively.

Early outcomes of migraine after erenumab discontinuation: data from a real-life setting

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Background: Monoclonal antibodies targeting calcitonin gene-related peptide, including erenumab, are migraine-specific preventive treatments, whose long-term effectiveness has still to be evaluated in real-life settings.

Aim: We aimed at assessing the consequences of erenumab discontinuation after a 12-month treatment in patients.

Methods: We evaluated the short-term outcomes after erenumab withdrawal in patients with migraine enrolled in a real-life multicenter register of migraineurs treated with erenumab. All patients had received monthly erenumab for 12 months and attended a follow-up of two months after drug discontinuation. We only included patients who reported less than half of baseline migraine days (MMDs) for at least the last 6 months of treatment. Outcomes were reduction in MMDs, acute medications days (AMDs), and pain intensity on a 0-10 Numerical Rating Scale (NRS).

Results: All 24 recruited patients registered a reduction in monthly migraine days from a mean value of 23 (IQR 12.25-30) at baseline to 3.5 (interquartile range (IQR) 2-5; P=0.001) at the 12th month. One month after treatment discontinuation, we observed an increase in monthly migraine days up to 7.5 (IQR 5-18.7; P=0.001 vs the 12th month and 0.001 vs baseline). Similarly, Numerical Rating Scale and acute medications days reduced during the 12-month treatment and slightly increased one month after treatment discontinuation, although staying lower than baseline. Eight patients resumed erenumab achieving good results soon after the new course. The remaining 16 patients had a sustained response two months after treatment withdrawal.

Conclusions: Erenumab discontinuation after a 12-month treatment led to a rapid increase in MMDs, AMDs, and NRS in some patients, who might benefit from prolonged duration of treatment; on the other hand, some patients showed long-lasting benefits.

Analysis of the DNA methylation pattern of the distal promoter region of calcitonin gene-related peptide 1 gene in patients with episodic and chronic migraine

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Background: Recent studies suggested that epigenetic mechanisms, including DNA methylation, are involved in migraine pathogenesis. The neuropeptide calcitonin gene–related peptide (CGRP), encoded by *CALCA* gene, has a key role in migraine. Surprisingly, very little is known about the methylation of the genes related to the CGRP-ergic system in migraine. The promoter of *CALCA* contains two different CpG-rich islands: a first distal promoter region (-2762 to - 2362 bp), and a second one encompassing the proximal promoter (-1662 to -1028 bp). In preliminary data, we found that DNA methylation profile at the proximal promoter region of *CALCA* is lower in episodic migraineurs when compared to controls, correlating with several clinical features of the disease.

Aim: The aim of the study was to evaluate DNA methylation pattern of the distal promoter region of *CALCA* gene in patients with both episodic and chronic migraine.

Methods: 22 patients with episodic migraine (F/M 15/7; mean age 39.7 ±13.4 years), 16 patients with chronic migraine (F/M 10/6; mean age 48.7 ±15.2 years), and 23 controls (F/M 15/8; mean age 40.7 ±14.9 years) were recruited. Genomic DNA was extracted from peripheral blood. Cytosine-to-thymine conversion was obtained with sodium bisulfite. The methylation pattern of the distal CpG island in the promoter region of *CALCA* gene was analyzed.

Results: After sequencing, we studied all the 30 CpGs units per this CpG island, and we found that C was methylated in a heterozygous state in 6 out of 30 CpG sites (positions -2736, -2601, -2592, -2555, -2423, -2405). No difference of methylation of the 30 CpG sites at the distal region of *CALCA* promoter was observed between migraineurs and controls. Furthermore, no difference in methylation pattern was found between patients with episodic and chronic migraine.

Conclusion: We report the first investigation of DNA methylation at the *CALCA* promoter distal region in migraine. Contrariwise to the proximal promoter region, DNA methylation pattern at the distal promotor region of *CALCA* gene was below 5% and did not show difference between migraine patients and controls. Additional investigations are needed to better define the role of the promoter region of *CALCA* gene in migraine.

Cortical abnormalities in pediatric patients with migraine without aura: analysis of gyrification morphology and cortical thickness

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Background: Studies on adult patients with migraine demonstrated cortical thinning in specific regions of the brain involved in pain processing. In addition, factors of disease duration and frequency of migraine attacks were predictors of these cortical abnormalities.

Aim: To verify the presence of abnormalities of the morphology of gyrification in pediatric patients suffering from migraine without aura and to identify the clinical-radiological correlations.

Methods: A search was carried out in the PACS using the terms "headache" and "migraine" between 01/01/2018 and 31/01/2020. A neurologist examined the patients' medical records (Pcs) to confirm the diagnosis of migraine without aura and to rule out psycho-physical comorbidities. A radiologist evaluated MRI examinations to rule out the presence of accidental findings, gross morphological and signal abnormalities. Estimation of cortical thickness and gyrification morphology was performed on the 3D T1 MPRAGE sequence without contrast medium of 48 patients and 26 controls. Permutational statistical analysis for linear models (1000 permutations) was carried out to evaluate the significance of the results obtained.

Results: A statistically significant difference in cortical thickness was demonstrated between migraine patients and healthy controls bilaterally, at the level of the convolutions: superior frontal; pre and post central; crawler; precuneo; wedge; calcarine fissure and superior parietal lobule ($p>0.001$); in the right hemiencephalon at the level of the convolutions: upper, middle and lower frontal; upper and middle temporal; supramarginal and insula ($p<0.05$).

Conclusions: A difference in cortical thickness of migraine patients was demonstrated at the level of cortical areas involved in the networks of nociception and pain processing, and of executive functions. Since the thickness of the cortex is a variable parameter over time and correlated to the pathology, the demonstration of anomalies in pediatric patients confirms the need for an early diagnosis and personalized treatment.

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

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Background: Perception of the surrounding environment results from the interaction of multiple sensory stimuli. 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 illusion is associated to changes in visual cortical excitability. Furthermore, it is known that migraineurs show an abnormal visual cortical excitability, even interictally.

Aim: We aimed to confirm SIFI differences between healthy subjects and migraineurs at baseline; then, we evaluated SIFI changes in migraineurs after three months therapy with erenumab 140 mg.

Methods: We enrolled 30 chronic migraine (CM) patients without aura (mean age 50 yrs $\pm$1.8; 24 F), who started erenumab (140 mg monthly) and 30 healthy control (HCs) subjects (25 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). Patients were examined at the beginning (t0) and after 3 months of 140 mg erenumab treatment (t3). Comparisons were performed through ANOVA with Duncan's test for post-hoc analysis.

Results: ANOVA showed that HCs refer a higher number of flashes compared to CM ($p=0.0002$) and such difference remained quite unchanged at t3 ($p=0.00003$). Differently, no significant changes of illusions scores were observed in patients between t0 and t3 ($p=0.4559$) at rmANOVA. However, planned comparisons showed a significant increase of 1F4B condition scores between t0 and t3 ($p=0.0297$).

Conclusion: In agreement with previous evidence, CM patients showed less fission illusions than HCs. 3-month erenumab 140 mg therapy was not able restore normal fissions perception even if a significant but limited SIFI increase was observed for the condition 1F4B at t3 in CM. The visual cortical hyperexcitability of CM patients is disease-pertinent and, as such, hardly modifiable by treatment; alternately, more time is needed for such changes to occur, maybe even because anti-CGRP MABs do not cross blood-brain barrier? Further exploration with longer treatment periods is needed to solve the matter.

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Transcranial brain parenchymal sonography in the migraine patient: literature review and data from a single center

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Background: Transcranial brain parenchimal sonography (TCS) is an emerging technique applied for the study and characterization of deep cerebral structures (substrantia nigra, raphe nuclei, basal ganglia and ventricular system). In the last decades this technique has been extensively applied as a valid supportive tool in the early diagnosis of Parkinson disease. As for migraine, the use of TCS has been so far limited to a small number of heterogeneous studies almost exclusively addressing patients with episodic migraine.

Aim: To use TCS for the study of midbrain raphe nuclei in patients with episodic versus chronic migraine, and to assess possible associations between sonographic data and clinical characteristics of our patients.

Methods: 35 migraine patients (20 episodic, 15 chronic) were enrolled at the outpatient clinic of the Neurology Department of S. Giacomo Apostolo Hospital. Twenty healthy age-matched subjects served as controls. Patients and controls underwent full clinical history and neurological examination; TCS was performed, and midbrain raphe was divided into two groups: normal (continuous raphe) or hypoechogenic (interrupted or invisible raphe).

Results: We applied a logistic regression analysis in order to identify possible clinical variants capable of determining raphe characteristics. An hypoechogenic raphe was not related to age (p=0.115), sex category (p=0.206), type of migraine (episodic or chronic, p=0.196), number of migraine attacks (p=0.769), medication overuse (p=0.213) or type of medications used (NSAID vs triptans, p=0.07), whereas there was a statistical association with disease duration (p=0.033).

Conclusion: In migraine patients, raphe characteristics were related to disease duration, rather than to migraine subtype (chronic vs episodic): patients with a longer history of disease had a higher probability of manifesting an altered (hypoechogenic) midbrain raphe. The presence of an hypoechogenic raphe could suggest a disease-dependent effect or identify a subgroup of patients doomed to longer disease duration and with a tendency towards chronicization.

Gender differences in pattern of use, baseline cardiovascular risk and concomitant use of serotoninergic medications among triptan users in Tuscany, Italy

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Background: Triptan vasoconstrictive properties and the possible occurrence of medication overuse headache (MOH) represent the main limitations to their use. Moreover, triptans should be used with caution in patients with serotoninergic medication (SM) due to the possible occurrence of serotonergic syndrome (SS).

Aim: To describe the pattern of triptan use, cardiovascular diseases (CVD) and SM use by gender in the general population of Tuscany, Italy, between 2008 and 2018.

Methods: The population-based regional administrative database of Tuscany region was used. Subjects with ≥1 prescription of any triptan (ATC: N02CC*) between 2008 and 2018 were identified and stratified by age groups. Prevalent users (PU) were patients with ≥1 triptan dispensing in the year of interest. New users (NU) were subjects with ≥1 triptan dispensing during the year of interest and none in the past. Patients already in treatment (AT) were those with 1≥ triptan dispensing during the year of interest excluding NU. Users with CVD representing an absolute (e.g. angina) or a possible (e.g. hypertension) contraindication to triptan use as well as those taking drugs potentially associated with SS were identified. Patterns of triptan use during one year follow-up were categorized as: sporadic, occasional, regular, and overuse. All analyses were stratified by gender.

Results: A total of 86,109 triptan users were identified between 2008 and 2018, of which 64,672 were NU (men: 26.3%; women: 73.7%). About 10% of both male and female NU users were aged 65+. Absolute CV contraindication was found in 4.4% and 2.1% of male and female NU, respectively, while male and female AT with absolute CV contraindication were 2.4% and 1.5%, respectively. Patients with SM were 17.2% and 21.9% of male and female NU, respectively. Overusers were 0.1% and 2.5% among NU and AT of both genders, respectively. Notably, about 60% of overusers concomitantly used SM.

Conclusion: Further investigations are needed to address safety concerns related to the use of triptans in non-recommended age-groups, in patients with CVD and those with SM, also taking in consideration possible gender differences. In particular, special attention should be paid to overusers concomitantly using SM.

A pilot, double-blind, randomized, placebo-controlled, dose finding, proof of concept study to evaluate efficacy, safety and tolerability of self-administered subcutaneous diclofenac sodium 25-50-75 mg/1 ml in the treatment of an acute migraine attack with headache

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Background: There is still
a need to develop new therapeutics or new formulations for migraine treatment, particularly dedicated to abort migraine attacks. Migraine patients would significantly benefit from subcutaneous formulations of NSAIDs that can be self-administered.

Aim: To evaluate the efficacy (primary end point: % of patients pain free at 2 hours after the study drug injection) and safety of diclofenac sodium (25-50-75 mg/1 ml) administered subcutaneously in comparison to placebo in the treatment of a single acute migraine attack.

Methods: Phase II, multicentric, double-blind, randomized, placebo-controlled study. Patient population included adult male and female with diagnosis of migraine, with or without aura, according to ICHD-3 criteria. The treatment was self-administered by patients at the earliest time they experience a migraine headache of moderate or severe intensity.

Results: A total of 128 patients were randomized to the assigned treatment, overall 122 patients were treated (6 patients discontinued before the treatment). A single subcutaneous injection of three different doses (25, 50 and 75 mg/1 ml) of diclofenac sodium showed a tendency to be effective in the treatment of a single acute migraine attack with headache compared to placebo. The 50 mg unit dose was the diclofenac dose strength with the best efficacy profile, as it showed, for the primary endpoint, a statistically significant difference as compared to placebo: 46.7% of patients were pain free at 2 hours compared to 16.1% of patients in the placebo group (p 0.01).
Consistently with the primary endpoint, the 50 mg unit dose showed a statistically significant difference as compared to placebo for part of secondary endpoints (% of patients with absence of photophobia and nausea at 2 hours, sustained pain freedom from 2 to 12, 24 and 48 hours after the injection, ability to function normally at 2 hours and % of patients requiring rescue medication within 48 hours).

All diclofenac dose strengths had an acceptable local tolerability profile as most of treatment-related AEs consisted of injection site pain of mild intensity. The general safety of all diclofenac dose strengths (laboratory parameters and vital signs) was comparable to that observed in the placebo group.

Conclusion: A subcutaneous injection of diclofenac sodium (50 mg/ml) can be a valuable option for the treatment of an acute migraine attack especially when gastrointestinal absorption of oral drugs cannot be warranted because of the concomitant presence of nausea and/or vomiting.


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Preliminary study for the use of neurofeedback in patients with headache using the latency and amplitude of the auditory and visual P300 associated with wavelet analysis of the single traces of the two ERP

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Background: Neurophysiology and psychophysiology of migraine.

Aim: With this study we verified the efficacy of neurofeedback in subjects suffering from primary headache both with and without aura, using the symptomatology change of the value of amplitude and wavelet analysis of the single traces as control parameters.

Methods: 4 subjects were enrolled, age 18-65 yrs both sex. The treatment included: open and closed eyes EEG recording for 10 minutes, recording of ERP (visual and auditory P300), analysis of the single traces (FZ CZ PZ) with wavelet analysis, 12 sessions of neurofeedback with electrodes placed in sequential order in: C3-C4; F4-F8; F8-F7; F7-F3 for a total time of 45 minutes. The frequency of the sessions was weekly, the registrations were done: at baseline 6 and 12 sessions.

Results: The data collected highlighted an increase in the amplitude in both visual and auditory P300, and better frequency composition. The frequency of cephalagic symptom decreased from 8/month to 2/month associated with mood enhancement.

Conclusion: These preliminary results show that neurofeedback treatment of the headache can be a useful tool if we use EEG registration with FFT analysis and ERP (visual and auditory P300) associated of the wavelet analysis of single trace.

Can headache be considered an altered function of attentive process? Comparison study between subjects with headache vs controls using visual and auditory P300 as control parameters

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Background: Neurophysiology and psychophysiology of migraine.

Aim: In this study we analysed the role played by cognitive evoked potentials in individuals suffering from headache vs. non-cephalalgic subjects. We used the amplitude and latency values of the visual and auditory P300 recorded in the FZ CZ PZ derivations as differential variables, two parameters involved in automatic attention process of the brain and how these alterations could be seen as an etiological element of cognitive overload and headache can be considered as a signal of this overload.

Methods: All subjects were subjected to a preliminary EEG recording lasting 10 minutes with opened and closed eyes to highlight the presence of irritative phenomena. Registration of ERP (Event Related Potential) took place as follows:
1. The subject sat in front of a stimulating video screen 45 cm away.
2. A cabled cap was applied on the head of the subject.
3. A conductive paste maintained resistance to the skin < of 5 kΩ.
4. At the beginning traces of EEG were registered with the 10-20 model, monitoring a phase with eyes opened and one with eyes closed for a total of ten minutes VISUAL and AUDITORY P300.
On the screen we showed 2 different stimuli:

VISUAL	CIRCLE RED	RARE STIMULUS (TARGET)
	CIRCLE GREEN	FREQUENT STIMULUS
AUDITORY	BEEP 1	RARE STIMULUS (TARGET)
	BEEP 2	FREQUENT STIMULUS

The rare stimulus was presented 70%; the frequent stimulus was presented 30%. The ODDBALL paradigm was used. The subject held a joypad in one hand and the task was to press a button every time that the target stimulus was seen. The ERP visual and auditory P300 was obtained for the control group and headache group after synchronized mean and the traces chosen were the derivation FZ CZ PZ, and for each one amplitude and latency were calculated.

Results: The subjects suffering from headache showed a worse level of education and a statistical significance for the amplitude values in the derivations used, both auditory and visual ERP.

Conclusion: From the results obtained from this study, we can say that attention deficit is present in the subjects affected by headache and that this fact could influence in a statistically significant matter their schooling and as a consequence their quality of life as well.
Thus, with these results, we believe that it is necessary to perform neurocognitive evaluations in subjects suffering from headache. For all the subjects in whom an attention deficit is evident, it should be essential to start the required procedures to reduce the negative impact on their quality of life and on their schooling. This aim could be accomplished by the use of two different methods to be used together: cognitive rehabilitation and neurofeedback, using the values of auditory and visual P300 as the control parameters. Eventually, it would also be helpful to do a short psychotherapy course with the aim of developing management strategies.

Headache and Arnold Chiari 1 syndrome (chapter 7.7 of ICHD-3): 4 case reports

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Background: Chiari malformation type 1 (CM1) is characterized by a structural abnormality of the posterior cranial fossa, with herniation of the cerebellar tonsils through the foramen magnum (>5mm). Headache is its main symptom.

Aim: We report the clinical history of 4 patients, assessed at the Headache Centre of L'Aquila.

Methods: We analyzed the patients' clinical histories, from onset of symptoms to the diagnosis of CM1.

Results: **Patient 1**: (M, 10), headache onset at 4, with the characteristics of a migraine without aura. Familiarity with migraine. Because of unresponsiveness to the usual therapy, brain and spine MRI was performed: herniation of the cerebellar tonsils of about 5mm and multiple dilations of the ependymal canal. **Patient 2**: (F, 14), headache onset at 13, temporal pain, pulsating, duration <2', daily, triggered by physical exertion (aerial dance, flex-extension of the head). After 2 weeks increase in frequency and intensity of the episodes. EON: difficulty in flex-extension and head rotation. Brain and spine MRI: cerebellar tonsils engagement of about 15mm and no syringomyelia. Cervical RX in two projections + epistropheus tooth: minimum anterolisthesis of C4 on C5 of 1.5 mm. **Patient 3**: (M, 9), headache onset at 9, stabbing pain, diffuse, lasting a few minutes or seconds, triggered by coughing, dysphagia and vomiting. Familiarity with migraine. Previous diagnosis of ADHD with mild degree intellectual disability. EON: disturbance of motor coordination. Brain and spine MRI: platybasia and descent of the cerebellar tonsils of about 13 mm, no syringomyelia. Dynamic cervical X-ray in normal range. **Patient 4**: (F, 14), previous diagnosis of moderate intellectual disability in malformative syndrome (suspicion of Cohen syndrome). Episodes of vertigo triggered by exertion (aerial dance, head flex-extension). MRI of the brain: asymmetrical engagement of the cerebellar tonsils (7 mm on the right and 3 mm on the left). For all patients PESS were in normal range, so the neurosurgical videat suggested a "wait and see" attitude, with strict indications on the habits of life and physical and sporting activity.

Conclusions: Changing headache quality is an indication for neuroradiological investigations. The triggers of CM1 symptoms are often linked to children's lifestyles (exaggerated flex-extension movements of neck or spine).

Patients' choice between paper and electronic headache diary

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Background: Headache diary is of paramount importance for the management of primary headaches. Therefore, patients need to feel at ease with its compilation, in order to supply the headache specialist with the most reliable data possible and maintain a reasonable compliance over time. Other studies have compared preference between paper and electronic diaries in headache, chronic pain and menstrual related disorders and reported a preference for the electronic ones. One study on general adolescent population reported that filling in the internet-based diaries was more bothersome. At the best of our knowledge there are no studies investigating patients' choice between the two types of diaries.

Aim: To study patients' choice when offered a paper or electronic based headache diary, in a population of outpatients of a second level headache clinic.

Methods: We selected all adult consecutive patients with diagnosis of either migraine or tension-type headache or both, presenting to our outpatient headache clinic for a first or a follow-up visit. We collected the following data: diagnosis, occupation, education, no. of headache years, no. of headache days per month, choice of type of diary (cellular phone app, paper based, both, none, do not know).

Results: One hundred thirty-eight patients had been consecutively enrolled in the study just before the Sars-CoV 2 restrictions: 109 females and 29 males, mean age 40.5 $\pm$ 13.3 years old, 108 seen as a first visit, 30 as a follow-up. One hundred-one patients had less than 10 days of headache per month while 28 had more than 15 headache days per month, mean headache days per month was 9.1 $\pm$ 8.7. Seventy-two had migraine without aura, 11 with aura, 22 chronic migraine, 10 probable migraine without aura, 10 tension-type headache. Forty-nine (35.5%) patients choose the app, 76 (55.1%) the paper based diary, 10 (7.3%) both, 2 (1.4%) did not know and 1 (0.7%) did not want to choose (λ^2 test p=0.003). There was a trend for more patients with chronic headache choosing the paper diary (67.8% vs 49.5% - λ^2 test p=0.1856). There were no statistically different rates among patients aged between 18-30 and 30-60 years old (44.4% versus 54.7%) and between males and females (48.3% vs 56.9%).

Conclusion: Significantly more patients choose a paper based diary to record their headaches in contrast with previous preference data. Probably a higher number of headache days per month is an important drive toward the choice of the paper diary.

Headache in the elderly: a case series from a tertiary headache center

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Background: Headache disorders are common and are associated with a high social and economic burden. Although rarer than those in young adults, primary headache disorders in patients older than 65 years of age might be severe and deserve preventive treatments.

Aim: We aimed at evaluating the proportion and characteristics of patients older than 65 years referring to the third-level Headache Center of Avezzano-L'Aquila.

Methods: In our prospective single-center study, we included patients older than 65 years of age referring from November 2019 to August 2020 for a first in-person visit. We evaluated the headache type, characteristics, comorbidities, and treatments.

Results: Out of 251 patients, 30 (12.0%) were over 65 years of age, with a mean age of 73 (IQR 69-79) years; 24 patients (80%) were female. The most frequent comorbidities were overweight (15 patients; 50%) and hypertension (14 patients; 43%). Seventeen patients were taking ≥3 drugs and 5 patients were taking 5 drugs for comorbid conditions. Twenty-two patients (73%) were diagnosed with migraine, three (10%) with tension-type headache, and the remaining five patients were prescribed diagnostic examinations to rule out secondary headache. Among migraineurs, 16 (53.3%) had a chronic and 6 (20%) an episodic form; medication overuse was present in 6 patients with chronic migraine (37.5%). Three patients with migraine were triptan users. Among migraineurs 22, were current or former users of prophylactic treatments; the most used drug categories were antiepileptics and antidepressants. We prescribed amytriptiline to five (17%) patients, botulinum toxin to four (13%), erenumab to three (10%), and flunarizine to one (3%).

Conclusions: Despite rarer than in young adults, headache may be a relevant concern in the elderly. So far therapeutic resources in older patients are more limited because of contraindication and interaction with another drug or lack of evidence. More research is needed to develop evidence-based treatment for elderly patients considering comorbidities, polytherapy and susceptibility to adverse events.

Effect of the combination of Erenumab and Onabotulinumtoxin A in patients with chronic migraine who are partial responders to either treatment alone: case series from a tertiary headache center

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Background: Treatments specific for chronic migraine (CM) include onabotulinumtoxinA (BTA) and monoclonal antibodies acting on the CGRP or its receptor. Evidence suggests that those two drugs have different mechanisms of action and can therefore be used in combination.

Aim: We aimed to assess the efficacy of combined treatment with BTA and erenumab in patients with CM.

Methods: We included consecutive patients, referring to our headache center between May and July 2020, who met ICHD diagnostic criteria for CM and who were partial responders (monthly migraine days [MMDs] reduction 15-50%) or had a wearing-off (loss of efficacy after at least two successful administrations) to BTA or erenumab used as single treatment. All patients were firstly treated with BTA alone, then started erenumab and thereafter, after at least 6 months of therapy with erenumab, BTA was added again in combination with erenumab. We evaluated MMDs at baseline, during treatment with BTA and erenumab alone, and after one month of combined treatment.

Results: Three women (age range 45-59 years) were treated with the combined treatment. Patient-1 had 24 MMDs at baseline. Average MMDs were 20 after 24 months treatment with BTA. During erenumab treatment, MMDs decreased to 12 after 5 months, and increased again to 24 after 9 months. After two months of combined treatment the MMDs were 18. Patient-2 had 30 MMDs at baseline. Average MMDs were 20 after 22 months treatment with BTA. During erenumab treatment, MMDs decreased to 4 after 5 months, and increased again to 10 after 7 months. After two months of combined treatment the MMDs were 5. Patient-3 had 30 MMDs at baseline. Average MMDs were 23 after 9 months treatment with BTA. During erenumab treatment, MMDs decreased to 10 after 2 months, and increased again to 15 after 5 months. After two months of combined treatment the MMDs were 9**.**

Conclusion: In this preliminary report, the combination of onabotulinumtoxinA and erenumab led to better clinical response than treatment with either of the two drugs alone. Randomized and controlled studies are needed to test this combination in very selected patients who have inadequate clinical response to either drug as single treatment.

Thalamo-cortical network activity in subgroups of migraine with aura patients

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Background: Due to this variability in clinical presentation, it has been suggested that migraine with aura is a condition characterized by a broad spectrum of clinical subtypes that are likely to differ in pathophysiological mechanisms.

Aim: We aimed to study resting-state functional connectivity (FC) between brain networks and its relationship with the microstructure of the thalamus in migraine patients with pure visual auras (MA), and in patients with complex neurological auras (MA+), i.e. with the addition of at least one of sensory and language symptoms.

Methods: 3T MRI data from 20 patients with MA and 15 with MA+ were collected and compared with data from 19 healthy controls (HCs). We collected resting state data among independent component networks. Diffusivity metrics values of bilateral thalami were calculated and correlated with resting state ICs Z-scores.

Results: As compared to HCs, both patients with MA and MA+ showed disrupted FC between the default mode network (DMN) and the right dorsal attention system (DAS). MA+ subgroup of patients showed lower microstructural metrics than those of both HCs and MA, and peculiar correlation with the strength of DMN. Despite the microstructural metrics of MA patients did not differ from those of HCs, they did not show the same correlations with the strength of DAS than HCs.

Conclusion: Present findings suggest that clinical heterogeneity of migraine with aura MRI profiles is associated with common and specific morpho-functional features of the nodes of the thalamo-cortical network.

Occipital Neuralgia in Chiari I Malformation: are they different faces of the same coin?

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Background: Occipital neuralgia (ON) is considered a rare and debilitating headache localized in the occipital area. It can occur in cases of irritation, compression, or traction of the occipital nerves, as in the pathologic processes of the neck vessels, bones, muscles, or tendons. Association with Arnold Chiari Malformation (CIM) is rarely reported, but the prevalence of a simultaneous occurrence of the two diseases is unknown. Treatment includes antidepressants, antiepileptics, infiltration of the nerve (anesthetic and corticosteroids), and botulinum toxin A. Diagnosis is clinical and is inferred from the response to local anesthetic block.

Aim: We describe a brief case report, where we focus on the importance of determining the source of pain in order to decide the best treatment for the patients.

Methods: We report the case of a 21-year-old woman reporting persistent refractory occipital and cervical pain, with occasional right paroxysmal attacks of stabbing pain, not exacerbated by postural changes or Valsalva Maneuver. Her medical history was negative (and no cigarette, alcohol consumption or hormone therapy were reported). She performed brain magnetic resonance imaging which revealed lowering of the cerebellar tonsils especially the right one, compatible with CIM. Neurological examination revealed a Tinel sign on percussion of a region about 3 cm near the occipital protuberance, which resulted highly suggestive for ON. Various attempts with amitriptyline, pregabalin, carbamazepine, various nonsteroidal anti-inflammatory drug resulted all uneffective.

Results: Local anesthetic blocks of the greater occipital nerve resulted effective and pain completely disappeared.

Conclusion: In case of a suspicion of both CIM and ON, it is useful to consider the diseases as two different events. Indeed, until now, no conclusive data on a causative link between ON and CIM have been reported in the literature.
We think that it could be considered reasonable, in case of patients with both diagnoses of CIM and ON to try to treat the second one before thinking about surgical decompression of CIM, especially if the pain is highly suggestive for ON.

The hidden migraine in the Emergency Department

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Background: Migraine represents the main cause of access to the Emergency Department (ED) among primary headaches, accounting for approximately 1.2 million ED visits annually. Most primary headache patients, however, are discharged from the ED with a diagnosis of headache "not otherwise specified" (NOS headache), leading to underestimation of migraine complaints.

Aim: Aim of the study was to analyze the prevalence and management of migraine in patients discharged from the ED with a diagnosis of NOS headaches.

Methods: We retrospectively analyzed the ED records of all the patients admitted in the two EDs of the University Hospitals of Trieste because of non-traumatic headache and discharged from the ED with NOS headache diagnosis during a one-year period. Only patients who performed one consulting visit at least and with consultants' diagnosis of migraine were included. The digital data recording system and the medical and paramedical guidelines in use are homogeneous in the two EDs. Demographic, clinical data, specialist examinations and discharge reports were analyzed.

Results: Out of 124 patients with NOS headache discharged from the ED, 26 patients (20.9%) [21 F, 5 M, mean age 44] were included. All patients were evaluated by a neurologist, two patients also by non-neurologist consultants (otorhinolaryngologist and oculist). Twenty-one (80.7%) were diagnosed as migraine without aura, 5 (19.3%) as migraine with aura. Only neurologists suggested the use of triptans as symptomatic drug in the ED in 9 cases (34.6%), the other patients were treated with NSAIDs (26.9%) or combinations (NSAIDs+BDZ [7.7%]; NSAIDs+opioids [7.7%]). Prophylaxis was prescribed only in one patient. Thirteen patients underwent a cranial CT scan. Twenty-one (80.7%) patients were referred to the Headache Centre after ED discharge.

Conclusion: About one-fifth of NOS headache who has been visited by a neurologist in the ED received a diagnosis of migraine that was not reported on the discharge sheet by emergency physicians. Triptans are rarely used in the ED despite a definite diagnosis of migraine. Most of the patients were addressed to the Headache Centre.

Paired pulse study with TMS in chronic and episodic migraine

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Introduction: Paired-pulse TMS paradigms can be used to test connectivity within the primary motor cortex in human subjects [1]. Aim of the present study was to provide additional information on short intracortical inhibition (SICI) and intracortical facilitation (ICF) using different intensities of the test stimulus (TS) in patients suffering from episodic migraine without aura (EM) and chronic migraine (CM).

Methods: We enrolled 24 patients suffering with EM, 9 patients with CM and 24 healthy subjects. EM and controls were randomly assigned to two groups: the first group underwent assessment of SICI, whilst in the second group we evaluated ICF. While in patients with CM we tested both ICF and SICI during the same experiment. All patients are tested interictally. We assessed SICI and ICF at three different suprathreshold intensities of the TS (110%, 130% and 150% of the resting motor threshold). Interstimulus intervals (ISI) of 2 ms and 10 ms were used for testing SICI and ICF respectively [2].

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

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

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The impact of social distancing on the lifestyle of patients with migraine: results from a multicenter cross-sectional study

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Background: Social distancing was the measure taken by governments to control the rapid spread of COVID-19 [1,2]. This restriction resulted in a sudden change in people's lifestyle, leading to an increase in sedentary behaviors, change in eating habits and sleep-wake cycle [3].

Aim: To estimate the levels of physical activity (PA), alterations in eating habits and the presence of sleep disturbances among patients with migraine before and during the last week of quarantine.

Methods: 261 patients affected by migraine completed a detailed interview comprehensive of three parts: an adapted version of the IPAQ-SF, which measured PA as energy expenditure (MET–minute/week); a questionnaire that measured the frequency of intake of the main foods; the insomnia severity index (ISI) questionnaire regarding the presence of sleep disorders. Participants were enrolled at the "Headache Clinic" of Palermo and Avezzano.

Results: 186 patients (71.3%) had chronic migraine; 227 patients (87.0%) were female; the mean age of patients was 44.5±12.3 years. During social distancing, 72 patients (28%) reported a headache worsening, 86 (33%) an improvement, and 103 (39%) a stable headache frequency.
We observed a significant decrease of the mean total amount of weekly PA levels during COVID-19 quarantine (-183 METs; p=0.008) in the whole sample and a specific decrease in walking (while increasing the sitting time) in each group (-197 mean METs; p<0.001). Moreover, patients who reported a worsening of headache during social distancing presented a significant increase in the time spent with computers (+0.8 mean hours; p<0.001) compared to patients who improved. No clear associations were found depending on eating habits, but a significant difference was reported regarding sleep disorders. In fact, patients who presented a stable or worsening headache reported an overall increase on ISI scores during social distancing (+2.0 mean points, p=0.006, and +1.0 mean points, p=0.007) compared with patients that reported an improvement in migraine (+0.6 mean points; p=0.351) during social distancing.

Conclusion: Our study confirmed that the measures to contain the spread of COVID-19 have affected the practice of PA levels and sleep quality among patients with migraine.

Two or three cycles of onabotulinumtreatment before assessing efficacy for chronic migraine treatment? The response from a real-life study

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Background: Onabotulinumtoxin A (BT-A) is the first approved treatment for chronic migraine (CM). Current guidelines suggest continuing BT-A treatment for 6-9 months before assessing responder status. However, it is unclear when it is worth to proceed to three administrations and when it is reasonable to stop treatment after two cycles.

Aim: We aimed to provide real-life data to guide treatment decision on minimal duration of treatment with BT-A before establishing efficacy.

Methods: We performed a retrospective analysis on collected data in 12 European headache centers from 2012 to 2020. We included all consecutive patients treated with BT-A for CM for at least three cycles or with equivalent follow-up. For each treatment cycle we defined patients as 'complete responders' if reporting a ≥50% reduction in monthly headache days compared with the three months before starting BT-A, 'partial responders' if reporting a 30-49% reduction, and 'non-responders' if reporting a <30% reduction or if stopping the treatment earlier than the third cycle.

Results: We included 1,800 patients with a mean migraine duration of 31.4±12.5 years. During the first cycle, 522 (29.0%) patients were complete, 349 (19.4%) partial, and 929 (51.6%) non-responders; the corresponding data were 670 (37.2%), 409 (22.7%) and 721 (40.1%) respectively during the second cycle, and 880 (48.9%), 214 (11.9%) and 706 (39.2%) respectively during the third cycle. Multivariate analyses showed that complete (OR 14.16; 95% CI 8.44-25.74; P<0.001) or partial response (OR 5.78; 95% CI 2.81-11.88; P<0.001) during the second BT-A cycle were the only factors independently associated with complete response during the third cycle.

Conclusion: According to our data, the proportion of patients with CM responding to BT-A treatment increased up to the third cycle. Complete or partial response during the second BT-A cycle was the only factor associated with complete response during the third cycle. Hence, it is reasonable to continue treatment in all patients until the second cycle and to proceed to the third cycle in those who have ≥30% reduction in monthly headache days.

Lifestyle changes during COVID-19 lockdown and migraine

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Background: The COVID-19 lockdown resulted in a deep lifestyle change in people. Social distancing, reduced physical activity (PA), changes in working habits and daily life routine were among the most often reported effects of the lockdown. These changes may influence migraine.

Aim: Aim of the study was to collect data about migraineurs lifestyle changes during the COVID-19 lockdown period and to relate these items to possible changes of migraine characteristics.

Methods: Patients with migraine who attended the Headache Centre of the University of Trieste from 01.06.2019 to 31.12.2019 were interviewed by neurologists specialized in headache. Patients were not assuming prophylactic therapy or they were on prophylaxis with the same therapy for at least 3 months. Exclusion criteria were spontaneous modifications of the prophylactic therapy, including starting a new therapy, disabling comorbidities, diseases that caused walking impairment, moderate/severe cognitive impairment or psychiatric conditions. Data about demographics, working routine, lifestyle, migraine characteristics and disability (HIT-6) and drugs consumption were compared between the first month of the lockdown (March 2020) and a reference month prior the lockdown (January 2020).

Results: Thirty-seven patients were analysed [migraine without aura (MwoA)= 26P, mean age 45 (31-53)]; migraine with aura (MwA) *plus* migraine with and without aura (MwA/MwoA)= 11P, mean age 38 (26-47)]. During the lockdown, 12 patients started remote working continuing their usual work, including the use of visual display terminals. No changes were reported for nutritional, sleep or working habits, while more patients with insufficient PA (65% vs 31%; p=0.012) were found. Reduced mean headache duration [3 h, (2-12) vs 2 h (1-8); p= 0.041], and HIT score [59 (51-63) vs 50 (44-57); p= 0.001] were found in patients with MwoA, while no changes resulted in patients with MwA *plus* MwA/MwoA). Severity of the attack and symptomatic drug consumption were the same before and during the lockdown.

Conclusion: During the lockdown, remote working was common. Duration of the attack and disability of migraine were reduced during lockdown, probably as a consequence of the increased time spent at home with less stressors and with the possibility to rest during the crisis.

Ketogenic diet in pediatric patients with chronic migraine

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Background: Ketogenic Diet (KD) is a safe and well tolerated therapeutic tool for different neurological disorders, including epilepsy. KD is characterized by a severe depletion of carbohydrates in favour of fat assumption. Its potential therapeutic efficacy on migraine has been poorly explored, above all in childhood.

Aim: Aim of this study was to evaluate efficacy, safety and feasibility of KD in children and adolescents with chronic migraine (CM).

Methods: We prospectively enrolled patients aged 10-18 years with CM unresponsive to previous prophylactic treatments or that refused other therapies. A biochemical screening was performed to exclude inborn errors of metabolism. KD was then introduced at 1:1 ratio. Biochemical analyses were repeated at 1 week, 1 and 3 months of treatment. Daily ketones and glucose measurements at home were required.

Results: We enrolled 16 patients (3M, 13F). Among them 8 decided not to initiate KD mainly due to concerns about dietary restrictions and difficult compliance. Therefore, KD was initiated in 8 patients (1 M, 7 F – age 11-18 years). In 3 patients KD was withdrawn in the first 3 months due to inefficacy. In one case KD determined a partial benefit, but the patient had an onset of bowel inflammatory disease and KD was withdrawn. In 2 patients, after an initial response headaches appeared again, and although at a lower frequency and intensity than before KD, both patients decided to stop KD due to unsatisfactory pros/cons ratio after 4 and 5 months of treatment. One patient was lost to follow-up, and one patient is still under treatment after 4 months, with reduction of headache frequency.

Conclusion: In our headache center we experienced difficulties in enrolling patients for KD, mainly due to concerns about palatibility. In patients enrolled we observed a partial efficacy in 50% of cases. However, benefits were transient in 2 of them, and were not considered sufficient to justify such a dietary regimen according to our patients. According to our experience, although KD has a potential to treat chronic migraine, it requires a significant effort by patients and their families, making it a hardly feasible option in childhood and adolescence.

Efficacy of galcanezumab in patients with migraine and history of failure in at least 3 preventive treatment categories: subgroup results from CONQUER

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Background: CONQUER was a Phase3, multicenter, randomized controlled trial in patients with episodic (EM) or chronic (CM) migraine who had 2-4 preventive category failures. We report efficacy outcomes from pre-specified subgroup of patients with ≥3 preventive category failures.

Methods: Eligible patients (18-75 years) in CONQUER had 4-29 migraine headache days/month and 2-4 migraine preventive medication category failures in the past 10 years (reasons: inadequate efficacy and/or safety/tolerability). Patients were randomized 1:1 to monthly subcutaneous injections of galcanezumab_120 mg (loading dose: 240 mg) or placebo during the 3-month double-blind treatment period. Evaluated endpoints included overall mean change from baseline (CFB) of monthly migraine headache days across Month 1-3, overall proportion of patients achieving ≥50% reduction in monthly migraine headache days (Months 1-3) and mean CFB on the migraine-specific quality of life role function-restrictive (MSQ RF-R) domain (at Month 3).

Results: Of 462 randomized patients, 186 had history of ≥3 preventive category failures (Demographics in EM/CM: Age, years, mean[SD]: 46.0[11.5]/45.5[12.5], Gender (female), n[%]: 83[83.0]/72[83.7]; Disease characteristics in EM/CM: Duration of migraine, years, mean[SD]: 21.4[13.8]/24.5[15.5], Migraine headache days/month, mean[SD]: 9.9[2.7]/18.8[4.7], Migraine attacks/month, mean[SD]: 5.8[1.7]/6.2[2.3], Headache days/month, mean[SD]: 11.1[2.5]/21.0[4.5], MSQ Role Function-Restrictive, mean[SD]: 48.4[16.9]/38.4[18.9], Acute Medication overuse, n[%]: 36[36.0]/63[73.3]). For these patients, galcanezumab_120mg led to a significantly larger overall LS mean (SE) reduction in monthly migraine headache days versus placebo -3.0 (0.8) in EM and -5.1 (1.3) for CM ($p<0.001$): EM: LS mean change (SE): galcanezumab_120mg: -3.6(0.6); placebo:-0.7(0.7); CM: galcanezumab_120mg:-6.7(1.2); placebo:-1.6(1.1). Galcanezumab was superior to placebo for ≥50% response (EM (estimated rate (SE); galcanezumab_120mg:41.1(4.9), placebo:16.5(4.1); odds ratio (95%CI) (vs. placebo):3.5(1.7,7.3) with $p<0.001$; CM (estimated rate (SE): galcanezumab_120mg:41.5(6.9), placebo:8.4(3.9); odds ratio (95%CI) (vs. placebo):7.8(2.4, 24.8) with $p<0.001$) and improvements in MSQ RF-R score (EM: LS mean change (SE): galcanezumab_120mg:22.7(3.4), placebo:14.5(3.6); LS mean change difference (SE):8.2(4.0) with $p<0.05$; CM: LS mean change (SE): galcanezumab_120mg:25.2(3.6), placebo:4.7(3.4); LS mean change difference (SE):20.5(4.2) with $p<0.001$).

Conclusion: In patients with ≥3 migraine preventive medication category failures, galcanezumab led to significant improvements in key efficacy outcomes over placebo.

How does headache of children change during the earthquakes and the Covid-19 pandemic: always post-traumatic stress disorder?

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Background: The COVID-19 pandemic is a real emergency condition and therefore creates all the conditions of a situation of psycho-physical stress, creating a negative impact on the quality of life of children and adolescents, especially those with psychosomatic disorders, as headaches.

Aim: The purpose of this research was to evaluate the effects of the pandemic on children and adolescents with primary headache and to compare these data with those already known for the earthquake 2009 in L'Aquila. Hypothesis of the study: the pandemic may change the headache's pattern and the quality of life in these individuals, such as the earthquake?

Methods: Subjects 6-18 years, selected on the basis of the diagnosis (migraine and tension headache) already made because they belong to Headache Center of L'Aquila. First contacted by telephone, with their consent, they received a link to an online questionnaire for the whole family to reply anonymously, during Phase 1 for 1 month (Time 0), and subsequently re-evaluated in person (Time 1).

Results: 71 subjects (6±18; μ: 11,6), 40 M (56%) and 31 F (44%) with primary headache. City of residence: L'Aquila, Teramo, Rieti, Pescara, Chieti and Frosinone. Time 0: almost all of the sample showed improvements in both intensity and frequency of headache attacks, while the quality of life appears to be dysfunctional: problems in sleep patterns, frequent awakenings and difficulty in falling back to sleep again, wake up after the scheduled time; abuse of media-devices; little physical activity. Headache analysis Time 1: increased frequency and intensity of pain especially among patients with tension headache with quality of life consequences compared to the previous months.

Conclusion: On the basis of previous data (SISC, 2010) referring to the 2009 earthquake we can conclude that this trauma behaved in a similar way in the acute immediate phase, but the distant effects were different with worsening in 100% of migraine sufferers even after 1 year. In about half of the subjects who had experienced the earthquake, the pandemic evoked the emotions already experienced. It has been confirmed that 25% of earthquake victims do not have PTDS and 65% have it in partial form.

Primary headaches and learning disabilities in childhood and adolescence

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Background: Primary headaches, mostly migraine and tension-type headache (TTH), and learning disabilities (LDs) are both common in the children and adolescents population.

Aim: The purpose of study was to assess the relationship between primary headaches and learning disabilities and assess the influence of these on the quality of life, like the inhibition of the activity of study and mostly school absences and presence of psychopathologies.

Methods: A group of children and adolescents 8-18 years, with diagnosis of primary headaches, were compared to a group with primary headaches + LDs, at the Headache Center of L'Aquila-Neuropsychiatric Clinic, San Salvatore Hospital-University of L'Aquila. Diagnosis of headache: criteria of ICHD-3 (2013 and 2018). Diagnosis of LDs: 1° and 2° level batteries (Cornoldi and Tressoldi). Psychopathology disorders: CBCL 6/18 and SAFA test (Achenbach, 2001; Cianchetti and Sannio Fancello, 2001). Statistical analysis: ANOVA.

Results: 193 patients, 156 (46.15% M and 53.85% F) with primary headache (episodic and chronic) and 37 LDs (56.76% M and 24% F). The sample was divided into three groups, **group 1**: only primary headache (122 pts); **group 2**: only LDs (37 pts); **group 3**: primary headache + LDs (34 pts). The prevalence of LDs in the cephalalgic cohort (9.44%) is higher than in the general population (3.2%) and the headache associated with LDs represents a true comorbidity and not a consequence, because the headache persists once diagnosed LDs. Among subjects with headache + LDs the prevalence of psychopathology disorders (anxiety disorders) prevails with statistical significance compared to patients with only headache ($p = 0.0500$). In addition, 50% of patients with TTH + LDs say they are often absent from school, while patients with tension-type headaches in absence of comorbidities with LDs record less school absences (22%).

Conclusion: The LDs can represent a cause of chronic headache, so for us it is crucial to make an early diagnose of LDs in a cephalalgic subject to prevent the worsening of the headache and quality of life.

Thalamocortical morphofunctional integrity and Resting State Networks haemodynamic activity characterization by fractal analysis in patients with chronic migraine

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Background: Chronic migraine (CM) can be associated with aberrant long-range connectivity of MRI-derived resting-state networks (RSNs).

Aim: Here, we investigated how the fractal dimension (FD) of blood oxygenation level dependent (BOLD) activity may be used to estimate the complexity of RSNs, reflecting flexibility and/or efficiency in information processing in CM patients respect to healthy controls (HC).

Methods: Resting-state MRI data were collected from 20 untreated CM without history of medication overuse and 20 HC. On both groups, we estimated the Higuchi's FD. On the same subjects, fractional anisotropy (FA) and mean diffusivity (MD) values of bilateral thalami were retrieved from diffusion tensor imaging and correlated with the FD values.

Results: CM showed higher FD values within dorsal attention system (DAS) and the anterior part of default-mode network (DMN), and lower FD values within the posterior DMN compared to HC. Although FA and MD were within the range of normality, both correlated with the FD values of DAS.

Conclusion: FD of DAS and DMN may reflect disruption of cognitive control of pain in CM. Since the normal microstructure of the thalamus and its positive connectivity with the cortical networking found in our CM patients reminds similar results obtained assessing the same structures but with the methods of neurophysiology, in episodic migraine during an attack, this may be yet another evidence in supporting CM as a never-ending migraine attack.

Smartphone walking, Nomofobia and Phubbing: as a link with the Headache!

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Background: Work and the working environment would have a decisive function in the development of symptoms which, in turn, can determine the onset of some forms of headache as well as increase the frequency and/or intensity of pre-existing forms. Techno-stress is one of the new occupational diseases. Under this term fall various dependencies: *video addiction, internet addiction disorder, social network mania, information overload, multitasking, cybersex addiction, email addiction*. Symptoms: headache, hypertension, anxiety, panic attacks, decreased concentration, gastrointestinal and cardiovascular disorders, depression, decreased desire to behavioral alterations and relational isolation. Smartphone walking, that is, walking while talking on the phone is an activity that causes more and more fatal accidents, which has infected Italians. Smartphone walking is present above all in the big cities. It is practiced mainly by managers (65%), entrepreneurs (62%) between 30 and 45 years and by young students (58%) between 16 and 29 years. Nomophobia is the uncontrolled fear of being disconnected from the mobile phone network. Phubbing is born from the combination of the English terms phone (telephone) and snubbing (snubbing, ignoring, neglecting) and is a neologism created to indicate the attitude, not courteous, of neglecting a person with whom one is engaged in any social situation continuously and compulsively controlling the telephone. Phubbing is not only bad education but it becomes serious due to the feeling of being left alone and to the sense of inadequacy that results from not being able to catalyze the attention of the other.

Conclusion: Today the dependence on work is still an undervalued and little recognized phenomenon in the field of psychological distress and from this it follows that it is diagnosed only when it is associated with other mental or physical problems. Headache, on the other hand, is one of the most common symptoms found in medical practice, frequent in people of working age, it is a common cause of absence from work and reduced productive yield. Establishing what role the job has in the onset of headache and what consequences it has on work efficiency is a reason of growing interest in scientific research.

Migraine without aura induced by administration of Iloprost: a case report

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Background: A migraine without aura is the most common type of migraine headache (about 60% to 80% of all migraines). There are many causes of headache. Among those of a pharmacological nature, the most common is nitroglycerin. But there are other substances that often induce headache. We want to analyze a case report of iloprost-induced headache.

Materials and methods: 32-year-old woman. Familial family history of headache (paternal line). Onset of school age. Subjected to pharmacological treatment with iloprost, 3 administrations e.v./month for the diagnosis of undifferentiated connectivity p-ANCA positive not responsive to steroid treatment. No migraine seizures occurred until iloprost was used. Diagnosis according to the criteria ICHD-III: migraine without aura. Iloprost has a vasodilatory and inhibitory platelet aggregation property, binds with the same affinity to the human prostacyclin PGI2 receptor, to stimulate vasodilation, and to prostaglandin receptors. *t* has a reduced selectivity as it binds and activates all four receptors for prostaglandin E2: receptor EP1, EP2, EP3, and EP4. Activation of EP2 and EP4 receptors causes vasodilation, but activation of the EP3 receptor causes vasoconstriction. Iloprost inhibits platelet aggregation by stimulating adenylate cyclase. The mechanism responsible for the pharmacological activity of iloprost is not yet clear.

Results: Following administration e.v. of iloprost the patient manifested towards the end of the administration (duration about 5 hours) migraine crisis without aura with photo-phonophobia, nausea, strong throbbing pain in the right frontal-temporal region that persisted after the administration up to sleep (about 8 hours after infusion) (VAS: 7-8). The migraine crisis occurred every time the patient underwent treatment with iloprost and each time she took ketoprofen drops with intensity reduction (VAS: 2-3) without total resolution of the crisis.

Conclusion: Iloprost causes the onset of headache as reported on the package insert. The clinical case described demonstrates this and a migraine occurred a thousand times when the patient underwent treatment, always with the same characteristics described above. It would therefore be appropriate to study the mechanisms of action of iloprost and how these induce headache or whether the onset may be compatible with an antibody-mediated mechanism.

Migraine and functional dyspepsia: a frequent association

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Background: It is very common in clinical practice to observe the onset of migraine in the post-prandial phase, this condition occurs more frequently in patients with functional dyspepsia; the latter is a condition listed among brain-intestine interaction disorders, not associated with lesions detectable with endoscopic or morphological investigations. According to the Rome IV classification of such disorders, 2 subgroups of patients with functional dyspepsia can be observed:
- The first, much more numerous, being able to represent from half to 4/5 of the patients, is characterized by the onset of abundance and early satiety in the post-prandial phase and is defined as post-prandial distress syndrome.
- The second, generally more limited, defined as epigastric pain syndrome, is characterized by the onset of pain, in the absence of particular relationships with food intake.

It has been shown that migraine, assessed in a neurological specialist environment, is present in more than half of patients with epigastric pain syndrome and does not have a clear relationship with meal intake. On the contrary, in the subgroup with post-prandial distress syndrome, up to ¾ of patients suffer from migraine and in almost 9 out of 10 its onset is related to meal intake. The severity of migraine in patients with postprandial dyspeptic symptoms appears significantly and inversely related both to the discomfort threshold, measured at gastric level by mechanical distension of the bowel, and to the severity of dyspeptic symptoms. Therefore, it is not yet possible to define the pathophysiological mechanism responsible for the onset of migraine in patients with functional dyspepsia classified in the epigastric pain syndrome subgroup. On the contrary, as regards the subgroup with postprandial distress syndrome, it is evident how mechanisms responsible for an altered modulation of the sensitivity thresholds at the visceral level can correlate with alterations in the secretion of neuropeptides involved in the genesis of migraine, such as for example the calcitonin-gene related peptide, able to reverberate the effects also at the peripheral level on the gastrointestinal sensorimotor pathways.

Neurophysiological changes and clinical outcome in a cohort of migraine patients treated with Erenumab

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Background: Migraine treatment is frequently complicated by the failure of preventive therapies. Recent studies reveal the role of Calcitonin Gene-Related Peptide (CGRP) in migraine pathogenesis. Erenumab is a fully human monoclonal antibody blocking the CGRP receptors, recently approved for the treatment of drug resistant migraine. Symptomatic drugs and preventive treatments modulate laser evoked potentials (LEP) amplitude and habituation in migraine patients.

Aim: To evaluate the effect of single dose of erenumab 70 mg on LEP and correlate the neurophysiological changes with clinical outcome on migraine frequency, intensity and allodynia after 6 monthly doses.

Methods: We included migraine patients not responding to at least three preventive drugs belonging to the tertiary Headache Centre of Applied Neurophysiology and Pain Unit of Bari Policlinico General Hospital from September to November 2019. All clinical and therapeutic data of these patients were collected. LEPs were recorded before, 1 hour and 15 days after erenumab 70 mg injection. LEPs were recorded by 61 scalp electrodes and for LEP stimulation, cutaneous heat stimuli were delivered by a CO2 laser. ANOVA analysis was performed including these covariates: percent rate of change of headache frequency, visual analogue scale (VAS) score and allodynia after 6 months treatment. For the topographical analysis of statistical changes of LEP amplitudes performed a point by point ANOVA analysis at 256 Hz resolution, with condition T0 vs T1 vs T2 as within factor.

Results: Statistical analysis showed a significant decrease of the N1 wave on the left temporal and central frontal regions, and N2 wave on bilateral temporo-parietal regions. The t test confirmed a significant amplitude reduction in T2 condition for the N1 and N2 waves, as compared to the basal T0 condition. In the T1 condition a slight decrease of the N2 wave on the prefrontal regions emerged. After six months of erenumab treatment, patients showed a significant improvement of headache frequency, intensity and allodynia. No correlation between neurophysiological changes and clinical data emerged.

Conclusion: Enerumab exerts an inhibiting effect on cutaneous a-delta fibers in the facial district, acting on the CGRP receptors widely represented in the trigeminal system.

Headache with neurological signs or symptoms: three cases in a Pediatric Emergency Department

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Abbreviations: Emergency Department (ED), Computed tomography (CT), Magnetic Resonance Imaging (MRI), electroencephalogram (EEG)

Background: The differential diagnosis in children with headache and neurologic signs or symptoms includes primary etiologies, such as migraine with aura, and secondary etiologies, such as vascular, neoplastic, and epileptic disorders. We report three pediatric cases with similar clinical presentation at the ED who received different final diagnoses.

Case report: 1) A 6-year-old female was brought to the Pediatric ED for frontal headache, dysarthria and confusional state. At the first evaluation at the ED she was oriented, with mild headache and intermittent dysarthria. Brain CT and brain MRI with angiography were normal; the EEG performed on admission showed left cerebral posterior slowing. She had spontaneous complete regression of symptoms two hours after the first evaluation in the ED. The EEG 24 hours later was normal. She was diagnosed with probable migraine with aura.
2) The second patient was a 6-year-old girl admitted to the ED for frontal headache, vomiting, dysarthria, confusional state, mild instability gait and transient loss of consciousness. On admission she was confused and unable to answer simple questions. Brain CT and brain MRI with angiography were normal; the EEG revealed left occipital spikes. She showed progressive clinical improvement with complete regression of symptoms after a few hours. She received diagnosis of benign occipital epilepsy and was discharged with rectal diazepam as needed.
3) The third patient (girl, 7-year-old) arrived to the ED because of recent history of left temporal headache, dysarthria, vomiting and right arm paresthesia. On admission she was completely asymptomatic with a normal neurological examination. The EEG was normal. The brain CT and MRI with angiography revealed two ischemic lesions on the semioval center and basal ganglia with stenosis of the petrous, cavernous and clinoid segments of the internal carotid artery. Rachicentesis, thrombophilia screening and metabolic analyses were normal; genetic test for inflammatory arteritis is still in progress. She was started on corticosteroid and antiaggregant therapy for the diagnosis of focal cerebral arteriopathy with subacute ischemia.

Conclusion: Pediatric headache with neurological signs or symptoms represents a true diagnostic challenge in the ED. In our cases accurate history collection, neurological examination and instrumental investigations allowed the correct diagnosis.

Benefit-risk assessment of galcanezumab versus placebo for the treatment of episodic and chronic migraine: results from EVOLVE-1, EVOLVE-2, and REGAIN

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Background: To evaluate the benefit-risk profile of galcanezumab (GMB) versus placebo (PBO) for the treatment of episodic (EM) and chronic migraine (CM) in adults.

Methods: Data from three pivotal phase 3 trials of GMB were used to estimate response rates (RR), a clinically meaningful outcome for decision makers, based on monthly migraine headache day (MHD) reductions in patients with EM (EVOLVE-1 and EVOLVE-2; 6-month treatment duration) and patients with CM (REGAIN; 3-month treatment duration). Corresponding numbers needed to treat (NNT) for one patient to benefit from drug and numbers needed to harm (NNH) for one patient to be harmed by drug based on discontinuation due to adverse events (DCAE) were estimated for each trial separately.

Results: For EVOLVE-1, NNT were 5 and 6 with GMB 120 and 240 mg, respectively, at 30% RR, 5 for both doses of GMB at 50% RR, and 6 for both doses at 75% RR; EVOLVE-2: 5 for both doses of GMB at 30% and 50% RR, and 7 and 6 with GMB 120 and 240 mg, respectively, at 75% RR; REGAIN: 8 for both doses of GMB at 30% RR, 9 for both doses at 50% RR, and 40 and 24 with GMB 120 and 240 mg, respectively, at 75% RR. In all trials, the proportion of patients achieving these RRs was significantly higher in patients treated with GMB 120 mg and 240 mg versus those treated with PBO. Corresponding NNTs were similar across trials (5 to 9) with the exception of those obtained for ≥ 75% RR in REGAIN (24 to 40). Across all trials, NNH based on DCAE were 92 and 57 (EVOLVE-1), 213 and 46 (EVOLVE-2), and not relevant as higher risk with placebo (NR) and 295 (REGAIN) with GMB 120 mg and 240 mg, respectively.

Conclusion: In all trials, GMB showed a favorable benefit-risk profile versus PBO based on low NNTs for RR and higher NNH for DCAE. Higher NNTs observed in patients with CM may be due to higher disease burden (higher baseline MHD and greater disability) of these patients and shorter treatment duration (3 versus 6 months).

Anxiety, depression and body weight in children and adolescents with migraine

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Background: An increasing body of literature has explored the link between body weight and headache. However, there is a lack of studies exploring the possible association between body weight, psychological symptoms and migraine severity in the pediatric populations.

Aims: Purpose of the study was to explore: 1) the association between body weight and the frequency of migraine attacks, 2) the possible differences in anxiety and depression symptoms according to the frequency of attacks and body weight, and 3) the possible mediating role of anxiety and/or depression in the association between body weight and frequency of migraine attacks in children.

Methods: One hundred and eleven children/adolescents with migraine were included (47 boys, 64 girls; mean age 11.7; ± 2.4 years). Patients were classified in: 1) high frequency patients, reporting from weekly to daily episodes, and 2) low frequency patients, with ≤ 3 episodes per month. According to their Body Mass Index Percentiles, patients were divided in "Normal weight" (from ≥ 5 to < 85 percentile), "Overweight" (from ≥ 85 to < 95 percentile) and "Obese" (≥ 95 percentile). Given the low number of obese patients, overweight and obese groups were considered together in the "Overweight" group. Anxiety and depression symptoms were assessed by Self-Administered Psychiatric Scales for Children and Adolescents.

Results: Fifty-four patients were normal in weight (49.6%), while 56 (50.4%) were overweight. The overweight patients showed higher frequency of attacks (64.7%; $p < .05$). Patients with high frequency of attacks reported higher scores in all SAFA-Anxiety subscales (SAFA-A Tot: $F = 15.107$; $p = .000$). Overweight patients showed a significantly higher score in "Separation anxiety" subscale ($F = 7.855$; $p = .006$). We found a mediating role between overweight and high frequency for total anxiety ($z = 2.11 \pm .03$; $p < .05$) and social anxiety ($z = 2.04 \pm .03$; $p < .05$).

Conclusions: Our results suggest that, among children suffering from migraine, overweight status is associated with higher frequency of attacks and separation anxiety symptoms. In particular, our study provides the first evidence of the role of anxiety in linking overweight and frequency of migraine attacks in children/adolescents.

Effects of galcanezumab on health-related quality of life in patients with treatment-resistant migraine: Results from CONQUER study

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Background: CONQUER assessed health outcome measures with galcanezumab in treatment-resistant episodic (EM) or chronic migraine (CM). Treatment resistance was defined as previous failure with 2-4 standard-of-care migraine preventive medication categories in the past 10 years due to inadequate efficacy and/or safety/tolerability reasons.

Methods: In the study, patients with treatment-resistant migraine were randomized 1:1 to receive galcanezumab 120 mg/month (with 240-mg loading dose) or placebo during a 3-month double-blind period. Migraine Disability Assessment (MIDAS) and European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L) scores were collected at baseline and Month 3, and Migraine-Specific Quality of Life Questionnaire v2.1 (MSQ) at baseline and monthly. Treatment comparisons were done at Month 3 using mixed model repeated measures and analysis of covariance models (single post-baseline measure).

Results: Baseline values for all scores were balanced between placebo and galcanezumab (intent-to-treat population, mean [SD]; MSQ role function-restrictive: placebo: 43.95[18.49]; galcanezumab: 45.81[16.00]; MSQ role function-preventive: placebo: 63.04[19.64]; galcanezumab: 63.84[19.12]; MSQ emotional function: placebo: 51.91[26.73]; galcanezumab: 54.80[24.59]; MSQ total score: placebo: 51.11[18.44]; galcanezumab: 52.89[16.27]; MIDAS total score: placebo: 50.96[45.50]; galcanezumab:50.90[45.96]; EQ-5D-5L VAS score: placebo: 73.15[18.23]; galcanezumab: 72.65[18.70]). In intent-to-treat population (N=462) and subpopulations with EM (N=269) and CM (N=193), there were significantly greater mean improvements from baseline with galcanezumab versus placebo for MSQ total (intent-to-treat population/EM subpopulation/CM subpopulation, LS mean change [SE]: galcanezumab: 21.67[1.26/21.70[1.66]/20.17[1.91], placebo: 10.08[1.25]/10.91[1.67]/7.67[1.86]) and all domain scores (Role function-restrictive: galcanezumab: 23.21[1.35]/23.39[1.79]/20.61[2.05], placebo: 10.68[1.34]/11.88[1.80]/6.71[1.99]; Role function-preventive: galcanezumab: 17.53[1.20]/18.44[1.55]/15.27[1.88], placebo: 7.68[1.19]/8.94[1.56]/5.37[1.83]; Emotional function: galcanezumab: 24.02[1.61]/22.52[2.06]/24.38[2.63], placebo: 12.02[1.60]/11.58[2.08]/11.09[2.57]; all p<.0001), and MIDAS total scores (galcanezumab: -21.10[3.32]/-18.96[3.63]/-20.27[6.40], placebo: -3.30[3.28]/-2.58[3.68]/-1.68[6.19]; intent-to-treat [p<.0001], EM [p=.0002], CM [p=.0142]). Mean improvement with galcanezumab versus placebo on EQ-5D-5L visual analog scale was significant in intent-to-treat population (LS mean change [SE]: galcanezumab: 3.38[1.31], placebo: -0.09[1.29]; p=.03).

Conclusion: Patients with treatment-resistant migraine treated with galcanezumab reported improvements in daily functioning and patient perception of health state, and decreased disability versus placebo.

Primary stabbing headache in children and adolescents: is it a "migraine precursor"?

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Background: In pediatric age, primary stabbing headache (PSH) is an uncommon, but not rare, primary headache.

Aims: The aims of our prospective study were to describe the clinical characteristics of the pediatric PSH and to investigate whether in young subjects PSH is related to more common primary headaches.

Methods: Nineteen consecutive patients with PSH, diagnosed according to the ICHD-III criteria, were recruited. There were 13 girls and 6 boys, aged from 4 to 16 years (mean age: 9.9±3.4 years).

Results: In our patients, pain had different locations, but it usually involved the bilateral fronto-temporal region. Four patients failed to identify a precise pain location. Stabs were very short, usually lasting less than 1 minute. Only in one patient, each attack included several stabs and lasted around 20 minutes. Pain intensity was usually judged to be mild to moderate. Strong pain intensity was referred only by 2 patients. Eight out of 19 patients presented with associated symptoms, such as photophobia (5), phonophobia (6), and nausea (3). Migraine was associated with PSH in 5 patients and tension-type headache (TTH) in one. Episodic syndromes which may be associated with migraine, such as infantile colic, motion sickness, limb pain, recurrent abdominal pain, and vertigos, were referred by 13 patients.

Conclusions: In our pediatric case series, PSH clinical features were very similar to those described in adulthood. However, while in adults PSH is frequently associated with migraine and TTH (Hagler et al., 2014), only 32% of our young patients referred another primary headache. It is noteworthy that around 70% of our PSH patients had a clinical history of episodic syndromes. These elements suggest that in pediatric age PSH can represent an age-related phenotype of the migrainous syndrome which will turn later into a more typical migraine. Longitudinal studies in which pediatric PSH patients are followed for several years will be needed to confirm this hypothesis.

Chronic daily headache in children and adolescent: identification of risk factors and multidisciplinary treatment for better patient management

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Abbreviations: Chronic daily headache (CDH), New-Daily Persistent Headache (NDPH), Magnetic Resonance Imaging (MRI)

Aim: To identify risk factors for a multidisciplinary approach, pharmacological prophylaxis and psychological treatment in children with CDH.

Methods: We retrospectively analysed the data of CDH patients referred to the Headache centre between 1 January 2015 and 31 December 2017. We collected follow-up data by the 4-month clinical report or by phone interview. Statistical analyses included descriptive and association analyses (significance level $p<0.05$).

Results: 8.5% of patients referred to the Headache centre had CDH (64.5% females; mean age 11.1 ± 2.6 years). Stressful life events were reported in 22.6% of these patients. According the ICHD-III classification, the migraine without aura was the most frequent subtype (32.5%) and NDPH was diagnosed in 38.7% of the patients.
Pharmacological prophylaxis was indicated in 87% of the patients and a psychological treatment in 64.5%. Analysis of the population according to the suggestion of psychological treatment did not show any difference between the 2 groups in age, sex, family history for headache, pharmacological prophylaxis, use of analgesic drugs. We found significant difference in MRI findings, stressful life events, frequency and severity of headache episodes, that confirms an adequate selection of the patients for psychological treatment.
At the follow-up evaluation 31% of CDH patients had started a psychological treatment (compliance 43%). The frequency of headache episodes was sporadic in 40% of the cases, daily in 33%, episodic in 11%, none in 16%. The pain severity was moderate in 41%, mild in 39%, intense in 20%. Analgesic use was reported as frequent in 9% of the patients, sporadic in 35%, none in 56% (no difference between the patients in psychological treatment compared with those not in treatment). We observed a significant association between analgesic use and the severity ($p<0.001$) and the frequency ($p=0.036$) of the headache episodes.

Conclusions: CHD is an increasing disease in children and adolescents in which family history of headache and stressful life events are important risk factors. The multidisciplinary approach allowed better pain management, by limiting medication overuse, in particular for intense headache episodes. Nevertheless, in our series this approach demonstrated an incomplete efficacy in headache evolution. A further evaluation including a longer follow-up would be helpful for all the patients.

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