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AL001

Overuse of analgesics can affect the fertility biomarker Anti-Müllerian hormone in females. A translational study

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Objective: Over-the-counter analgesics (OTC) have been associated with disrupted male endocrinology, while effects on female endocrinology remains nearly unknown. The aim was to understand the effect of long-term analgesic exposure in females with medication overuse headache (MOH) on Anti-Müllerian Hormone (AMH), a surrogate measure of female fertility.
Methods: Using a translational approach, an observational prospective clinical study was conducted to determine AMH-levels in females with MOH, in combination with pre-clinical investigation of primary granulosa cells (GC) to understand the effects of analgesics on GC-function.
Results: We included 21 females (mean-age 30.0 years; SD (7.3)) for AMH-measurement. AMH increased by 21% from baseline (mean 20.1 pmol/L; SD (8.7)) after withdrawal of analgesics ((mean 24.3pmol/L; SD (12.0)); p=0.0023). Exposing primary GCs to analgesics (acetaminophen (100 and 200 µM, n = 9–10) and ibuprofen (150 and 200 µM, n = 12–13)) did not reduce AMH-levels. In contrast, *de novo* DNA synthesis in GCs (n=6) exposed to acetaminophen was reduced with 78% (p=0.0036) compared to controls, suggesting that cellular proliferation was restricted.
Conclusion: Frequent use of OTC was associated with repressed AMH-levels likely through disruption of GC proliferation. Further research is crucial to investigate a potential effect of analgesics on adult female reproductive endocrinology.

AL002

Sex differences in RAMP1/RAMP2 expression in the human middle meningeal artery match functional response to CGRP

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Objective: CGRP induces vasodilation after binding to the CGRP receptor (CLR-RAMP1), but can activate the adrenomedullin receptor (CLR-RAMP2) as well. Previously, age-dependent sex differences were observed for CGRP-induced relaxation of human middle meningeal arteries1. In addition, RAMP1 and RAMP2 mRNA expression was highly variable between patients2. The current study aims to investigate whether RAMP1 and RAMP2 expression differs between men and women and varies throughout life.
Methods: RNA was isolated from homogenized human middle meningeal arteries (14 F, 12 M, age 51±3 years) and qPCR was performed for RAMP1 and RAMP2 mRNA expression. The ratio between RAMP1 and RAMP2 expression with increasing age was investigated for men and women separately.
Results: The RAMP1/RAMP2 ratio significantly decreases with age in men, while a positive trend can be observed for women. These findings match the pattern of maximum relaxation to CGRP as observed in a previous study1, with a significant decrease with age in men and a trend for increased maximum relaxation with age in women.
Conclusion: The current study suggests that the maximum effect of CGRP-induced relaxation of human middle meningeal arteries matches the ratio of RAMP1/RAMP2 expression, and changes in a sex-dependent manner with increasing age. Interestingly, migraine is generally most prevalent in pre-menopausal women. Here, these young women show a relatively high RAMP2 and low RAMP1 expression, suggesting predominance of the adrenomedullin receptor over the canonical CGRP receptor in this population. Possibly, increased exposure of CGRP in young women results in downregulation of RAMP1. Future research should investigate whether RAMP1 and RAMP2 expression is altered in migraine patients.

Conclusion: This work provided the first real-world description of migraine characteristics among these patients. Additional research is needed to further characterize patients and assess real-world outcomes with rimegepant use.

P104

Exploring comorbidities in resistant and refractory migraine: results from the REFINE study

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Objective: Does identifying the specific comorbidities in Resistant Migraine (ResM) and Refractory Migraine (RefM) uncover pathophysiological mechanisms and potential new treatment targets linked to migraine?
Methods: The REFINE is a multicenter, prospective observational study involving participants from 15 different headache centers. Participants were categorized into three groups based on the EHF criteria: non-resistant and non-refractory migraine (NRNRM), ResM and RefM. We collected demographic details, information on headache characteristics and comorbidities.
Results: Of the 689 patients included in the study (82.8% women), median age 47 [Interquartile Range (IQR) 38–56] 262 (38.0%) were classified as having ResM, 73 (10.4%) as RefM, and 354 (51.4%) as NRNRM. We found a significant difference in several of the considered comorbidities among the three groups. All comorbidities were more common in the RefM group compared to the ResM and NRNRM groups: anxiety (34.7% vs. 25.2% vs. 11.3%; p<0.001), bipolar and other psychiatric disorders (13.9% vs. 9.2% vs. 5.1%; p=0.032), cerebrovascular diseases (16.7% vs. 2.3% vs. 2.3%; p<0.001), depression (39.7% vs. 34.1% vs. 15.8%; p<0.001), sleep disturbances (33.3% vs. 40.3% vs. 28%; p=0.025), temporomandibular joint disorders (23.6% vs. 13.6% vs. 10.7%; p=0.033), and trigger points (33.3% vs. 21.3% vs. 12.4%; p<0.001). Patients with chronic migraine showed significant differences among the three groups regarding anxiety (p<0.001), asthma and rhinitis (p=0.013), bipolar and other psychiatric disorders (p=0.049), cerebrovascular diseases (p<0.001), depression (p<0.001), obesity (p=0.002), thyroiditis (p<0.001), and trigger points (p=0.008)
Conclusion: Our findings suggest that ResM and RefM show a substantial burden of comorbidities, potentially influencing migraine progression from manageable to treatment-resistant forms. Further research is necessary to explore whether addressing these comorbidities can prevent migraine progression or improve treatment outcomes.

P105

Multicenter study on the evolution of insomnia in patients with migraine treated with anti-CGRP: expanding the impact of new treatments

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Objective: Insomnia is one of the most frequent and least studied comorbidities in patients with migraine treated with anti-CGRP drugs. The objective of the present study was to evaluate the usefulness of these drugs and their influence on insomnia in patients with migraine.
Methods: We present a prospective multicenter study in patients with migraine and anti-CGRP drugs. Demographic and clinical variables, anxiety scales (HAD-S/BAI), depression (HADS-D/BDI-II), impact (MIDAS/HIT6) and insomnia (ISI) were recorded quarterly/semestrally. The primary objective was to evaluate the effectiveness/safety of anti-CGRP in patients with and without insomnia. As secondary objectives, demographic variables, improvement in ISI scale, as well as predictors of improvement were studied using a logistic regression model.
Results: 135 participants were included, 119/135(88%) women, mean age 46 (SD:11.9) years[18–70 years]. A reduction in monthly headache days (MHD) of 9 and 11 days at 6 and 12 months, respectively, was observed without statistically significant differences depending on insomnia. An improvement in ISI at 6–12 months was found in 75/135 (56%). Likewise, a greater consumption of supplements ($P = 0.028$), greater anxiety ($P = 0.029$) and greater depression ($P = 0.004$) at baseline will be observed in patients with insomnia, with depression ($p = 0.0171$) being an independent predictor of improvement in the ISI scale at 6–12 months in the regression model.
Conclusion: Anti-CGRP drugs are effective and safe in patients with migraine with and without insomnia, with depression being an independent baseline predictor of improvement in ISI. These findings underscore the importance of addressing baseline comorbidities to optimize treatment outcomes.

P106

Selenium serum levels and Selenium-rich dietary sources are associated with lower risk of migraine in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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