

MEETING ABSTRACTS

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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 μ M, $n = 9-10$) and ibuprofen (150 and 200 μ M, $n = 12-13$)) 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.



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Results: From July 2023 to July 2024, 185 patients completed the survey. Headache diagnosis distribution was: 1) Low frequency episodic migraine: 62 (33.6%), 2) High Frequency Episodic Migraine: 72 (38.2%) 3) Chronic Migraine: 19 (10.5%) 4) Medication overuse headache: 18 (9.9%) and 5) Other non-migraine headaches: 14 (7.8%). Twenty-four patients (12%) were included in RCTs. During the same period, 47 patients had been enrolled in migraine RCTs in our Headache Unit and 24/47 (51%) were referred by the MIGRAGILE tool.

Conclusion: MIGRAGILE tool helped to increase the number of patients included in RCTs in our Headache unit and may be a useful approach for other Headache Units.

P220

Structural connectivity changes in migraine involving the cerebellum

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Objective: Although the pathophysiology of migraine remains poorly understood, structural disruptions across brain networks have been reported. Migraine connectivity studies primarily focus on cortical networks, neglecting crucial subcortical (SC) regions like the thalamus and the cerebellum (CB), which are known to play a significant role in migraine pathophysiology. Here, we investigate structural connectivity in a group of episodic migraine patients without aura compared to controls using diffusion-weighted MRI (dMRI).

Methods: Multi-shell dMRI data was acquired in Hospital da Luz Lisboa and structural connectivity was determined using two brain parcellations (Schaefer+SC+CB and AAL116). The connectivity was assessed using the network-based statistics (NBS) toolbox and graph metrics were calculated including the global efficiency (GE) and the characteristic path length (L) and their correlation with clinical data. Groups were compared using the Wilcoxon Rank Sum Test. A p-value of 0.05 was considered significant.

Results: Results showed significant connectome differences in patients, with increased structural connectivity between the left crus and left posterior lobe of the cerebellum (PLC) and between the occipital lobe/visual network and cerebellar regions (Figure 1). Patients showed decreased L and increased GE in both parcellations (Figure 2), with a positive correlation ($r=0.56$) between L and disease duration (Figure 3). The cerebellum plays an inhibitory role in pain processing, having several connections to the prefrontal cortex (via the thalamus). The increased connectivity between the cerebellum and other regions may indicate a dysfunctional negative feedback loop where the inhibitory signal is not sensed by the thalamus. The decreased L and increased GE can be indicative of higher pain information dissemination in the brain circuitry.

Conclusion: These results showcase cerebellum's importance in migraine pathophysiology, highlighting the necessity of including it in connectome studies.

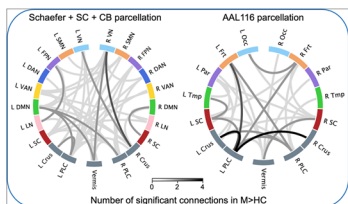


Fig. 1 (Abstract P220). See text for description

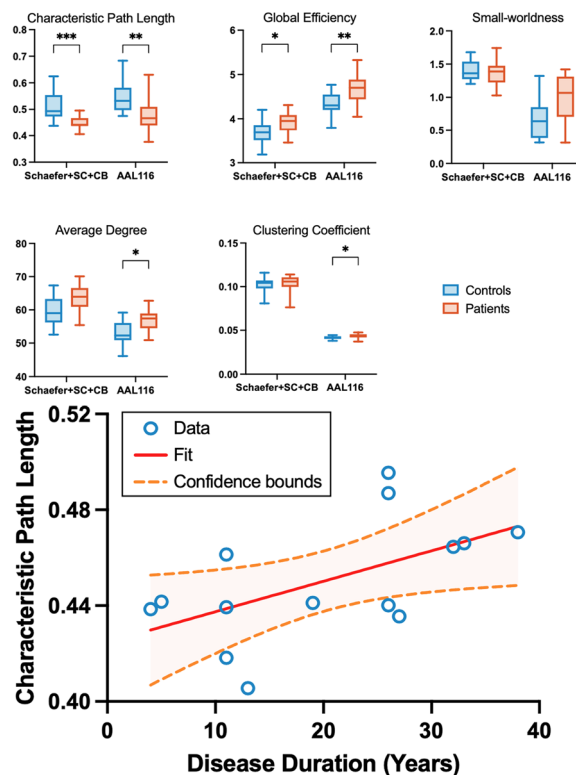


Fig. 2 (Abstract P220). See text for description

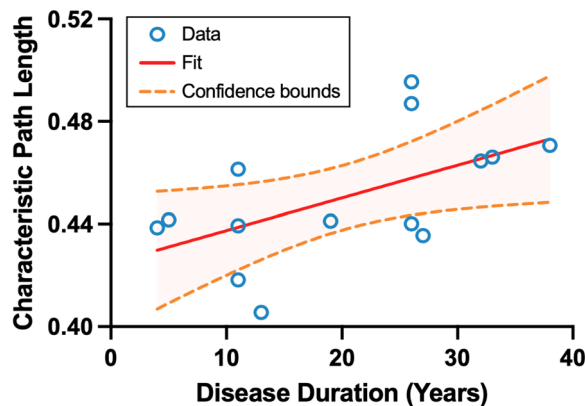


Fig. 3 (Abstract P220). See text for description

P221

Effectiveness of laser acupuncture for anxiety and depression among patients with chronic migraine – propensity score matching study

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