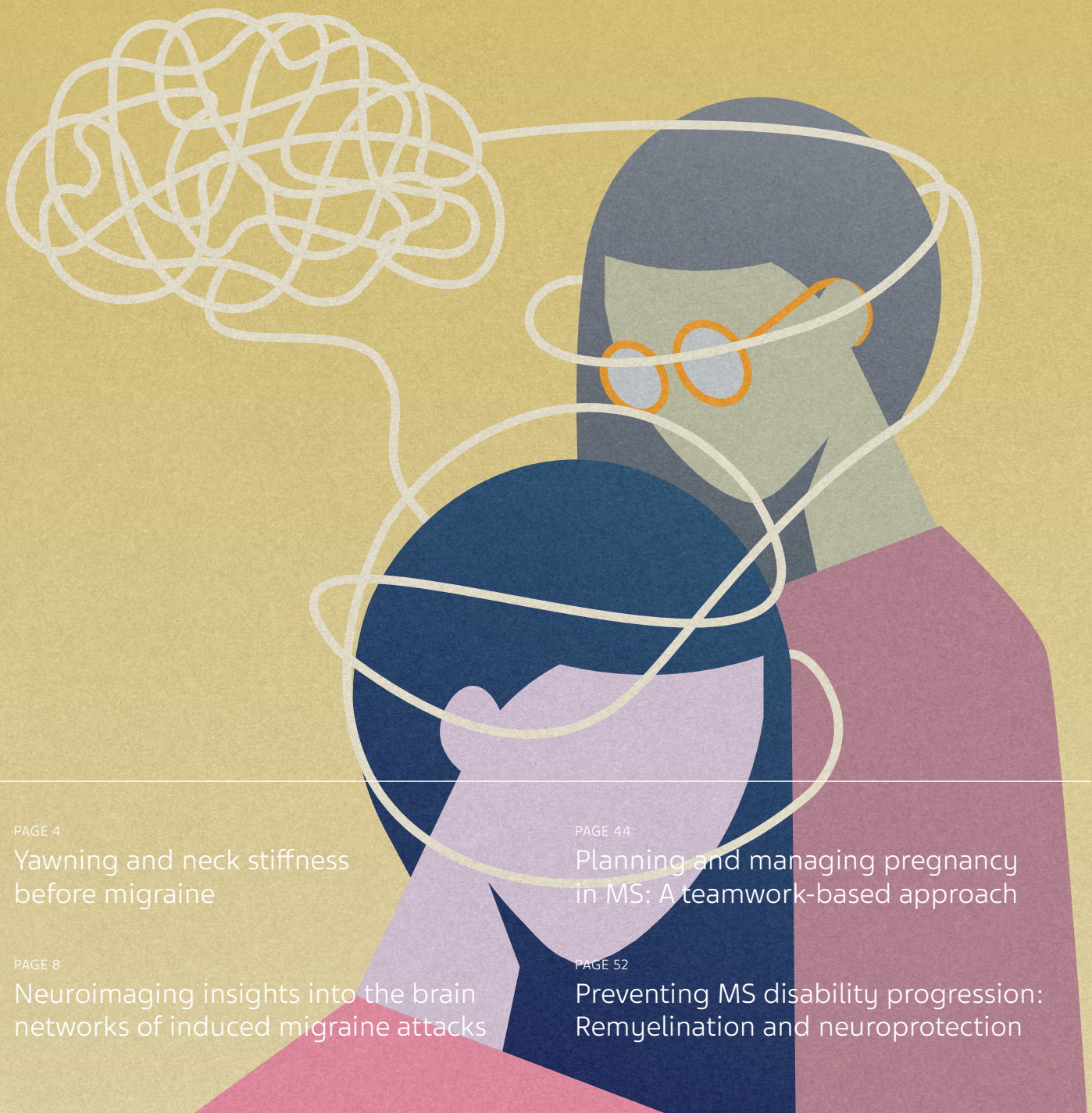
EAN 2020

Coverage from the 6th Congress of the European Academy of Neurology



The Neurologybytes team brings to you this comprehensive post-congress report from the recent, fully virtual 6th Congress of the European Academy of Neurology (EAN) held through 23–26 May 2020. For the first time, EAN forwent its physical gathering scheduled in Paris, France and executed its program completely online—a phenomenal venture—and accomplished an extraordinary feat of keeping the scientific discourse alive while prioritizing the health and safety of the community. This year's theme "Time for Action: Predict, Prevent, Repair" felt more relevant than ever, in a virtual gathering filled with engaging sessions by renowned experts in a wide range of neurology topics.

We hope you enjoy our full compilation of major EAN highlights around migraine and multiple sclerosis (MS). Migraine content includes updates on migraine physiology, patient burden, symptoms, treatment and prophylaxis, while MS updates include topics on structural repair, functional recovery, pregnancy, disability progression, therapy, and more.

We appreciate your continued engagement and support. Please be sure to follow us on LinkedIn and Twitter to stay up to date on our content and additional upcoming congresses.

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Yawning and neck stiffness before migraine

The premonitory phase in migraine is the period hours or days before the onset of headache with symptoms including headache, yawning, mood changes, or changes in appetite. The symptoms that occur during the premonitory phase suggest involvement of the hypothalamus, brainstem, limbic system, and certain cortical areas,[1] which has been recently supported by neuroimaging studies.[2,3] An ePoster on premonitory symptoms in patients with episodic migraine, presented by Dr. Bülent Güven (University of Health Sciences, Ankara, Turkey) at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, provided insight into the frequency of symptoms occurring during the premonitory phase of migraine attacks and its association with different characteristics of migraine.

NECK STIFFNESS AND YAWNING ARE THE MOST COMMON PREMONITORY SYMPTOMS

In the study presented by Dr. Güven, 330 patients with migraine with or without aura were prospectively recruited from a neurology outpatient clinic and followed up for 1 or 4 months based on the frequency of migraine. Through the use of questionnaires and headache diaries, premonitory associated symptoms and characteristics of the patient's migraine attack were recorded.

The study revealed that 59.4% of patients reported premonitory symptoms during migraine attacks. The most commonly reported ones were neck stiffness in 21.2% of the study population, followed by yawning in 19.1% of patients and irritability/anxiety in 16.4% of patients. These data support those of an earlier study by Güven et al.[1] in which yawning was shown to be a common self-reported symptom in the premonitory phase.

PREMONITORY SYMPTOMS ARE ASSOCIATED WITH AGE, GENDER, AND MIGRAINE WITH AURA

The study presented by Dr. Güven also looked into the demographic and clinical characteristics of patients with migraine and premonitory symptoms. Dr. Güven presented the results of a univariate logistic regression analysis, which revealed that a number of factors were statistically and significantly associated with premonitory symptoms, including age, gender, migraine with aura, and duration of disease. Other factors including severity of headache, unilateral and bilateral lateralization of pain, accompanying vomiting, photophobia, cranial autonomic symptoms and cutaneous allodynia, and relation to menstruation, were also found to be statistically and significantly associated with premonitory symptoms.

MORE PREMONITORY SYMPTOMS IN PATIENTS WITH LONG DURATION OF DISEASE

Patients were also asked to report on the number of premonitory symptoms occurring during migraine attacks. Whereas most patients (91) experienced only one premonitory symptom, 2–3 premonitory symptoms were reported by 59 patients and more than 3 premonitory symptoms by 46 patients. It was found that the duration of migraine disease was longer for patients with 2–3 or 3 premonitory symptoms than for patients with only 1 premonitory symptom.

> “Longer disease duration and diversity of accompanying symptoms in patients with premonitory symptoms may suggest that these symptoms facilitate the occurrence of each other and reflect the increase in brain excitability over time.
>
> Bülent Güven

THE HYPOTHALAMUS HAS AN IMPORTANT ROLE IN THE PREMONITORY PHASE

Neck stiffness and yawning were seen to be the most commonly reported premonitory symptoms in the patient population included in Dr. Güven's study. Patients with premonitory symptoms also reported more severe headaches and the presence of more frequent non headache symptoms. In Dr. Güven's opinion, the results of this study can be explained with the role of the hypothalamus in modulating pain and alterations in complex networks involving areas of the cortex, thalamus, and brainstem. This study provides further evidence on the prevalence of premonitory symptoms in patients with migraine. Such studies are essential in furthering research in to the enigmatic premonitory phase of migraine, which together with recent brain imaging studies,[2] are providing more insights into migraine onset.

1 Güven B, Güven H, Çomoğlu SS. Migraine and Yawning. *Headache* 2018;58:210-6.

2 Karsan N, Goadsby PJ. Imaging the Premonitory Phase of Migraine. *Front Neurol* 2020;11:140.

3 Gago-Veiga AB, Vivancos J, Sobrado M. The premonitory phase: A crucial stage in migraine. *Neurologia* 2017.

MIGRAINE SESSIONS
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Neuroimaging insights into the brain networks of induced migraine attacks

Neuroimaging studies have changed the way we understand migraine and cluster headache, supporting a key role of the brain in their pathophysiology.[1] Functional magnetic resonance imaging (fMRI) is a functional neuroimaging procedure based on MRI that is able to measure variations in brain activity by detecting local changes in blood flow.[2] At the recent virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, Dr. Daniele Martinelli (Mondino National Neurological Institute Foundation in Pavia, Italy) spoke in a session on "Headache and Pain." In his presentation entitled "Brain networks in migraine: A pilot study using advanced fMRI techniques in experimentally-induced attacks," Dr. Martinelli discussed the latest pilot study results in applying advanced fMRI technique to evaluate the pain process during provoked migraine attacks.

THERE IS A HIGH COMPLEXITY OF NETWORK INTERPLAY DURING MIGRAINE

Dr. Martinelli expressed that current research has identified the different structures involved in migraine, including pain modulation in the brainstem and the processing of sensory input by the thalamus and the neocortex. However, the interplay between these structures is not clearly understood.

Since the seminal positron emission tomography (PET) study by Weiller et al. in 1995,[3] several MRI studies have described the main brain regions involved in the various migraine phases.[1] Dr. Martinelli articulated that there is complexity in the various brain regions involved during a migraine attack; however, these known brain activities only capture a single phase of a migraine attack and there is a gap in understanding the comprehensive evaluation of this complex event.

A PILOT STUDY TO EVALUATE BRAIN ACTIVITY IN MIGRAINE

Dr. Martinelli explained that the aim of their study was to evaluate the brain activity in each phase of an induced headache attack in episodic migraineurs with the use of advanced fMRI techniques. As is well-described in literature,[4] the nitroglycerin paradigm was used where an oral nitroglycerin administration causes a migraine attack and pain is only quenched with an anti-inflammatory drug once patients reach a pain intensity of 5 out of 10.

According to Dr. Martinelli, 10 patients were enrolled, 5 with episodic migraine without aura that experience drug-induced migraine attack with clinical characteristics and 4 healthy subjects as controls. Data were analyzed with seed based component analysis. The mean effect for each phase was normalized to its baseline and a functional connectivity quantification was performed to rank the strongest difference in coupling between brain regions during a migraine attack.

> "A pain model that captures pattern fMRI activity within and across brain regions can move us forward in understanding the neurological basis of pain and hopefully in finding a reliable biomarker for migraine."
>
> Daniele Martinelli

FUNCTIONAL CONNECTIVITY AMONG BRAIN REGIONS DURING MIGRAINE

Based on the results of this study, Dr. Martinelli concluded that the brainstem elements involved in the pain circuitry and the thalamus depended on the migraine cycle and exhibited an outer functional coupling, particularly during the prodromal phase. Dr. Martinelli further emphasized that the thalamus strongly altered its coupling with the frontal, temporal, and cerebral cortex and therefore showed a greater involvement during the full-blown phase. Therefore, Dr. Martinelli stressed that there is a key role in the interaction between the brainstem circuitry and the thalamus-hypothalamus axis, which suggests that a migraine attack is not led by a single brainstem generator, but rather a more complex process as a cyclical oscillation between networks.

fMRI IN RESEARCH IDENTIFIES BRAIN REGIONS TO ENABLE BETTER MIGRAINE CARE

Dr. Martinelli summarized that using fMRI and a pain model to capture brain activity could help elucidate the neurological basis of pain. According to Dr. Martinelli, establishing a variety of techniques and approaches will clarify migraine pain signature and help find a reliable biomarker. These approaches will help address the needs of patients, predict their progression and their response to a particular treatment.

1 Messina R, Filippi M, Goadsby PJ. Recent advances in headache neuroimaging: *Curr Opin Neurol.* 2018;31(4):379–85.

2 Lovati C, Giani L, Mele F, et al. Brain plasticity and migraine transformation: fMRI evidences. *Expert Rev Neurother.* 2016;16(12):1413–25.

3 Weiller C, May A, Limmroth V, et al. Brain Stem Activation in Spontaneous Human Migraine Attacks. *Nat Med.* 1995;1(7):658–660.

4 Demartini C, Greco R, Zanaboni AM, et al. Nitroglycerin as a comparative experimental model of migraine pain: From animal to human and back. *Prog Neurobiol.* 2019;177:15–32.

MIGRAINE SESSIONS
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Detoxification from medication-overuse in chronic migraine: Responses in CGRP and microRNA

Chronic migraine (CM) is primarily defined by the occurrence of headache attacks on more than 15 days per month for more than 3 months, and is associated with greater disability and reduced quality of life compared to episodic migraine (EM).[1] Previously, medication-overuse was considered an exclusionary criterion for CM, but current guidelines define CM both with and without medication-overuse.[1] During the "Headache and pain" ePresentation session at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, Dr. Chiara Demartini (University of Pavia, Italy) explained her latest findings on the physiological effects of detoxification from medication-overuse in patients with CM.

CGRP AND microRNA IN CHRONIC MIGRAINE

Calcitonin gene-related peptide (CGRP) is one of the main mediators of migraine pathology, involved in neurogenic inflammation and vasodilation.[2] Dr. Demartini claimed that current evidence suggests CGRP is likely to be strongly involved in chronification, or the progression of episodic to chronic migraine. Because preclinical studies have shown prolonged sumatriptan exposure causes elevations in CGRP plasma levels,[3] she hypothesized that increased CGRP levels in the trigeminovascular system through medication-overuse may aggravate headache.

Dr. Demartini also stressed that microRNAs, or short non-coding RNA molecules that influence gene expression, "also deserve attention." Alterations of microRNA expression have been reported during headache attacks in patients with migraine, as well as in pain-free periods between attacks.[4] According to Dr. Demartini, microRNA expression patterns may be useful as disease biomarkers and predictors of individual risks of chronic pain.

BASELINE CGRP PLASMA AND microRNA LEVELS ARE ELEVATED IN CHRONIC MIGRAINE

Dr. Demartini presented unpublished data from her group examining CGRP plasma levels and the expression of two microRNAs relevant to migraine, miR-34a-5p and miR-382-5p, in peripheral blood cells of patients with EM and patients with CM with medication-overuse (CM-MO). At baseline, the CM-MO cohort had significantly higher levels of CGRP and of both microRNAs, compared to the EM cohort.

> "Decrease of these microRNAs may be useful for migraine outcome.
>
> Chiara Demartini

HEADACHE FREQUENCY, CGRP, AND microRNAs LEVELS ARE ALTERED AFTER DETOXIFICATION FROM MEDICATION-OVERUSE

Dr. Demartini's group next investigated changes in headache frequency 2 months after detoxification in patients with CM-MO. According to Dr. Demartini, compared to baseline, headache frequency significantly decreased after detoxification in about 50% of the patients.

Post-detoxification, these patients were then stratified into EM or CM groups according to their new monthly headache days and further analyzed. Levels of CGRP and both microRNAs were significantly decreased in patients in the EM category post-detoxification, compared to their levels at baseline. In contrast, patients in the CM category did not show significant decreases in CGRP plasma levels compared to their levels at baseline, while significant decreases in microRNA levels were still observed.

CGRP AND microRNAS MAY BE POTENTIAL BIOMARKERS FOR CHRONIC MIGRAINE

Though elevated CGRP plasma levels may be related to activation of the trigeminovascular system in association with chronic migraine, their role in CM-MO is still unclear, according to Dr. Demartini. In her opinion, the downregulation of both microRNAs observed in all CM-MO subjects provides evidence for a positive feedback response to detoxification, regardless of disease status. With further regression analysis, Dr. Demartini hopes to assess the relationships between these potential biomarkers and other clinical variables including age, sex, disease duration, and drug intake.

When questioned about her pathophysiological hypothesis for the microRNAs, Dr. Demartini elaborated that they affect the expression of GABA (gamma aminobutyric acid) receptors and interleukins. She claimed that downregulation of these microRNAs may be useful for migraine outcomes, and that her studies provide physiological evidence that alteration of medication-overuse can be important for patients with chronic migraine.

1 Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine Progression: A Systematic Review. *Headache* 2019;59(3):306–38.

2 Lambru G, Andreou AP, Guglielmetti M, Martelletti P. Emerging drugs for migraine treatment: an update. *Expert Opinion on Emerging Drugs* 2018;23(4):301–18.

3 Meng ID, Dodick D, Ossipov MH, Porreca F. Pathophysiology of medication overuse headache: insights and hypotheses from preclinical studies. *Cephalalgia* 2011;31(7):851–60.

4 Andersen HH, Duroux M, Gazerani P. Serum MicroRNA Signatures in Migraineurs During Attacks and in Pain-Free Periods. *Mol Neurobiol* 2016;53(3):1494–500.

MIGRAINE SESSIONS
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The humanistic burden of episodic and chronic migraine in France, Spain, and the United Kingdom

Migraine affects more than 1 billion people globally as one of the most disabling lifetime conditions, ranking second for years lived with disability according to the Global Burden of Disease.[1] Chronic migraine (CM) is associated with even greater disability and reduced quality of life compared with episodic migraine (EM).[2] During the ePresentation session titled "Headache and pain" at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, Dr. Samuel Díaz-Insa (Hospital Universitario y Politécnico La Fe de Valencia, Spain) presented his latest findings on the humanistic disease burden of episodic and chronic migraine in France, Spain, and the United Kingdom (UK).

PATIENTS WHO HAVE FAILED PREVENTIVE TREATMENTS EXPERIENCE GREATER DISABILITY

Disease burden and health-related quality of life (HRQoL) of patients with migraine who have failed multiple prior treatments is one of Dr. Díaz-Insa's major research interests. Previous data have shown that for patients who had failed 2 or more prior preventive treatments, 83% had cancelled plans, 59% felt their headache interfered with daily activities a lot or constantly, and 57% lacked energy to complete tasks of daily living.[3]

EMPLOYMENT AND EDUCATION BURDEN FOR PATIENTS IN THE UK, FRANCE, AND SPAIN ARE SIMILAR

Based on these findings, Dr. Díaz-Insa sought to evaluate disability and HRQoL in patients with EM or CM who had failed 2 or more migraine preventive treatments in the UK, France, and Spain. In a non-interventional study based on a cross-sectional web-based survey in these regions, patients diagnosed with EM or CM over the age of 18 years who had failed 2 or more preventive medications (from 2 or more different classes prior to current treatment) were assessed for disability and HRQoL based on EQ-5D-5L (5-level EuroQol 5-Dimension) and MIDAS (Migraine Disability Assessment) scores.

> "The percentage employment full time is much lower in patients with chronic migraine, and also their educational level [compared to patients with episodic migraine].
>
> Samuel Díaz-Insa

Across the populations in the UK, France, and Spain, Dr. Díaz-Insa found that 70.4% of patients with EM were employed full time, as opposed to 56.6% of patients with CM, consistent with differences in disability. Additionally, as opposed to 35.8% of patients with EM, only 19.7% of patients with CM had graduated college. There were no significant differences observed in the burden of employment and education among patients in the UK, France, and Spain.

DISABILITY FOR EM AND CM VARIED BY COUNTRY

Dr. Díaz-Insa's data also showed that disability, as measured by MIDAS, was more severe for patients with CM compared to patients with EM across the overall population. However, scores were stratified between countries—disability was most severe in Spain (31.6 points), then in France (24.3 points), and least severe in the UK (13.8 points) among patients with EM.

Consistently, HRQoL measured by EQ-5D-5L was worse for patients with CM compared to patients with EM across the overall population, both in the cases of index score and visual analog scale (VAS), according to Dr. Díaz-Insa. Particularly for VAS, the HRQoL scores followed a similar pattern as MIDAS where Spain (50.5) had the lowest score, followed by France (53.6), with the UK having the highest HRQoL (70.4) among patients with EM.

UNMET NEEDS MAY BE GREATER IN CERTAIN COUNTRIES

Based on these results, Dr. Díaz-Insa concluded that migraine was associated with substantial disability and negative impact on HRQoL, both of which were greater in patients with CM than in those with EM, and varied by country for patients with EM. Dr. Díaz-Insa stressed that these results reveal substantial migraine-related disability and impact of migraine on HRQoL among patients who have failed previous preventive therapies, and that unmet needs may be greater in certain countries over others.

1 Stovner LJ, Nichols E, Steiner TJ, et al. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology* 2018;17(11):954–76.

2 Bigal ME, Rapoport AM, Lipton RB, Tepper SJ, Sheftell FD. Assessment of migraine disability using the migraine disability assessment (MIDAS) questionnaire: a comparison of chronic migraine with episodic migraine. *Headache* 2003;43(4):336–42.

3 Martelletti P, Schwedt TJ, Lanteri-Minet M, et al. My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. *J Headache Pain* 2018;19(1):115.

MIGRAINE SESSIONS
AT EAN 2020

The individual burden of migraine: The patient experience

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Migraine is not just a headache, its burden extends beyond the pain.

Michel Lanteri-Minet

Headache is a major global public health concern with migraine being a significant cause of disability worldwide[1] Migraine impacts all domains of life[2] and is associated with depression and anxiety.[3] As part of the satellite symposium on "Anti-calcitonin gene-related peptide monoclonal antibodies and the evolving migraine prevention landscape" at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, Dr. Michel Lanteri-Minet (University Hospital Nice & FHU InovPain, Nice, France) provided an overview of the burden of migraine from a patient perspective in his presentation "The true cost of migraine in Europe: The patient experience."

BURDEN OF MIGRAINE IN EUROPE

Dr. Lanteri-Minet began by providing an overview of recent burden of disease studies showing that migraine affects almost 1 billion people globally,[1] causing 45 million years of life lived with disability.[1] In Europe, the prevalence and societal burden is similar,[1] with costs to society reaching €111 billion.[4] The majority of costs are indirect,[2] with migraine impacting private, social, and professional domains of life in more than two-thirds of patients.[2] Furthermore, Dr. Lanteri-Minet noted significantly higher numbers of patients with migraine reporting absenteeism and presenteeism in their work life compared with non migraine controls.[5]

IMPACT OF MIGRAINE ON QUALITY OF LIFE

Significant decreases in quality of life are also reported for patients with all types of migraine.[5] From a patient perspective, the decrease in quality of life can exist between attacks; one quarter of migraine sufferers are not symptom free, with around 10–15% declaring interictal anxiety or interictal avoidance.[6] Dr. Lanteri-Minet also explained that both anxiety and depression have been shown to be psychiatric comorbidities of migraine, another facet of the individual burden of migraine, with nearly 30% of patients reporting anxiety and around 20% reporting both anxiety and depression.[7] Additionally, Dr. Lanteri Minet stated that anxiety appears as a unique consequence of the psychiatric comorbidity of migraine. He also commented that this is complex for the patient who experiences both the psychiatric and emotional impacts of the disease, and questioned whether the effects are additive or synergistic.

UNMET NEEDS IN MIGRAINE PREVENTION

The last important aspect of the individual burden of migraine discussed in Dr. Lanteri Minet's presentation was the use of preventive treatment. Results from the Eurolight and FRAMIG studies showed that very low numbers of patients with migraine more than five days per month were using preventive treatments (1.6–6.4%, except for study patients in Spain),[8,9] which highlights that a large proportion of patients with migraine are undertreated. Furthermore, in Dr. Lanteri-Minet's own experience, less than half of patients suffering from chronic migraine who were referred to his department had already received preventive treatment. Expanding on this, Dr. Lanteri-Minet commented on how the unmet needs in migraine prevention can be illustrated by the rate of early discontinuation seen for all pharmacologic classes, with almost half of patients stopping treatment after approximately one month due to lack of efficacy or side effects.[10,11]

MORE THAN JUST HEADACHE PAIN

In conclusion, Dr. Lanteri-Minet reiterated that the individual burden of migraine extends beyond headache pain, impacting all aspects of individual life. He closed by emphasizing that more effective and better preventive treatments are needed to tackle the issues of poor adherence to oral drugs and relieve the high individual burden of migraine. Following the presentation, Dr. Lanteri-Minet commented that not only is depression a risk factor for migraine, it is also a real comorbidity, impacts the severity of migraine, and is a risk factor for migraine chronification.

1 Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018;17:954-76.

2 Martelletti P, Schwedt TJ, Lanteri-Minet M, et al. My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. *J Headache Pain* 2018;19:115.

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5 Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *J Headache Pain* 2018;19:82.

6 Lampl C, Thomas H, Stovner LJ, et al. Interictal burden attributable to episodic headache: findings from the Eurolight project. *J Headache Pain* 2016;17:9.

7 Lantéri-Minet M, Radat F, Chautard MH, Lucas C. Anxiety and depression associated with migraine: influence on migraine subjects' disability and quality of life, and acute migraine management. *Pain* 2005;118:319-26.

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9 Lucas C, Chaffaut C, Artaz MA, Lantéri-Minet M. FRAMIG 2000: medical and therapeutic management of migraine in France. *Cephalalgia* 2005;25:267-79.

10 Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). *Headache* 2013;53:644-55.

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MIGRAINE SESSIONS
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CGRP and migraine pathophysiology: New insights for targeted prevention

Migraine is the most prevalent neurological disorder worldwide[1] and has been, until now, treated with preventive therapies originally indicated for other diseases.[1] Recently, blocking calcitonin gene-related peptide (CGRP) has emerged as a target for migraine prevention.[1] As part of the satellite symposium on "Anti-calcitonin gene-related peptide monoclonal antibodies and the evolving migraine prevention landscape" at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, Dr. Antoinette Maassen van den Brink (Erasmus MC, Rotterdam, The Netherlands) gave an overview of CGRP in her presentation entitled "Migraine pathophysiology: New insights for targeted prevention."

CALCITONIN GENE-RELATED PEPTIDE

Dr. Maassen van den Brink opened her presentation with an introduction to the neuropeptide αCGRP, a vasodilator and messenger in nerve cells,[2] and noted that the main player in migraine is the aCGRP isoform. She went on to explain that the first arguments for a causative role of CGRP in migraine date back to the 1980s[2] and to initial experiments showing an increase in CGRP in the blood during a migraine attack compared to the interictal period.[3] Later experiments showed that CGRP may induce migraine-like headache in migraine patients.[4] CGRP and its receptor have also been shown to be abundantly expressed in locations involved in migraine like the trigeminovascular system.[5]

NEW INSIGHTS FOR MIGRAINE TREATMENT

On the topic of migraine treatment, Dr. Maassen van den Brink commented that acute treatments are evidence based with the gold standard being triptans; novel therapies include ditans and gepants, the latter of which is an antagonist at the CGRP receptor.[2,6,7] Preventive treatments include anti-hypertensives and anti-epileptics that coincidentally are effective against migraine.[8] Additionally, new evidence-based preventive treatments include anti-CGRP compounds.[2]

CALCITONIN GENE-RELATED PEPTIDE BLOCKADE

The presentation transitioned to elaborating on small molecule receptor antagonists, or gepants, that started in development around 20 years ago, with second generation gepants being more recently developed. Some are in clinical development for prophylactic treatment of migraine, while some are approved for acute treatment of migraine.[2,7] Pharmacological studies on certain gepants on human cranial arteries provided evidence for the presence of CGRP receptors in the smooth muscle of cranial arteries.[9] In Dr. Maassen van den Brink's opinion, pharmacological characterization of treatments is important, as small molecule receptor antagonists may have an affinity to signal receptors, thereby making quantification of their potency essential at these different receptors.

MONOCLONAL ANTIBODIES

Dr. Maassen van den Brink then moved on to mentioning monoclonal antibodies, which bind to either the αCGRP and βCGRP peptide or the canonical CGRP receptor.[7,10] She presented data that showed CGRP's large effect in the distal coronary artery, which can be displaced by a monoclonal antibody acting at the CGRP receptor,[11] with a more limited effect on the proximal coronary artery.

THE SITE OF ACTION OF GEPANTS AND MONOCLONAL ANTIBODIES

To address the question of whether gepants act in the periphery or in the brain, Dr. Maassen van den Brink presented research on the site of action, showing that it is extracerebral or in brain structures outside of the blood—brain barrier[12] She also noted that the trigeminal ganglion is not protected by the blood–brain barrier.[13] She further commented that the site of action of CGRP antibodies is likely to be mainly outside the blood—brain barrier, and emphasized the importance of the neurovascular effects of CGRP.[2]

TO BLOCK THE PEPTIDE OR THE RECEPTOR?

Dr. Maassen van den Brink then explained the consequences of using antibodies to block the CGRP peptide or the CGRP receptor. She noted that several receptors may be activated by CGRP and in turn, several other peptides may activate the CGRP receptor, which could lead to different therapeutic effects and side-effect profiles in various therapeutic antibodies.[10,14]

POSSIBLE SIDE EFFECTS

With regards to blocking CGRP or its receptor, Dr. Maassen van den Brink explained that the differences in mode of action of treatments may influence the therapeutic efficacy as well as side effect profiles. CGRP and its receptor are located throughout the body and are involved in several physiological processes.[1] Normally, CGRP has a limited role in typical physiology, but may be protective in the cases of hypertension and myocardial or cerebral ischemia.[10] According to Dr. Maassen van den Brink, the distal coronary artery may be involved in myocardial infarction in women, and as CGRP is more important in the distal than in the proximal coronary artery, it may be important to focus on women when studying treatment side effects.

Dr. Maassen van den Brink's thorough overview of migraine pathophysiology and the role of CGRP provided thought-provoking insights into the development of the first migraine specific, evidence-based preventive medicines.

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5 Edvinsson L, Villalón CM, MaassenVanDenBrink A. Basic mechanisms of migraine and its acute treatment. *Pharmacol Ther* 2012;136:319-33.

6 Tfelt-Hansen PC. Triptans and ergot alkaloids in the acute treatment of migraine: similarities and differences. *Expert Rev Neurother* 2013;13:961-3.

7 de Vries T, Villalón CM, Maassen Van Den Brink A. Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans. *Pharmacol* Ther 2020.

8 Demaagd G. The pharmacological management of migraine, part 2: preventative therapy. *P t* 2008;33:480-7.

9 Edvinsson L, Chan KY, Eftekhari S, et al. Effect of the calcitonin gene-related peptide (CGRP) receptor antagonist telcagepant in human cranial arteries. *Cephalalgia* 2010;30:1233-40.

10 MaassenVanDenBrink A, Meijer J, Villalón CM, Ferrari MD. Wiping Out CGRP: Potential Cardiovascular Risks. *Trends Pharmacol* Sci 2016;37:779-88.

11 Rubio-Beltrán E, Labastida-Ramírez A, Haanes KA, et al. Characterisation of vasodilatory responses in the presence of the CGRP receptor antibody erenumab in human isolated arteries. *Cephalalgia* 2019;39:1735-44.

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MIGRAINE SESSIONS
AT EAN 2020

Unmet needs of migraine treatment—a patient's perspective

Patient adherence to oral preventive migraine treatments has been shown to be less than 30% at six months, and further drops to below 20% at 12 months.[1] Over 70% of people with migraine selected 'lack of efficacy and tolerability/safety' as the reason for discontinuing or switching preventive treatment.[2] From the patient's point of view, efficacious migraine preventive treatment seems to remain an unmet need, resulting in poor treatment adherence.[2] At the recent virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, Ms. Caitlin Thomas (Evidera, United Kingdom) presented an ePoster on the results from a focus group study on patient perspective and valuation of preventive migraine treatment.

Nine different in-person focus groups were conducted in the United Kingdom, the United States of America, and Germany. Ms. Thomas explained that participants were guided through a three-part, semi-structured interview with an initial open discussion on the participants' experience with migraine preventive treatment, a hands-on device testing session, and a final interactive ranking discussion. Five unbranded demonstration devices—two pre-filled syringes and three auto-injectors—were given to participants. Ms. Thomas began presenting the study results, starting with the population characteristics. Of the 47 total participants, 28 were people with episodic migraine and 19 with chronic migraine. Patients described taking the following migraine preventive treatments over the previous five years: antiepileptics (43%), antidepressants (36%), beta blockers (36%), and calcitonin gene related peptide (CGRP)-targeting monoclonal antibodies (11%). The four main areas of discussion identified by the authors of this study were treatment experience, treatment expectations, treatment concerns, and device characteristics.

PREVENTIVE TREATMENT THAT REDUCES MIGRAINE FREQUENCY AND SEVERITY IS WARRANTED

Ms. Thomas proceeded to list the key themes discussed by patients within the treatment experience, expectations, and concerns areas. The reported migraine symptoms included hypersensitivity, fatigue, and vision impairment. The inability to conduct daily activities during a migraine episode was highlighted by Ms. Thomas. Across all nine focus groups, participants described the need for preventive treatment that reduced the frequency and intensity of migraine episodes. Furthermore, patients expected that treatment should provide symptom relief and improvement in quality of life. Ms. Thomas also highlighted the patients' desire for fewer side effects. It was further emphasized that the patients' treatment concerns were centered around physical, psychological, and drug-associated side effects, and underscored how side effects affecting cognitive functions interfered with work and school, and hampered social interactions.

EASE OF HANDLING AND ADMINISTRATION ARE IMPORTANT FOR SELF-INJECTING DEVICES

The study also identified six sub-categories when patients described device characteristics: ease of handling, administration/preparation, needle, dose confirmation, injection time, and portability. Ms. Thomas commented that easily handled and administered devices were considered as valuable by the study participants. Other drivers of device valuation included needle visibility, injection angle, and skin pinching prior to injection. The ePoster further mentioned that short injection times (3 seconds) were preferred to longer injection times (15 seconds), and that a small packing size of the device was seen as preferable when discussed in the context of travel and storage.

Ms. Thomas concluded from the study that patients feel that there is an unmet need for efficacious preventive migraine treatments—in her opinion, people with migraine would consider self-injectable preventive treatment that is effective and offers a good safety profile.

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MULTIPLE SCLEROSIS
SESSIONS AT EAN 2020

Potentiating neuronal functional recovery in MS

Multiple sclerosis (MS) is often seen as a myelin disease that can also exhibit axonal loss and consequent loss of communication between neurons, leading to effects like cognitive impairment.[1] To combat this, synaptic plasticity is seen as a compensatory mechanism by which communication between neurons can be restored, therefore minimizing the effects of this kind of neuronal damage.[2] As part of the topical symposium on promoting structural repair and functional recovery in MS at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, Professor Diego Centonze (IRCSS Istituto Neurologico Mediterraneo Neuromed, Pozzilli, Italy) provided an overview on the recovery of neuronal function via long-term potentiation (LTP)—a form of synaptic plasticity—and how exercise and pharmacological administration can enhance LTP.

EXERCISE AND LTP IN FUNCTIONAL RECOVERY

Prof. Centonze started his presentation by explaining that LTP is the most studied form of synaptic plasticity, which can potentially minimize the effects of neuronal damage and prevent clinical disability in MS patients.[2] He continued saying that though lifestyle modifications like exercise favor synaptic remodeling and plasticity, certain pharmacological interventions (e.g. blockade of N methyl-D-aspartate [NMDA] receptors) can also prevent training-induced plasticity[3] and disrupt any clinical compensation of MS damage.[4]

PHARMACOLOGICAL ENHANCEMENT OF LTP AND FUNCTIONAL RECOVERY

Prof. Centonze elaborated on specifics of LTP, further clarifying that there are 3 receptors types responsible for LTP induction: NMDA, Cannabinoid CB1, and dopamine receptors. To elaborate on each type and their effects, he explained that: Pharmacological enhancement of NMDA receptor signaling with D aspartate—commercialized as a food supplement—increases synaptic LTP, spine formation and grey matter volume,[5] and enhances synaptic plasticity in progressive MS;[6] exercise stimulates LTP through Cannabinoid CB1 receptors and individuals with genetic mutations in this receptor show impaired LTP;[7] and a dopamine receptor blockade—pharmacological[8] or genetic[9]—will abolish LTP. Additionally, low levels of brain-derived neurotrophic factor gene (BDNF) impair LTP in humans.[10]

OPPORTUNITIES FOR LTP INDUCTION IN REHABILITATION TREATMENT

Having provided an overview of how LTP induction manifests in MS recovery and treatment, Prof. Centonze highlighted that "clinical disability in MS and in other neurological disorders appears when the synaptic plasticity (LTP) reserve of surviving neurons is exhausted and that rehabilitation exerts clinical benefits by preserving or enhancing synaptic plasticity (LTP) brain reserve." He suggested that "pharmacological interventions aimed to enhance NMDA, Cannabinoid and dopamine receptor signaling as well as BNDF release, could enhance the beneficial effects of rehabilitation treatment in MS patients by favoring synaptic plasticity." Despite these options potentially benefitting certain patients with MS, Prof. Centonze reminded that they do not come without some caveats. He warned that "LTP can also be impaired by acute inflammation and raised the possibility that effective treatment with disease modifying drugs (DMDs) could favorably impact the effects of rehabilitation."

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MULTIPLE SCLEROSIS
SESSIONS AT EAN 2020

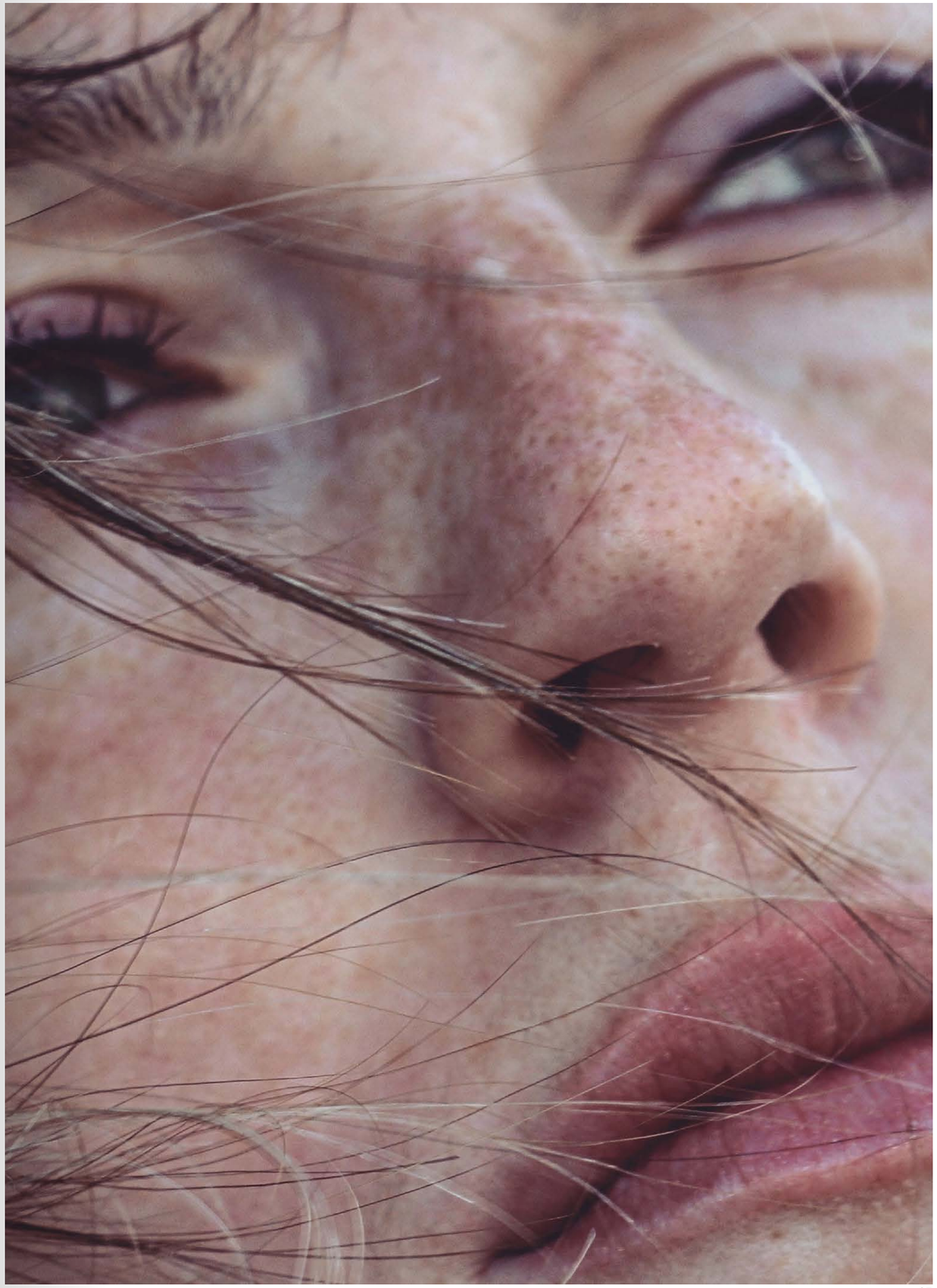
Seeing multiple sclerosis

Multiple sclerosis (MS) can be diagnosed by using brain scans that reveal the brain areas affected by myelin loss, called lesions, by "looking" inside the brain. These brain-imaging techniques are also used in the context of clinical trials to evaluate therapeutic effects on disease evolution. As part of the topical symposium on promoting structural repair and functional recovery in MS at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, Professor Benedetta Bodini (Sorbonne University, Paris, France) provided an overview of several imaging techniques used to evaluate remyelination and neuroprotection as a means to get as close as possible to the biology of the disease.

SEEING MYELIN LOSS: MRI AND PET TECHNIQUES FOR MYELIN LESION ANALYSIS

A critical step to assess the processes of remyelination and neuroprotection after MS treatment is the use of high definition imaging techniques. Prof. Bodini gave an overview of current imaging techniques—magnetic resonance imaging (MRI) and positron emission tomography (PET)—in the MS clinical setting to analyze lesion dynamics.

Prof. Bodini then introduced four common imaging techniques used in MS lesion analysis: inhomogeneous magnetization transfer (ihMT), diffusion-weighted imaging (DWI), myelin water fraction imaging, and susceptibility-weighted imaging. In Prof. Bodini's opinion, the main issue of MRI-based imaging techniques to determine myelin lesion dynamics is the low specificity to myelin, although ihMT has high myelin sensitivity[1] and a strong correlation with clinical scores. Conversely, PET, through the use of radio labelled tracers that bind to myelin, allows for much greater specificity.



Prof. Bodini explained that over the years, several imaging tracers have been developed to specifically bind to myelin. Using these specific tracers to analyze MS patient's brains, she reported seeing dynamic changes in demyelination and remyelination over time. The remyelination potential is critical to determine disease evolution and disability.[2] According to Prof. Bodini, despite low resolution and high costs, PET is the best possible choice of myelin imaging technique due to its myelin specificity, and should be used as a validation tool for new MRI techniques.

SEEING NEUROPROTECTION: MRI AND PET TECHNIQUES FOR POTENTIAL NEUROPROTECTION

Different MRI and PET techniques are available to evaluate potential neuroprotection in the context of MS, which Prof. Bodini explained in detail. Whole-brain atrophy is the most widely used method to measure potential neuroprotection because it is easy to implement and correlates with clinical/cognitive patient scores. However, according to Prof. Bodini, it lacks specificity and is not suitable to detect early neuroprotective effects. Instead, she believes thalamic atrophy could be a promising primary MRI endpoint for phase II trials, as it shows a consistent volume decline across MS clinical subtypes, is sensitive to early disease phases, despite it requiring larger sample sizes.[3,4] Also relevant to this topic is spinal cord atrophy imaging being very similar to thalamic atrophy imaging, which Prof. Bodini described. She went on to explain that DWI-based techniques can quantitively assess axonal density and could be valuable in the context of clinical trials, although it may be challenging to measure small diameter axons. She further mentioned that the development of neuron-specific tracers (i.e ^{11}C Flumazenil and ^{11}C UCB-J) has allowed the use of PET, in addition to MRI imaging, in assessing neuronal damage.

NEW TECHNIQUES FOR SEEING NEURODEGENERATION

According to Prof. Bodini, a turning point in the study of MS will be the ability to image the key mechanisms leading to neurodegeneration. Energy dysregulation has been shown to be one such key mechanism and currently, there are some imaging techniques that address this dysregulation. Additionally, it is now possible to image other mechanisms leading to neurodegeneration in the MS context, such as innate immune cell activation.[2,5]

Prof. Bodini concluded her presentation by stating that MRI and PET imaging should be employed in phase II clinical trials that test promyelinating and neuroprotective treatments in MS. The measurement of future MS treatment outcomes will, she thinks, include imaging techniques of neurodegeneration mechanisms, while PET should be used to validate single MRI sequences or a combination of multiple MRI measures to improve MRI specificity for myelin and neurons.

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MULTIPLE SCLEROSIS
SESSIONS AT EAN 2020

Stem cell therapy in multiple sclerosis

> We thought that tissue replacement was the only way to use stem cell therapeutic approach but we were able to show that there was another way to promote the regeneration of tissue.
>
> Gianvito Martino

STEM CELL THERAPY IN MULTIPLE SCLEROSIS

Stem cell therapy use in multiple sclerosis (MS) has been a difficult task due to the disease's complexity and its multifocal properties. Traditionally, stem cells are injected specifically into the affected area, as in the case of Parkinson's disease for example. As part of the symposium on promoting structural repair and functional recovery in MS at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, Professor Gianvito Martino (Università Vita-Salute San Raffaele, Milan, Italy) provided an overview of the history of stem cell transplantation and the journey of stem cell therapy in MS.

FROM HISTORICAL OVERVIEW TO MODERN STEM CELL THERAPY

Prof. Martino gave a historical overview of brain transplantation with mention of a successful brain graft by Gilman Thompson in 1890. He continued highlighting the achievements across the decades that lead to functional reintegration of neuronal cells in animals and humans.

Earlier transplantation techniques were complicated, explained Prof. Martino, and it was only with technological advancements in obtaining stem cells from different tissues and deriving them into multiple cell types that it became feasible to use stem cells as an actual therapy.

STEM CELL USE IN MS

MS is a complex disease to treat via stem cell therapy—there is not a single region which is affected in MS, explained Prof. Martino, as the disease has a multifocal pathology. In line with this, he considers there to be four qualities of the 'gold therapy' of MS: Specificity, being targeted, flexibility, and being of clinical grade (i.e. easy to use).

When trying to apply the 'gold therapy,' Prof. Martin's group performed several studies that injected neural stem cells in the blood or cerebrospinal fluid (CSF) of MS animal models. In these studies, it was noted that stem cells could sense inflammation and migrate to the brain where they mostly remained undifferentiated. But in certain conditions, they would differentiate into oligodendrocytes and myelinate neurons. He continued explaining that these migrated neural stem cells can 'decide' on what action to take depending on the microenvironment they encounter.

THE BYSTANDER EFFECT

According to Prof. Martino, inflammation is the driver of the bystander effect—the prevention and repair of tissue damage via transplantation of undifferentiated neural progenitor cells (NPCs) secreting neuroprotective factors.[1] The microenvironment also plays an important role in the bystander effect in MS animal models, as it instructs the neural stem cells to respond in the required way.[2]

MOVING TO CLINICAL TRIALS

Prof. Martino shared his team's results from the pre-clinical studies in mouse models that have suggested that intrathecal neural stem cell administration is the best treatment administration option[3] and that adhesion molecules and chemokine receptors are the underlying mechanism by which administered cells reach the inflammation area.[4] In 2017, his team started clinical trials using selected neural stem cells, with progressive patients having less than 20 years of disease. According to Prof. Marino, the patients with the higher dosage exhibited the bystander effect and their CSF environment changed from pro inflammatory to anti-inflammatory.

SHIFTS IN STEM CELL THERAPY PARADIGM AFFECT MS THERAPY

Reflecting on the history of stem cell therapy to date, Prof. Martino considers that there has been a shift in the stem cell therapy paradigm from tissue replacement therapy to "secretome" therapy, where stem cells secrete immunomodulatory molecules and trophic factors that support lesion recovery. This shift has led to new approaches in MS therapy.

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MULTIPLE SCLEROSIS
SESSIONS AT EAN 2020

Planning and managing pregnancy in MS: A teamwork-based approach

> MS by itself is not 'forbidding' for pregnancy, but it's very important to plan every step ahead—this is very reassuring not only for the woman, but also for her neurologist(s). Because having a plan is helping to face the fear of the unknown, which is the worst.
>
> Letizia Leocani

While pregnancy was historically discouraged for patients with multiple sclerosis (MS), a crucial study in 1998 reported a measurable change in MS relapse rates during and after pregnancy.[1] Since then, in combination with the advent of new disease modifying drugs (DMDs), the "demand for more knowledge has risen—and it became evident that we must learn more about how to manage pregnancy in patients with MS," Professor Leocani (Vita Salute San Raffaele University, Italy) stressed in her "Pregnancy in MS" presentation at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020.

THE EVOLUTION OF DISCUSSIONS ABOUT PREGNANCY AND MS

"Pregnancy in MS is a hot topic because it affects mostly young women when their lives—including work, social life, and even family planning—are at their fullest," stated Prof. Leocani, as she explained that debates and research around this topic have flourished in the last 20 years. Because pregnancy in MS is often plannable, Prof. Leocani conceptualizes pregnancy in the current MS landscape as a teamwork based plan and management effort by both the woman and her neurologist(s).

QUESTIONS TO ASK BEFORE PREGNANCY PLANNING

Prof. Leocani claimed that for patients, "dealing with both MS and the will to have children brings up many questions," and thus it is important for clinicians to plan ahead and be proactive, starting discussions on pregnancy early after MS diagnosis "because this has an impact on our management of the disease itself." MS interferes with women's choices of having children, as 30–35% of women avoided or delayed pregnancy for reasons linked to MS in one study.[2] Prof. Leocani explained that reasons ranged from disability, fear, and concerns about treatment, to skepticism about disease inheritance. She expressed that newer evidence should empower women to increasingly and freely make personal decisions based on confidence, knowledge, and management.

However, "ideally all pregnancies should be planned, but the reality is that it does not always happen that way," Prof. Leocani admitted, and recommended that risk of postpartum relapse, effects of pregnancy on disease course and progression, potential changes to DMD treatment course, risks of fertility treatment, and risks of fetal exposure to DMDs are questions that must be discussed early on with women of child-bearing age with MS.

BALANCING THE RISKS WHEN CONSIDERING TREATMENT DURING PREGNANCY, DELIVERY, POSTPARTUM, AND BREASTFEEDING

Ultimately upon considering pregnancy, patients and clinicians should come up with a plan that considers a balance between providing MS treatment (implicating possible risks to the baby) and not treating (implicating possible risks to the mother and her disease course), in Prof. Leocani's opinion. She referred to recently updated British guidelines for some current treatment options and their risks.[3]

Prof. Leocani stressed that although pregnancy and delivery for MS patients are not risks per se, the risks of postpartum relapse are a reality, as a 70% reduction in relapse rates in the third trimester followed by a rebound like postpartum tendency for a 3 fold increase in relapse—if left untreated—is "definitely a very delicate phase for women with MS." She emphasized that neurologists should be prepared and have a plan in place during or even before pregnancy, as postpartum relapses are associated with long-term disability progression.[4] The relationship between breastfeeding and risk of relapse is still unclear to Prof. Leocani, but she feels there may be avenues to treat MS during breastfeeding on a case-by-case basis.

A TEAMWORK-BASED APPROACH TO PLANNING AND MANAGEMENT

Prof. Leocani closed by stating that "we are not alone—we are a team, and together we can handle this complex issue involving the relationship, not only involving the woman and her child, but also many specialists working together," urging careful and mindful planning between women with MS and their clinicians when openly discussing all of their available treatment options.

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MULTIPLE SCLEROSIS
SESSIONS AT EAN 2020

The “forgotten” cells in multiple sclerosis

“
Microglia are not among 'other cells' but more one of the primary cell types of interest in trying to understand the pathophysiology of MS, and also as an important therapeutic target of MS.

Sarah Starossom

Microglial cells are vital in embryonic brain development and play a role in the adult central nervous system (CNS) during maintenance and immune defense, making them relevant in the context of multiple sclerosis (MS). As part of the topic-focused workshop on the emerging importance of "other cells" in MS at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, Dr. Sarah Starossom (Institute of Medical Immunology, Charitè – Universitätsmedizin Berlin, Germany) provided an overview of the genesis of microglial cells and their role in healthy and MS patients' brains.

ROLES OF MICROGLIA DURING DEVELOPMENT

Dr. Starossom started her presentation with an introduction to the genesis of the microglial cell, stating that microglia are derived from yolk sack macrophages and colonize the brain during embryonic development. She continued by explaining that microglia are involved in many aspects of brain development, such as neurogenesis, neural migration, oligodendrogenesis[1] and that in the adult brain, they make up 10% of the CNS cells. She claimed that microglia are the resident macrophages of the CNS, functioning in immune defense and CNS maintenance. Specifically, their roles include synaptic pruning, tissue surveillance and phagocytosis, neural development, and aid in oligodendrocyte myelination. She clarified to the audience that microglia and macrophages are two transcriptionally distinct cell populations despite the fact that, in MS, macrophages enter the brain and assume a similar morphology and express similar markers to activated microglia.

ROLES OF MICROGLIA IN DISEASE—TREATMENT EXAMPLES

Microglia in the human brain are heterogeneous and form distinct clusters in healthy and MS brains,[2] noted Dr. Starossom while explaining microglia's role in disease. She continued stating that activated microglia are present at the demyelination and axonal damage sites and correlate with axonal lesion severity.[3] In her opinion, microglia activation determines degenerative or regenerative function during neuroinflammation.

Dr. Starossom then provided examples of current clinical and pre-clinical treatments that affect microglia and provide positive outcomes—including a decrease in demyelination and a shift from a pro- to anti-inflammatory microglial profile—before sharing that targeting microglia as a treatment for MS involves modulating microglial clusters from a pro- to anti inflammatory microglial state. She presented results showing that a clinically used drug for MS treatment affects microglia activation and improves oligodendrocyte repair *in vivo*,[4] and that microglia activation patterns influence disease severity. Particularly important for a favorable outcome is the anti-inflammatory profile of microglia, she claimed. Dr. Starossom continued, noting that a compound used in her studies ameliorates clinical neuroinflammation by targeting pro-inflammatory microglia, switching them into an anti inflammatory, pro-regenerative profile that aids oligodendrocyte myelination by inducing oligodendrogenesis.[5]

Dr. Starossom concluded her presentation, summarizing that microglia exhibit both a degenerative and regenerative function during neuroinflammation, and that a better understanding of microglial heterogeneity, as well as the role of distinct microglia subpopulations or activation states, may lead to a better understanding of the pathophysiology of MS. According to Dr. Starossom, directly targeting activated microglia may be useful for inhibiting neurodegeneration and inducing myelin repair in MS.

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MULTIPLE SCLEROSIS
SESSIONS AT EAN 2020

Preventing MS disability progression: Remyelination and neuroprotection

> The debate is still ongoing as to the identity of the cells in charge of remyelination in MS.
>
> Catherine Lubetzki

Multiple sclerosis (MS) is a chronic inflammatory disease leading to demyelinated and damaged axons and nerves.[1] Most people with MS experience both clinical and cognitive disability owing to the inflammation and neurodegeneration, and this disability can progressively worsen when the damage to the myelin sheaths and nerves advance.[1] As part of the plenary symposium "Time for action: Predict. Prevent. Repair." at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020, Professor Catherine Lubetzki (Sorbonne University, Paris, France) gave a presentation about remyelination and nerve repair in the central nervous system (CNS) in a session titled "Preventing disability progression in multiple sclerosis: from basic science to clinical care."

MS PATHOPHYSIOLOGY: THE BASICS

Prof. Lubetzki began her talk by introducing the basic view of MS pathophysiology, starting with the inflammation and the immune responses that lead to acute axonal damage and demyelination of nerves, followed by delayed axonal damage and loss of the chronically demyelinated axons. She noted that both the acute and delayed axonal damage pave way to MS disability progression.

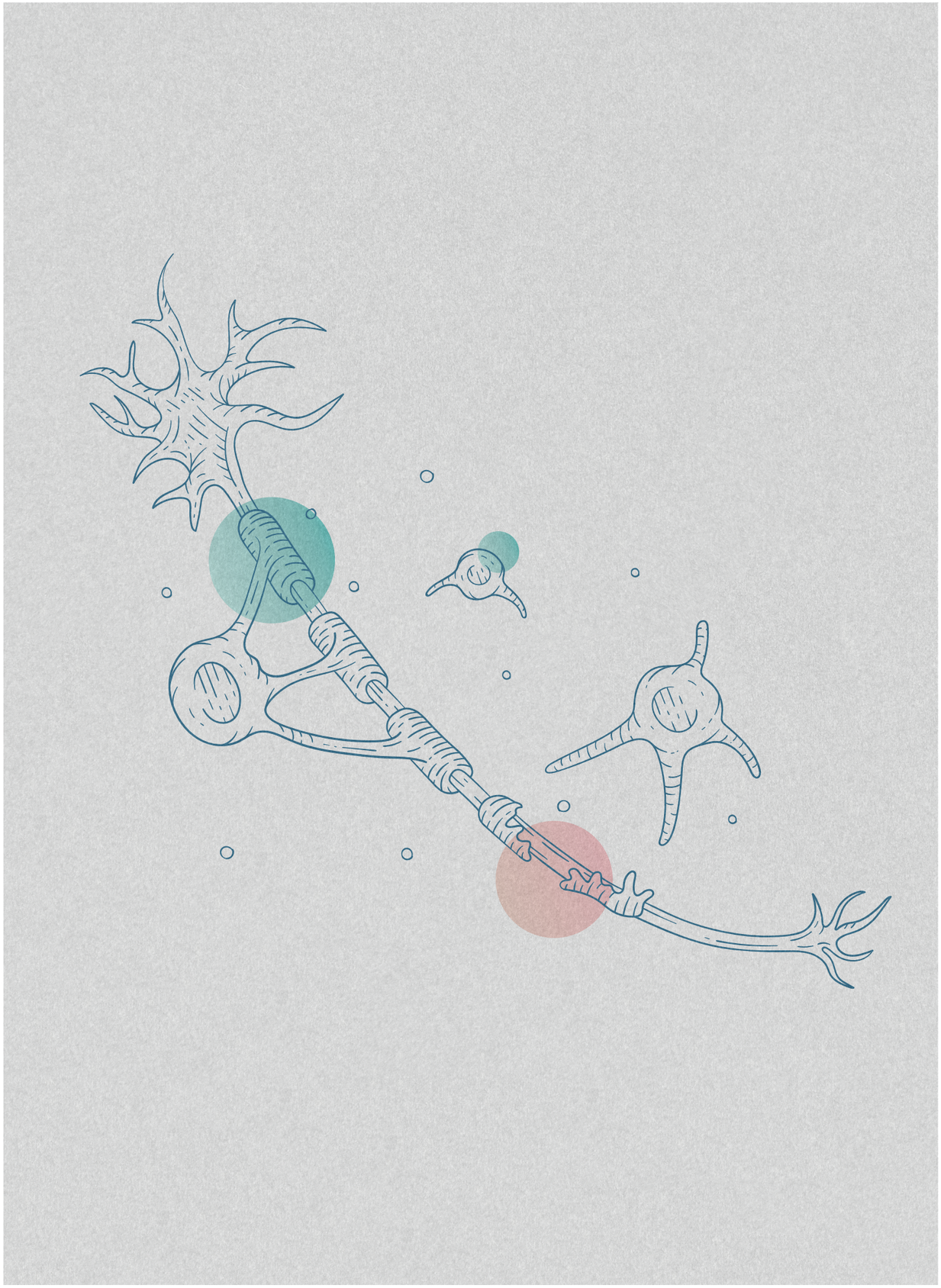
PREVENTING MS DISABILITY PROGRESSION

"To prevent disability progression, we need to prevent axonal damage," Prof. Lubetzki explained. She went on to say that this has been successfully done with immunotherapies, which have changed the way MS patients are treated. However, Prof. Lubetzki noted that the current immunotherapies are not yet sufficient to prevent the accumulation of irreversible nerve damage. In order to efficiently prevent disability progression, it is important to find strategies that promote neuroprotection and remyelination.

REMYELINATION IN MS

Introducing remyelination, Prof. Lubetzki brought up the ongoing debate around the identity of the cells in charge of remyelination of nerves in MS. She pointed out that it has long been known that oligodendroglial precursors and subventricular zone progenitors are capable of remyelinating nerves in the adult CNS. Last year, a study came out suggesting that mature oligodendrocytes might also have this capacity, adding new fuel to the debate.[2]

Prof. Lubetzki went on to discuss the identification of novel molecular pathways and targets involved in remyelination, and mentioned that several of these recently identified molecules are currently in clinical trials being assessed for their potential to promote remyelination in MS.



A FOCUS ON NODES OF RANVIER

In the second part of her talk, Prof. Lubetzki shifted focus to the nodes of Ranvier—the gaps between the myelin sheaths—which have a key role in the rapid, saltatory conduction of myelinated nerves. She emphasized that this rapid conduction of the nerve signal is made possible by the specific protein composition of the nodes of Ranvier, in particular the aggregation of voltage-dependent ion channels. Moving on to other roles of the nodes of Ranvier, Prof. Lubetzki described recent results from her laboratory, showing that the nodes of Ranvier may also be involved in myelination by localizing and initiating the myelin wrapping process.[3] In addition, she mentioned the nodes of Ranvier as a hub for neuroglial communication. Research in Prof. Lubetzki's laboratory has also detected contacts between the nodes of Ranvier and glial cells in MS tissue, but as of now, the functional impact of this interaction is unknown.

Prof. Lubetzki went on to discuss the known role of the nodes of Ranvier in disease, specifically in demyelinating pathologies such as MS. Upon demyelination, the nodes of Ranvier are disturbed and the ion channels redistributed, leading to slowed nerve conduction velocity and axonal degeneration.[4-6] These insights have led to clinical trials targeting ion channels in MS, although in Prof. Lubetzki's opinion, the results so far have been mixed and not overly positive.

PROMOTING CLUSTERING OF NODAL PROTEINS: A NOVEL WAY OF MS REPAIR?

To conclude her presentation, Prof. Lubetzki presented her working hypothesis on the role of nodal proteins in MS. In her opinion, clustering of nodal proteins prior to remyelination might positively influence nerve conduction velocity, as well as favor remyelination and neuroprotection. Ultimately, a goal of Prof. Lubetzki's is to use the novel oligodendroglial proteins that promote nodal clustering as treatments to favor neuroprotection and nerve repair in MS, and thus prevent disability progression.

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MULTIPLE SCLEROSIS
SESSIONS AT EAN 2020

Classification and profiling of cognitive phenotypes in MS

> By defining cognitively homogenous groups, this classification can be useful for defining personalized management approaches and rehabilitative strategies in clinical practice.
>
> Ermelinda De Meo

Cognitive impairment affects 40% to 70% of patients with multiple sclerosis (MS),[1] and this can lead to social and personal difficulties for patients despite minimal concurrent physical disabilities.[2] Dr. Ermelinda De Meo (Vita-Salute San Raffaele University, Italy) provided evidence for new classifications of cognitive impairment in MS during her presentation titled "Defining cognitive phenotypes of MS patients" at the virtual 6th Congress of the European Academy of Neurology (EAN) held 23–26 May 2020.

COGNITIVE IMPAIRMENT IS UNDER-INVESTIGATED IN MS

The most common cognitive deficits in MS include slow cognitive processing speed and episodic memory decline, followed by executive function, verbal fluency, and visuospatial analysis.[2] Furthermore, cognitive decline often emerges early in the disease course, with increased prevalence in progressive MS compared to relapsing MS.[3] Dr. De Meo claimed that even though patients with MS often report difficulties with multitasking and word finding, these areas are under investigated, especially at the individual patient level. To aid in developing increasingly efficient rehabilitative strategies for individual patients, Dr. De Meo sought to "classify cognitively homogenous subgroups of patients with MS, which may be defined as cognitive phenotypes."

A LARGE-SCALE COGNITIVE STUDY OF PATIENTS WITH MS

Dr. De Meo characterized cognitive domains using data from a large cohort, including 1,212 patients with MS, and 196 control subjects. Her group identified six cognitive domains to examine, including verbal memory, visuospatial memory, executive functions, attention, information processing speed, and semantic fluency, using a variety of cognitive tests and thorough statistical analysis. Dr. De Meo assured that "between-group comparisons of demographic and clinical parameters were performed using age- and sex adjusted linear models or non parametric tests as appropriate."

FIVE COGNITIVE PROFILES IDENTIFIED IN MS

When cognitive phenotypes in patients with MS were measured across these six cognitive domains, Dr. De Meo identified and coined five distinct cognitive profiles within patients with MS: preserved cognition, mild verbal memory/semantic fluency, mild multi domain, severe attention/executive, and severe multi domain. Her results showed that patients who fit the preserved cognition and mild verbal memory/semantic fluency profiles were younger and experienced shorter disease duration than the other groups. Furthermore, Dr. De Meo observed lower clinical disability in the preserved cognition group compared to other groups.

Dr. De Meo then explained the intersection between clinical and cognitive phenotypes, in relation to severity and disease course. According to her data, a progressive reduction of cognitive function was observed when comparing patients with early RRMS (relapsing remitting MS), RRMS, SPMS (secondary progressive MS), and PPMS (primary progressive MS). Generally, the relative frequency of preserved cognition declined, and the frequency of severe attention/executive to severe multi domain phenotypes increased with more severe or progressive disease according to Dr. De Meo. However, interestingly, she observed a high frequency of mild verbal memory/semantic fluency in patients with PPMS, uncovering a potential clue about differences in cognitive phenotypes between clinical presentations of MS.

COGNITIVE PHENOTYPES SHOULD BE CONSIDERED FOR PERSONALIZED MS MANAGEMENT

Although cognitive impairment was generally more severe and frequent in progressive patients or later in the disease course, Dr. De Meo stressed that her data provide evidence that cognitive impairment can occur from even the earliest stages in the disease. She concluded that the five homogenous cognitive phenotypes identified in these studies can aid in increasing the understanding of cognitive impairment in MS, as well as in defining personalized management approaches and rehabilitative strategies in clinical practice, including modifying pharmacological management to better manage cognitive symptoms.

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