Neurologybytes

5th Congress of the European Academy of Neurology (EAN)

JUNE 29 – JULY 02, 2019
OSLO, NORWAY

CONGRESS HIGHLIGHTS
MAGAZINE

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EAN 2019 CONGRESS HIGHLIGHTS MAGAZINE

Genetic Biomarkers

As part of the Focused Workshop "Biomarkers in headache disorders" at the 5th Congress of the European Academy of Neurology (EAN), Dr Bendik S. Winsvold (Oslo University Hospital, Norway) discussed the recent advances in genetic biomarkers in migraine and other headache disorders.

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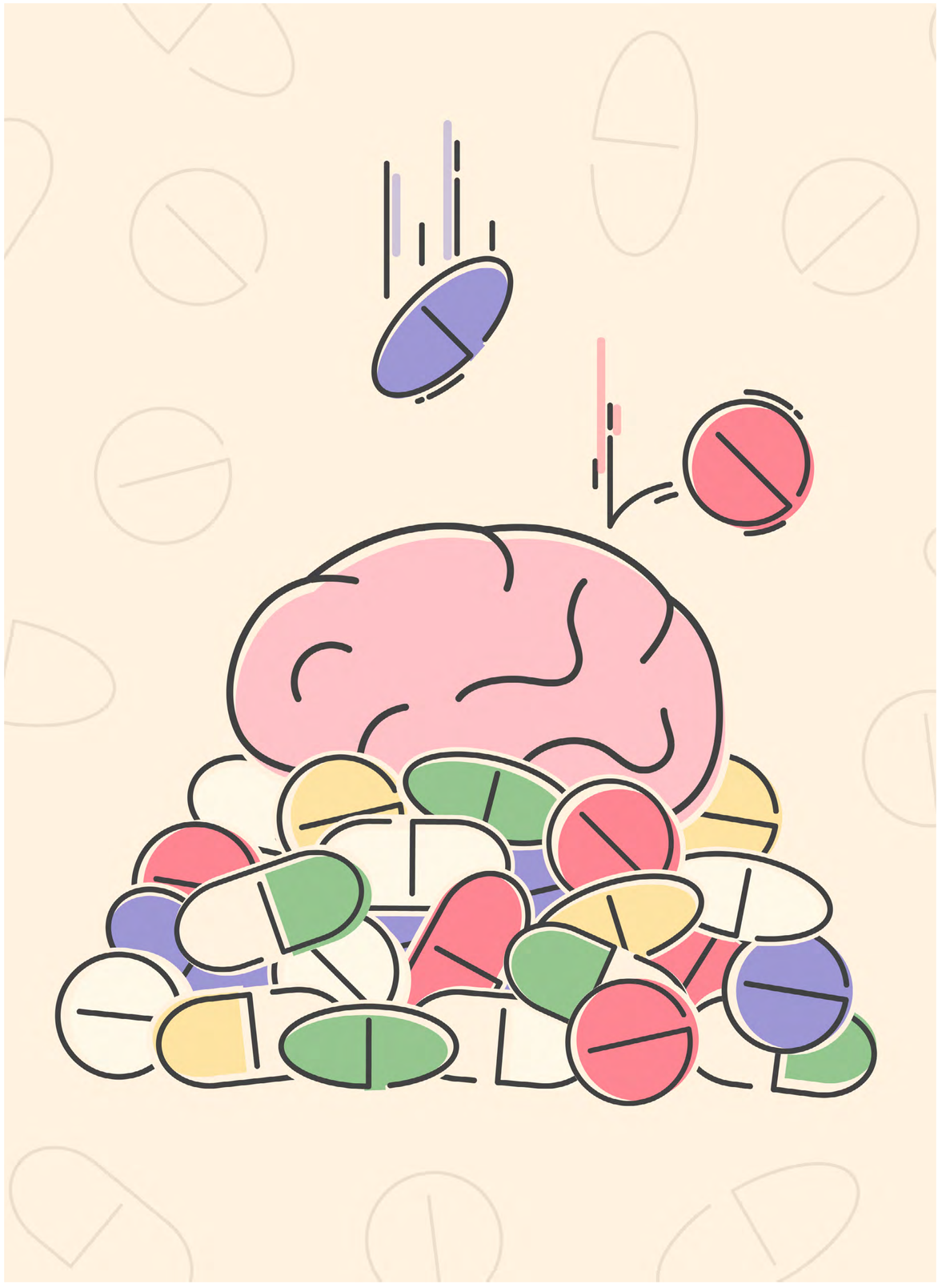
Migraine Sessions
at EAN 2019

Medication-overuse headache

Medication-overuse headache (MOH) – also known as ‘drug-induced headache’, ‘medication-misuse headache’ and ‘rebound headache' – is classified as a chronic headache disorder associated with regular medication overuse secondary to a pre-existing headache syndrome.[1] While MOH is often considered a preventable condition usually resolving once overuse is stopped, it is estimated to affect around 63 million individuals worldwide.[2] As part of the educational CME topical symposium on unmet needs in migraine treatment at the 5th EAN Congress, Prof. Zaza Katsarava (University of Essen-Duisburg, Germany) provided an overview covering the history, diagnosis criteria, and management of MOH.



History of MOH and its diagnosis criteria

In the 1930s, some patients taking ergotamine for migraine reported having more frequent migraine attacks. Interestingly, patients reverted back to their baseline migraine frequency once treatment was discontinued. This was the first observation of the paradoxical association between migraine medication intake and increased migraine frequency. The current diagnostic criteria for MOH are defined by the occurrence of headache on at least 15 days a month in patients with pre-existing headache syndromes who have been regularly using acute/symptomatic headache treatment for more than 3 months.[1] Other than ergotamine, triptans, analgesics and opioids are known to induce MOH.

Chronic headache and its implications to MOH

In light of the chronic nature of MOH, Prof. Katsarava discussed the topic of chronicity in headache disorders. Because more frequent migraine attacks (i.e. 13 headache days or more per month) are associated with significant psychosocial impairment,[3] defining chronic headache, including MOH, as a disorder in which patient experience 15 headache days or more a month is appropriate. Furthermore, he explained that the impact of chronic headache is not restricted to higher frequency of headache attacks. Indeed, several comorbidities are associated with chronicity including depression and anxiety,[4] and stress has been identified as a trigger factor for chronic migraine attacks.[5] In Prof. Katsarava's opinion, moments of intense stress can drive an at-risk patient to acute medication intake that could ultimately lead to MOH.

> It is important that doctors recognise medication-overuse headache and intervene.

Zaza Katsarava (University of Essen-Duisburg, Germany)

Management of MOH

Educational materials targeting both at-risk patients and health-care professionals explaining the risk of developing MOH represent an essential component of MOH management. In terms of treatment discontinuation, it should be known that the complete withdrawal of the treatment causing MOH is generally more effective than restricting its intake.[6] Healthcare professionals should focus on monitoring their patients' medication use and providing them with the necessary information to prevent MOH. In Prof. Katsarava's opinion, MOH is one of the few conditions in neurology were less medication is more, and optimal patient care relies on a clever understanding and management of the condition. To conclude, he enjoined the audience to think about MOH when choosing the appropriate therapy for their patients, including newly available agents.

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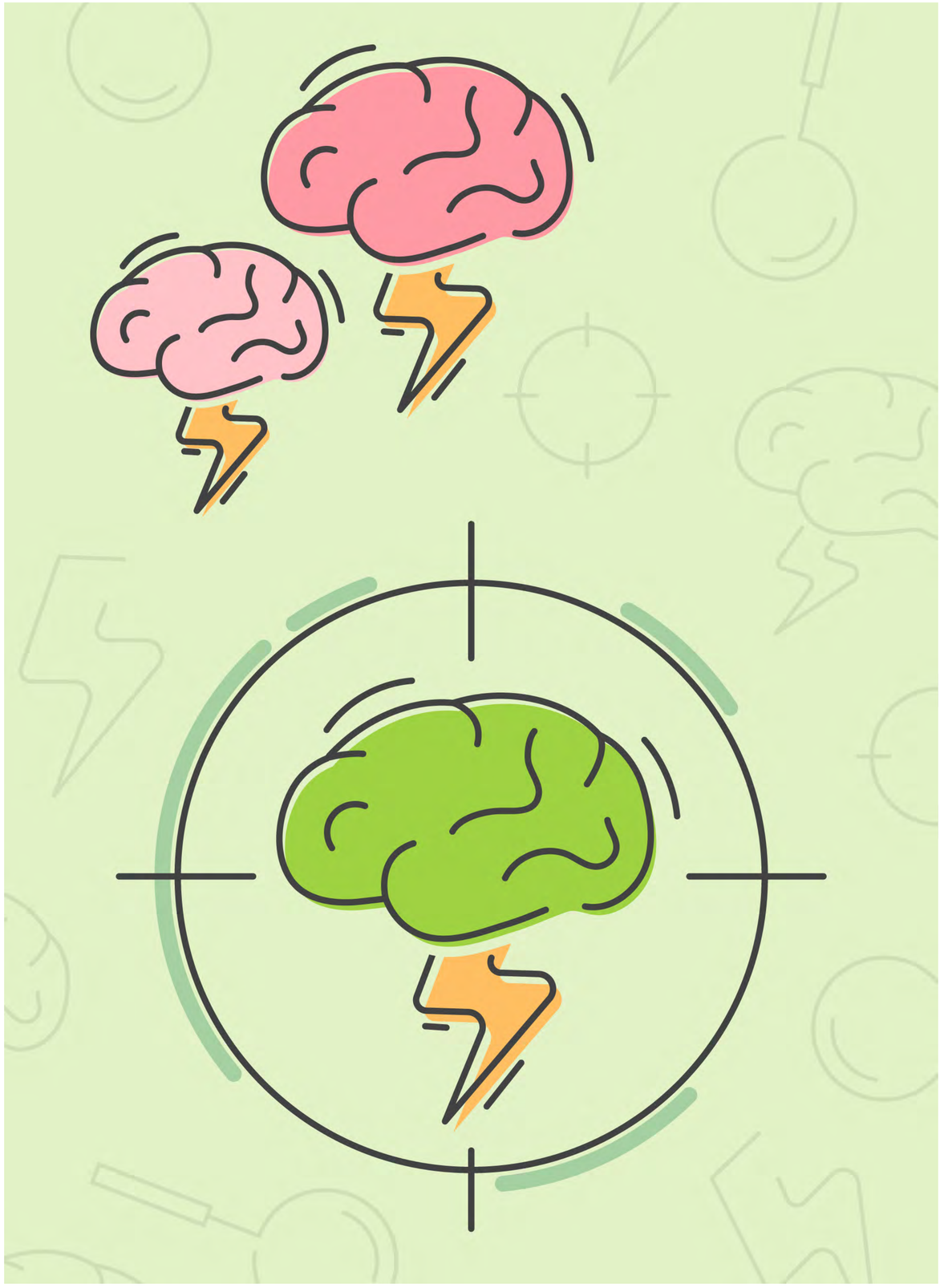
Migraine Sessions
at EAN 2019

Rare migraine syndromes

Many migraine subtypes are rare syndromes that may be difficult to distinguish and diagnose. As part of the CME topical symposium on unmet needs in the treatment of migraine at the 5th EAN Congress, Prof. Stefan Evers (University of Münster, Germany) provided an overview on rare migraine-related syndromes, and highlighted the need to identify and learn more about these syndromes.



Episodic syndromes that may be associated with migraine are a group of migraine-related syndromes classified as its own subgroup of migraine in the third edition of the International Classification of Headache Disorders.[1] These syndromes, previously called Childhood periodic syndromes, were initially considered as migraine precursors that only occurred in childhood.[2] However, current knowledge suggests that these episodic syndromes may also occur in adults.[2] According to Prof. Evers, patients often have a family history of migraine, and affected children may develop typical migraine after puberty. Episodic syndromes that may be associated with migraine include cyclical vomiting syndrome, abdominal migraine, benign paroxysmal vertigo and benign paroxysmal torticollis.

Cyclical vomiting syndrome

Cyclical vomiting syndrome is characterized by intense nausea and vomiting that occurs at least 4 times an hour for at least 1 hour.[1] This syndrome is usually stereotypical for each individual patient, and occurs with predictable periodicity, usually in the night or early morning. The prevalence of cyclical vomiting syndrome in children is 2%, and it first manifests around 5 years of age.[3]

Abdominal migraine

Abdominal migraine is an idiopathic disorder of recurrent attacks of moderate to severe abdominal pain, associated with vasomotor symptoms, nausea and vomiting.[1] Other symptoms include pallor and lethargy. Abdominal migraine is not accompanied by headache or gastrointestinal pathology. The attacks last from 2 to 72 hours, with complete freedom from symptoms between attacks.[1]

> “There is an unmet need to detect and understand syndromes associated with migraine.

Stefan Evers (University of Münster, Germany)

Benign paroxysmal vertigo

Benign paroxysmal vertigo is a disorder characterized by recurrent brief attacks of vertigo, occurring without warning.[1] The attacks resolve spontaneously after minutes to hours, without loss of consciousness. Associated symptoms may include ataxia, vomiting, pallor, and fearfulness.[1] The average age of onset of the attacks is 4 years, with spontaneous resolution around 6 years.[4]

Benign paroxysmal torticollis

Benign paroxysmal torticollis is a condition with recurrent episodes of head tilt to one side, and may also involve vomiting, irritability, pallor and malaise.[1] The attacks remit spontaneously after minutes to days, and tend to occur monthly.[1] Benign paroxysmal torticollis affects predominantly infants and small children, and may delay motor development.

Prof. Evers concluded his presentation by discussing why these syndromes may be linked to migraine. Do they have a common genetic background? Are they different symptomatologies of the same etiology? Is there a place for calcitonin gene-related peptide (CGRP) in their management? In Prof. Evers' opinion the questions are still many, and the paucity of research and controlled trials presents a challenge for both accurate diagnosis and effective treatment.

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Migraine Sessions
at EAN 2019

Anti-CGRP (Calcitonin Gene-Related Peptide) biologics: a new era for migraine prevention

There have not been any major developments over the past years in the field of migraine; the last major advance was the introduction of triptans in the early 1990s. We are now entering a new era for migraine prevention with the development of drugs targeting calcitonin gene-related peptide (CGRP) or its receptor. As part of the Teva Satellite Symposium titled "Optimism and opportunities with anti-CGRP biologics in migraine – where are we today?" at the 5th EAN Congress, Prof. Anthony Dickenson (University College London, UK) provided a background on the biological role of CGRP and its important place in modern migraine prevention.

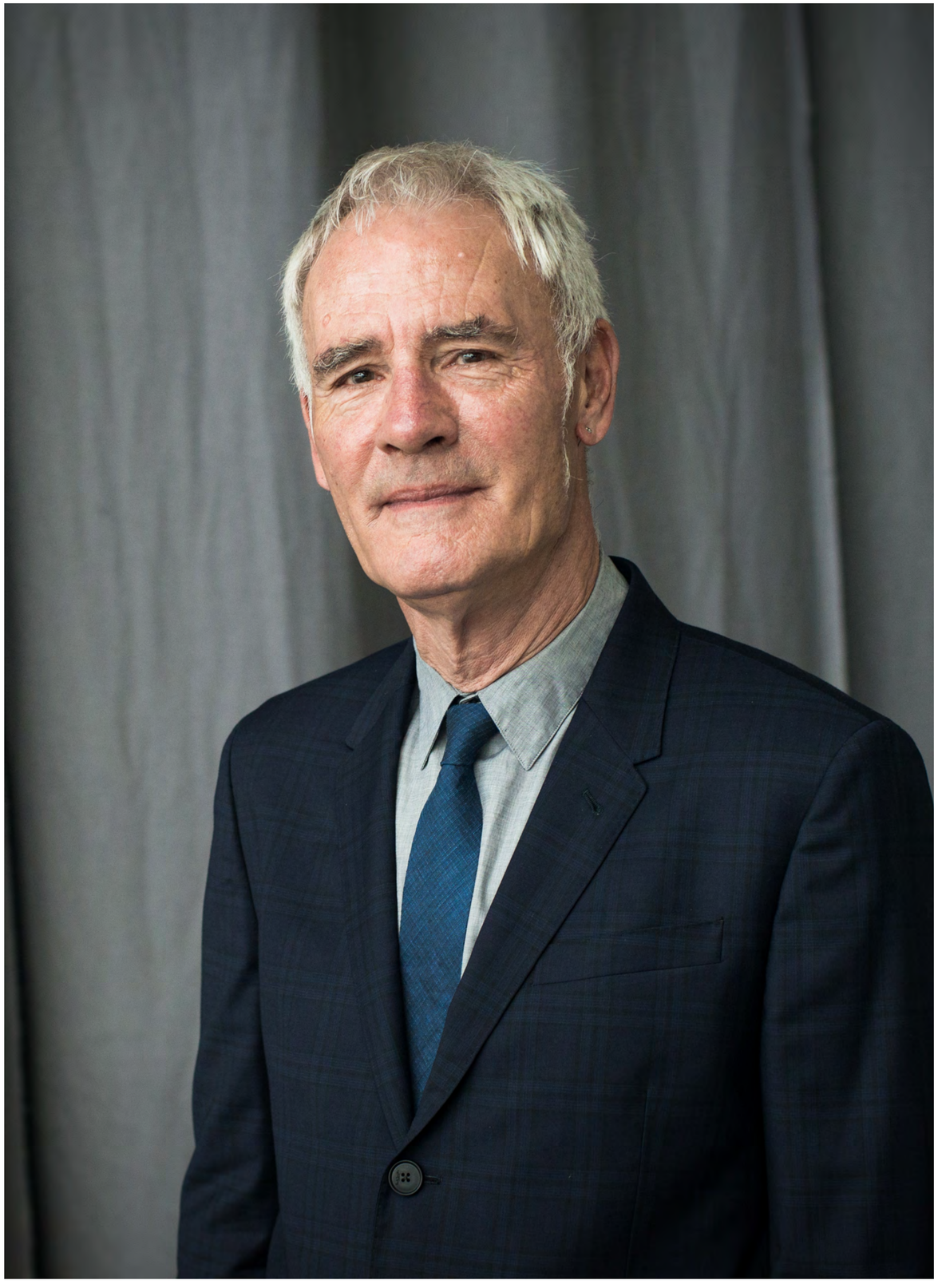
Migraine pathophysiology

The current understanding of migraine pathophysiology suggests a generalised neuronal hyperexcitability involving multiple neuronal systems.[1] This abnormal functioning of the central nervous system (CNS) can explain the particular sensitivities patients with migraine have towards changes in sleep and diet patterns, as well as light and stress stimuli.[1] In Prof. Dickenson's opinion, a migraine attack occurs when abnormal messages from the peripheral nervous system – coupled with other disturbances – reach the hyperexcitable brain. CGRP represents one of these peripheral messages and understanding its role in migraine pathophysiology has led to the development of anti-CGRP biologics.

CGRP as a target for migraine treatment

CGRP is primarily located in C and Aδ sensory fibres originating from the dorsal root and trigeminal ganglia, as well as the CNS.[2] Activation of the trigeminal system results in the release of CGRP, which in turn leads to vasodilation and release of nitric oxide, and ultimately causes pain.[2] CGRP is widely distributed in the central and peripheral nervous systems, where increased levels are found in patients with migraine.[3] In addition to the therapeutic potential of CGRP, it could also serve as a diagnostic biomarker of migraine.

Stopping pain where it starts



Prof. Dickenson explained that a migraine attack originates in the CNS and activation of the trigeminal ganglion acts to amplify pain. Presence of CGRP and the activation of the trigeminovascular pain pathway trigger ascending CNS pain pathways, which ultimately result in headache pain.[4] Anti-CGRP biologics – CGRP receptor antagonists, anti-CGRP monoclonal antibodies and anti-CGRP receptor antibodies – sequester CGRP from the peripheral nervous system, thus interrupting the message leading to migraine before it reaches the CNS.

At the end of his presentation, Prof. Dickenson shared his optimism that there is great promise in CGRP and CGRP therapies. He predicted we could see further advances, not only in the understanding and management of migraine (e.g. role as a diagnostic and treatment response biomarker), but also in the management of other headache disorders and even different therapy areas (e.g. neurogenic pain and inflammation, arthritis, diabetes and obesity).

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Migraine Sessions
at EAN 2019

Changing pathways, changing lives: taking control of migraine management

Migraine is a highly debilitating disease that is still both underdiagnosed and undertreated. However, the preventative treatment options for migraine has evolved from the first introduction of beta blockers in the 1960's[1] to the recent emergence of small molecule antagonists and monoclonal antibodies blocking the *calcitonin gene-related peptide (CGRP)*[2]. As part of the Teva Satellite Symposium titled "Optimism and opportunities with anti-CGRP biologics in migraine – where are we today?" at the 5th EAN Congress, Prof. Zaza Katsarava (University of Essen-Duisburg, Germany) discussed current preventative migraine treatment options and presented data from recent phase III clinical trials of anti-CGRP biologics.

Prof. Katsarava began his presentation by giving an overview of the existing monoclonal antibodies targeting CGRP or its receptor for migraine prevention. Currently there are three anti-CGRP (ligand or receptor) antibodies approved for the treatment of migraine: fremanezumab[3], erenumab[4] and galcanezumab[5]. These antibodies have demonstrated efficacy in both episodic migraine (EM) and chronic migraine (CM), and are generally well tolerated.[3,4,5] A fourth one, eptinezumab[6], is under development, but is not yet approved.

Prof. Katsarava continued by showing data from recent phase III studies of fremanezumab. He stated that in all the placebo-controlled trials, the incidence of adverse events in patients receiving fremanezumab was comparable with placebo-treated patients.[7]

HALO EM and HALO CM

The HALO EM study assessed the efficacy of fremanezumab compared with placebo in EM prevention.[8] The results show that fremanezumab significantly reduced the number of migraine days per month compared with placebo over 3 months.[8] The proportion of patients achieving ≥50% reduction from baseline in migraine days per month over 3 months was also significantly higher with fremanezumab.[8] In HALO CM, fremanezumab treatment led to significantly fewer headache days per month over 3 months in patients with CM.[9]

> The new anti-CGRP migraine treatments will change the life of many migraine sufferers.

Zaza Katsarava (University of Essen-Duisburg, Germany)

HALO Long-Term Study

The HALO Long-term study evaluated the long-term efficacy and safety of fremanezumab.[10] The results showed that the reduction in monthly migraine days with fremanezumab was maintained over 12 months in patients with EM.[11] Likewise, the reduction in monthly headache days in patients with CM taking fremanezumab was maintained over 12 months.[11] The proportion of patients with ≥50% reduction from baseline in monthly migraine days (patients with EM) or monthly headache days (patients with CM) were further sustained during the 12-month study period.[11]

FOCUS

The FOCUS study evaluated fremanezumab in patients with EM or CM who had failed prior preventative treatments.[12] The study included patients with documented inadequate response to 2–4 classes of prior preventative migraine treatments. The findings showed that fremanezumab significantly reduced monthly migraine days vs placebo over 12 weeks in patients with either EM and CM.[12] Furthermore, use of any acute headache medication was significantly reduced in patients with EM or CM taking fremanezumab vs placebo.[12]

To conclude his presentation, Prof. Katsarava summarized the positive features of anti-CGRP treatments for migraine: reduction in migraine days, rapid onset of effect, favorable safety and tolerability, as well as reduction of use of abortive drugs. In Prof. Katsavara's opinion, there may be cause for optimism for migraine sufferers today.

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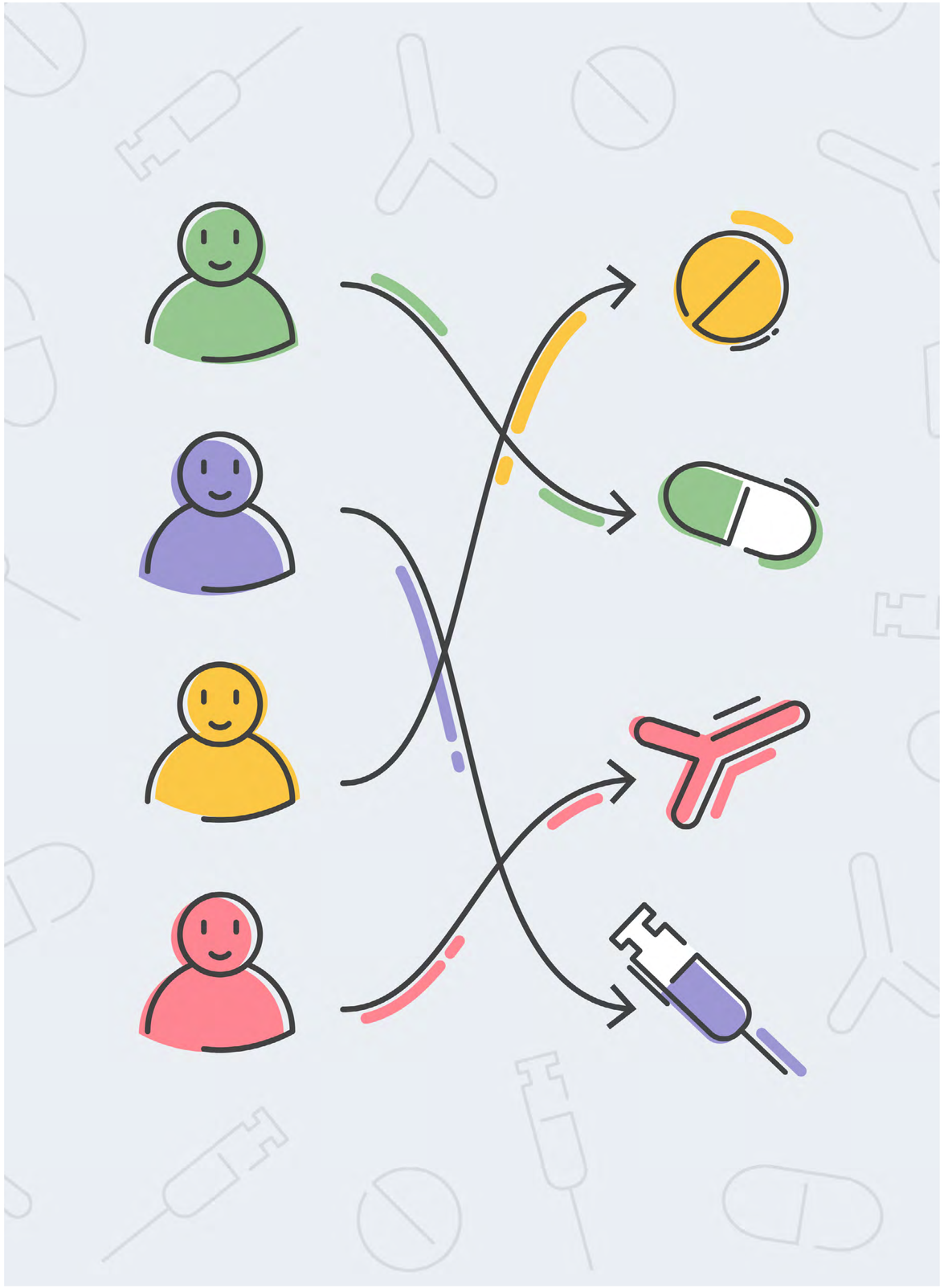
Migraine Sessions
at EHF 2019

The right treatment for the right patient

As part of the Teva Satellite Symposium "Optimism and opportunities with anti-CGRP biologics in migraine – where are we today?" at the 5th EAN Congress, Prof. Patricia Pozo-Rosich (Vall d'Hebron University Hospital of Barcelona, Spain) discussed the importance of patient preferences in treatment decisions.



A collaborative approach between physicians and patients

In Prof. Pozo-Rosich's opinion, defining the 'right' treatment and the 'right' patient are matters of perspective. Indeed, physicians need to be aware that there is no single 'right' answer and that their patient's perspective needs to be considered in the treatment decision-making process. While the overall goal of treatment for both physicians and patients is to improve life and minimise burden, it is crucial to enquire about which specific treatment outcomes are the most important for a particular patient. It is only when physicians and patients collaborate that the principles of precision medicine can be applied and the 'right' treatment is chosen for the 'right' patient.

Incorporating patient preferences and patient-reported outcomes into clinical practice

Patient preferences can be used to inform physicians on desired treatment outcomes. According to the results obtained from a patient questionnaire, most patients agreed that efficacy is the most important treatment outcome in headache disorders, for both symptomatic and preventative treatment.[1] Safety comes second, and only a minority of patients indicated that route of administration is of high importance.[1] Patient preferences and global treatment satisfaction are essential components when deciding on a treatment course. Prof. Pozo-Rosich proceeded to highlight that patient-reported outcomes (PROs) allow for a more precise quantification of patient preferences compared with global satisfaction. She further stressed that learnings from PROs monitored in clinical trials should also be incorporated into clinical practice.

As outlined in a recent review, several different PRO tools were used in clinical trials of CGRP antibodies.[2] These agents met their primary endpoint and demonstrated a reduction in disability, as well as improvements in quality of life (QoL) and workplace productivity.[2] However, questions remain about the validity of the selected tools and outcomes. In particular, Prof. Pozo-Rosich pointed out that current tools capture baseline and final

> "The right patient needs the right treatment when migraine has a disabling impact on their life.

Patricia Pozo-Rosich
(Vall d'Hebron University Hospital of Barcelona, Spain)

outcomes, and that new evaluations are needed to better represent the progressive changes experienced by patients during treatment. Furthermore, based on unpublished data from Dr Gil-Gouveia and colleagues, 41% of physicians disagreed with patients when evaluating treatment outcomes. These results suggest a disconnect between physicians and patients with respect to the selection of desired treatment outcomes.

Finding middle ground

For both patients and physicians, treatment should result in fast and significant improvements when migraine has a profoundly disruptive impact on the patient, their family, their work and society as a whole. Physicians should consider different aspects of the patient's life, use appropriate PROs and leverage their own clinical experience when deciding on a treatment course. Physicians should also look out for patient cues to help guide them towards the 'right' treatment for that person. Prof. Pozo-Rosich ended her presentation by encouraging the audience to incorporate patient preferences and PROs into their daily clinical practice.

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Migraine Sessions
at EAN 2019

Childhood chronic migraine (CM)

As part of the Case-based Workshop "Coping with refractory headache disorders of children and adolescents" at the 5th EAN Congress, Prof. Aynur Özge (Mersin University, Turkey) provided an overview of migraine in children and its management.

Prof. Özge started her presentation by stating that migraine in children and adolescents presents as more than just a headache. Several manifestations can precede a migraine attack, including abdominal discomfort, dizziness, vertigo, motion sickness, and behavioural and sleep disturbances. Medical comorbidities such as atopy, epilepsy, psychiatric and rheumatological disorders have been reported in young patients with migraine. Additionally, cranial autonomic symptoms often occur prior to the migraine attack.

Chronic migraine in children

Migraine has an estimated prevalence of 7.7%–17.8% in children[1] and is greatly disruptive for patients and their families. Chronic migraine (CM) affects 1.7% of chidren[1]; additionally, episodic migraine in children can evolve into the chronic condition. Identified risk factors for CM in children are increasing age, female sex, and father and sibling headache histories.[2]

The diagnosis of CM is not differentiated between adults and children. The two main diagnostic criteria for CM are 1) headache on 15 or more days per month for at least three months, and 2) occurring in patients who have had at least five attacks fulfilling the criteria of migraine without aura and/or migraine with aura.[3] There are, nonetheless, key differentiating features between migraine in children and that in adults. Migraine attacks in children tend to be frontal and bilateral, which is in sharp contrast to the temporal and unilateral migraine in adults. Furthermore, a migraine attack in children can last minutes to hours, while in adults the duration range is 4–72 hours.

The features of the premonitory phase also differentiate migraine in children to that in adults. Episodic syndromes that may be associated with migraine – previously known as childhood periodic syndromes or periodic syndromes of childhood – include cyclic vomiting syndrome, abdominal migraine, benign paroxysmal vertigo and benign paroxysmal torticollis.[3]

Management of migraine in children

Management of migraine in children starts with education. Physicians, patients and their families, need to be aware of the vast number of syndromes and comorbidities that can occur in children and adolescents with migraine. Prof. Özge stressed that the management plan should be inclusive of the patient's entire social circle. Indeed, migraine has a disruptive impact on the patient, their families as well as their schools and friends.

The goals of migraine treatment in children are to improve quality of life, to develop adaptive pain-coping strategies, and to reduce disability and the risk of disease progression. Preventative treatment is recommended when migraine attacks occur 3–4 times per month and their severity impacts daily function or quality of life. An in-depth investigation of effective attack medication, potential triggers, life-style related aspects and analgesic overuse should be conducted. Additionally, a rigorous tracking of phenotypic changes is necessary because episodic syndromes change as children grow older. In Prof. Özge's opinion, there is no perfect treatment for migraine in children. Physicians need to consider comorbidities as well as patient-specific aspects when deciding on a treatment course.

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Migraine Sessions
at EAN 2019

Genetic Biomarkers

Migraine is one of the most disabling disorders worldwide,[1] and yet, its diagnosis remains purely clinical. Identification of specific migraine biomarkers would aid diagnosis, provide insights into pathophysiology, and potentially lead to the development of new therapeutics. As part of the Focused Workshop "Biomarkers in headache disorders" at the 5th EAN Congress, Dr Bendik S. Winsvold (Oslo University Hospital, Norway) discussed recent advances in genetic biomarkers in migraine and other headache disorders.

Dr Winsvold started his presentation by defining biomarkers as measurable indicators of a condition. According to Dr Winsvold, biomarkers can be divided in clinically applicable biomarkers and biomarkers that increase our understanding of the disease.

Insights from monogenic disorders

Recent advances in genetic studies, particularly genome-wide association studies (GWAS), have contributed substantially to the identification of common genetic variants in migraine.[2] Dr Winsvold discussed three subtypes of migraine with identified genetic components: familial hemiplegic migraine, associated with mutations in CACNA1A, ATP1A2 and SCN1A; hemiplegic migraine, associated with mutations in PRRT2; and monogenic typical migraine with aura, associated with mutations in KCNK18 (encoding TRESK). The common denominator for impaired function of the involved genes is neuronal hyperexcitability, with resulting increased susceptibility to cortical spreading depression (CSD).[3]

In addition to monogenic migraine disorders, Dr Winsvold noted that a number of primarily vascular disorders are caused by mutations in single genes, which often are accompanied by migraine features.[4] Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a cerebrovascular disease caused by mutations in NOTCH3. CADASIL is characterized by ischemic strokes and dementia, but up to 40% of patients also experience migraine.4 Mutations in the TREX1 and COL4A1 also cause vascular disorders that are often associated with migraine.

Insights from common migraine

The GWAS approach has been used to identify several new independent loci associated with common migraine. Dr Winsvold presented a study conducted on 59,674 patients with migraine and 316,078 controls that identified 44 independent single-nucleotide polymorphisms (SNPs) mapped to 38 distinct genomic loci significantly associated with migraine.[5] Several of these loci are enriched for genes that are expressed in vascular and smooth muscle tissues. However, Dr Winsvold mentioned a yet unpublished large migraine study by the International Headache Genetics Consortium that identified several new independent SNPs within non-vascular genes.

> “We are working hard on identifying clinically meaningful biomarkers, but we are not there yet.
>
> Bendik S. Winsvold (Oslo University Hospital, Norway)

Exploring other primary headache disorders

The current use of genetic biomarkers is mainly limited to monogenic forms of migraine, but the search for biomarkers in other headache disorders is ongoing. Dr Winsvold is part of the International Consortium for Genetic Studies in Cluster Headache that includes research groups from more than 10 countries. The Consortium is currently analysing clinically diagnosed patients with cluster headache using the GWAS approach with the hope of identifying clinically meaningful biomarkers.

Dr Winsvold concluded his presentation by stating that GWAS findings have no direct clinical application yet. Identification of robust and clinically meaningful biomarkers for migraine and other headache disorders is a challenging but highly important task. Dr Winsvold is hopeful that genetic biomarkers could in the future be used to identify genetic subtypes of migraine, as well as to predict treatment effects of migraine drugs.

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MS Sessions
at EAN 2019

Rethinking disease progression in MS

We know that relapses, being a defining clinical feature of MS, contribute to meaningful neurological disability over the short term. However, their contribution towards long-term disability progression is controversial: long-term disability progression studies and natural history studies have delivered conflicting results. In a recent large MSBase study, a high annualised relapse rate, particularly on-treatment relapse, was an indicator for disease progression.[1,2] Did data from this year's EAN support this possibility? Here we discuss this and other emerging predictors of disease progression and how these advances will determine treatment approaches.

What causes disease progression in MS?

As mentioned above, relapses are thought to play an important part is disease progression.[1] Data from 2,015 patients with RRMS enrolled in the Danish MS Registry treated with disease-modifying therapies (DMTs) were presented by Dr Magyari at this year's EAN congress. The researchers observed that the mean adjusted EDSS increase was 0.205 units in study intervals with relapses and only 0.065 without relapses, confirming a significant role for relapses on disability progression. However, the contribution of relapses to disease progression depended on the stage of disease progression in which the relapse occurred. For example, for patients whose EDSS scores were ≥ 4.0 at the start of the study interval, there was no clear effect of relapses on disability worsening. Data from another study of patients with secondary progressive MS (SPMS), suggest that relapses that occur in the early years (first 3 years and 3–5 years) after SPMS onset increased the risk of irreversible EDSS worsening. In contrast, no such association between relapses and EDSS worsening was observed in the later years (after 5 years) of SPMS.[3,4]

Relapse-dependent progression can be contrasted with so-called 'silent' progression, a term suggested by the MS-EPIC Team at the University of San Francisco, USA, to describe long-term worsening that is independent of relapse or new lesion formation in patients who are considered to have RRMS. This silent loss of function may be so gradual that it is not noticed by the patient or the physician and only becomes apparent at higher levels of EDSS. It is possible that there are two simultaneous pathological process – one causing focal demyelinating lesions and correlating with relapses and a separate, more diffuse, process that contributes to brain atrophy and leads to 'silent' progression in RRMS and is responsible for SPMS when clinical worsening is more evident.[1]

Other correlates of progression

Looking to other correlates of progression, Dr Dalla Costa presented data from 255 patients diagnosed with MS in a long-term follow-up study considering clinical and paraclinical markers of disability progression. Patients who presented with clinically isolated syndrome suggestive of MS with a minimum follow up of 2 years were included in the study. Factors that were predictive

of disability progression over medium- and long-term follow up included low serum levels of 25-OH-vitamin D, smoking, female gender and, in particular, presence of spinal cord lesions at disease onset. A further study found that higher vitamin D levels over 10 years were associated with lower long-term disability progression. With these two studies in agreement, vitamin D seems an attractive tool for predicting both short- and long-term disease progression.[5,6]

A fresh look at monitoring disease progression

Novel data presented at this year's EAN has brought to light some promising ways for measuring disease progression at different stages of the MS disease course. A fresh view on disease progression measures was presented that combined measures of both cognitive processing speed (Symbol Digit Modalities Test) and physical disability (EDSS). When used individually, these measures mostly captured two distinct disability groups (patients tended to progress according to one but not the other measure and a minority progressed on both measures) and when combined into a composite endpoint, this provided a comprehensive measure of clinically relevant disease progression in SPMS.[7]

A further marker, a combination of different evoked potentials (EPs) in the form of a numerically scaled score, was shown to predict disease progression in early MS. An EP score > 13 was shown to be a significant predictor of sustained accumulation of disability (SAD), with those participants with an EP score ≤ 13 showing a 74% relative risk reduction for SAD.[8]

Data on the potential predictive value of the IgM index as a biomarker for disease prognosis were also presented: in a 1-year study, 88% of patients with RRMS had a negative IgM index and 42% of patients with PPMS had a positive IgM index. A positive IgM index was likely associated with a more severe form of MS and could be correlated with many aspects of MS disease evolution.[9]

> "If we have reliable disease progression measures, then we would be able to choose those patients who require a more effective treatment from the start and those who can start with a more moderately effective treatment

Per Soelberg Sørensen (Danish Multiple Sclerosis Center, Denmark)

What are the treatment implications of these advances in disease progression understanding?

The confirmation that relapses are associated with worsening of disability in patients with RRMS beyond the recovery phase (EDSS ≥ 4.0) led Magyari and colleagues to make some recommendations. They concluded that a treatment strategy offering the best chance of preventing relapses should be used to maximise prevention of disease progression. Fortunately, evolving diagnostic criteria are allowing earlier diagnosis and treatment initiation with DMTs. This approach will allow attenuation of the frequency of these early relapses and subsequently long-term disability.[3,1]

Furthermore, the results showing an ability to define an individual's disease progression risk profile at the first demyelinating event can potentially guide neurologists in their treatment decisions and personalise therapy for patients from the onset.[5]

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MS Sessions
at EAN 2019

How to improve the advice given to patients with MS who are planning a pregnancy: insights from EAN 2019 and recent publications

In this article we look at how data presented at EAN 2019 or published recently may inform the advice given to a patient with MS who is planning a pregnancy.

Currently, prepregnancy counselling is frequently overlooked: in a survey of people with MS (pwMS) who wanted to start a family, 60% (188/311) did not receive any prepregnancy counselling at all, and 16% (55/349) were discouraged to become a parent, most frequently by medical personnel. The Association of British Neurologists (ABN) recommends that at or soon after diagnosis, all women with MS of childbearing age should be offered prepregnancy counselling and this should be repeated at regular intervals (at least annually), particularly for those who are on or considering starting medication.[1,2] The ABN recommends covering the following:

- No effect of MS on fertility
- Do not routinely defer DMT
- Consider effect of exposure in males
- Pregnancy does not affect long-term disability outcomes
- Relapse risk during and after pregnancy.

There appears to be an unmet need for educational information to complement or facilitate prepregnancy counselling: a survey presented at EAN of educational resources from 51 countries identified 13,321 individual resources, but the category including information on pregnancy planning ('resources for families') accounted for only 5.7% (753/13,321) of these resources.[3]

There is currently limited evidence to inform prepregnancy counselling.[2] This year at EAN, several presentations provided further evidence to increase the reliability of advice given to patients and to support the treatment plan.

How pregnancy affects disease activity

It is thought that the increases in levels of gestation-related steroid hormones reduce the risk of relapses during pregnancy (particularly the third trimester) and that the risk then increases in the postpartum period. For example, in a recent retrospective administrative claims database study including 2,158 patients treated in the USA, the odds of relapse declined during pregnancy, but the monthly adjusted relapse rate increased from

> "It's becoming more and more important to discuss planning a pregnancy with both female and male patients. The MS population today is very different from the population from the 1990s … they want to have a normal life, which includes a pregnancy

Doriana Landi (University of Rome Tor Vergata, Italy)

0.99% in the third trimester to 2.56% in the 6-week puerperium period. At EAN 2019, a systematic review of 27 articles showed that relapse rates decreased in pregnancy, with reported annualised relapse rates of 0.0 ± 0.0 to 0.4 ± 0.6. Although it is usually thought that relapse risk decreases most during the third trimester, the relapse rates reported in the systematic review were similar in the first, second and third trimesters. Five studies confirmed a higher relapse rate in the postpartum period compared with both before and after pregnancy. Four studies showed that disease activity before and during pregnancy may be an indicator of postpartum relapse.[4,5,6]

The effect of breastfeeding on relapse risk is controversial because studies that have suggested a protective effect may have been biased by the fact that patients with more active disease may be less likely to breastfeed. In the systematic review, two studies indicated that exclusive breastfeeding may reduce the risk of relapse while one study found no effect on MS activity. In addition, there is evidence that exclusive breastfeeding may offer the infant protection from MS later in life. A recent study of 2,055 pwMS showed that those who had been breastfed for at least 6 months had a 4.2-year later age of MS onset than those who had been fed with formula milk.[6–10]

How pregnancy could affect the treatment plan

Vukusic et al suggest that as soon as a woman with MS is considering pregnancy, a treatment plan should be established. Such treatment plans should balance the risk posed by the DMT with regard to teratogenicity and fetotoxicity with the risk for potential for further disease progression. DMTs are often discontinued in patients planning a pregnancy: in a study presented at EAN 2019, among 80 pwMS who discontinued their oral DMT, patient preference or pregnancy planning was the reason for discontinuation in 34.6%. Discontinuation was associated with clinical and/or MRI activity in 75.7%, among whom 54% discontinued owing to patient preference or pregnancy planning.[11,12]

The EAN/ECTRIMS consensus recommendations provide some suggestions for DMTs that may be considered prior to or during pregnancy (see recommendations for details), but the majority of DMTs are FDA category C for use in pregnancy (‘risk not ruled out’; no studies in humans but potential benefits may warrant use of the drug in pregnant women). Glatiramer acetate is FDA category B (‘no risk in other studies’; either no risk in animal studies or no risk demonstrated in controlled studies in pregnant women) and the summary of product characteristics states ‘Current data on pregnant women indicate no malformative or feto/neonatal toxicity of glatiramer acetate. To date, no relevant epidemiological data are available. As a precautionary measure, it is preferable to avoid the use of glatiramer acetate during pregnancy unless the benefit to the mother outweighs the risk to the foetus.’ Data presented at EAN 2019 reported pregnancy outcomes in pwMS who were exposed to DMTs prior to or during pregnancy, as well as pwMS who were treated throughout pregnancy. These data may provide some guidance for neurologists deciding to continue DMT during pregnancy in pwMS at high risk of relapse.[2,13–16]

As mentioned above, the relapse risk generally increases after parturition, and consequently Coyle and colleagues advise rapid reintroduction of DMT in patients with at relatively high risk of postpartum relapse (very active disease before pregnancy, poor prognostic profile, relapse during pregnancy, and/or no previous DMT use). In the systematic review presented at EAN 2019, two studies supported early reintroduction of DMTs while two others showed no benefit of this strategy.[4,5,6]

Conclusion

Women with MS do not seem to present a significantly higher risk of obstetric and neonatal complications.[17] At this stage of a patient’s journey, providing accurate advice is an important part of a neurologist’s role, and gradually, more data are accumulating to inform this advice.

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MS Sessions
at EAN 2019

The varied challenges of psychiatric comorbidities in MS: a perspective from EAN 2019

The association of MS with other conditions is attracting increasing attention among physicians and researchers owing to the effect of comorbidities on important considerations such as time to diagnosis, progression of disability and health-related quality of life (QoL) among patients with MS (pwMS).[1] Authors of one recent cohort study in 6,932 pwMS and 68,526 matched controls reported that pwMS have an increased risk of several major comorbidities unrelated to MS, including peripheral vascular disease, depression, fracture and infection, and this was evident even before the diagnosis of MS.[2]

Psychiatric comorbidities are of particular interest as they are associated with a negative impact on QoL, intensification of some of the symptoms of MS (e.g. fatigue, sleep quality, disability), and reduced adherence to DMT.[3,4] Some studies suggest that psychiatric comorbidities in MS are under-recognised and undertreated.[1,5]

Prevalence of psychiatric complications in MS

According to a recent systematic review, depressive and anxiety syndromes are the most common psychiatric comorbidities in MS, with a prevalence of around 31% and 36%, respectively, compared with 21% and 29% in the general population. However, other less common psychiatric symptoms such as obsessive–compulsive syndrome, schizophrenic syndrome and bipolar syndrome have a greater impact on QoL of pwMS than depression or anxiety.[3,4]

At this year's EAN, Dr Carrasco García and colleagues presented data from a retrospective case series investigating the prevalence of less common psychiatric disorders among pwMS. Among 345 pwMS, 13 presented with a psychiatric pathology, including paranoid schizophrenia (4/13), bipolar disorder (4/13), personality disorder (3/13), neurotic disorder (1/13) and transient acute psychotic disorder (1/13).[6]

Despite the general tendency for an increased prevalence of psychiatric disorders in MS compared with the general population, this is not universally the case: Dr Benjaminsen and colleagues presented a study of 654 patients with MS treated in Norway, in which the prevalence of psychosis (0.6%) was lower than expected among pwMS. The reasons for this observation were not discussed, although it was noted that the validity of these results should be confirmed in other Norwegian cohorts.[7]

Effect of psychiatric complications in MS

Given the general increased prevalence of many psychiatric conditions among pwMS, it is important to consider the impact of the conditions on symptoms of MS. Dr Vukorepa and colleagues presented a study in 54 pwMS showing a significant association between level of depression (as measured using the Beck Depression Inventory) and level of fatigue, as measured using multiple scales. This finding has important implications for the treatment of MS, suggesting that the mutual impact of different symptoms should be considered in order to improve or maintain QoL.[8]

A common underlying pathology?

It is not yet clear whether MS increases susceptibility to psychiatric disorders or whether they both have a common underlying pathology. This point was discussed at EAN by Dr García Carrasco, who noted that it was important to consider both potential associations because of the repercussions for treatment, functionality and prognosis of the disease.[6]

Psychiatric side of effects of DMTs

Although the aetiology of the increased burden of psychiatric disorders in MS is not completely understood, it has long been thought that the medications used in MS may be one contributing factor. For example, corticosteroids are known to cause a variety of neuropsychiatric side effects, while some platform therapies were initially reported to confer an increased risk of depression, although this was later disputed.[9,10]

A recently published systematic review concluded that none of the second-generation DMTs studied were associated with a statistically significant increased risk of any adverse psychiatric effect. Indeed, the study reported that some DMTs may in fact reduce the incidence of depressive symptoms, either directly or indirectly through a positive impact on the disease course. This is an important finding in terms of delivering optimal treatments to pwMS, as well as supporting the mental health needs of patients.[9]

> “It is unknown whether there is a common pathophysiological mechanism or if lesions, stress associated with chronic lesions or treatment of MS predispose to the appearance of psychiatric disorders
>
> Dr García Carrasco

Conclusion

Considerable evidence is available to show that pwMS tend to have an increased risk of psychiatric conditions. Psychiatric comorbidities can exacerbate symptoms of MS, and vice versa, and therefore the early identification and management of psychiatric syndromes is essential in order to optimise QoL in this population.

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JOB CODE:
HQ/CNS/19/0027

DATE OF PREPARATION
JULY 2019