4th EAN Congress

European Academy of Neurology

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PEER-REVIEWED CONFERENCE REPORT

Progressive MS in the Limelight

Significant progress has been made in understanding the pathogenesis of progressive MS, resulting in numerous clinical trials. Even when negative, they still attribute to understanding pathology and finding biomarkers.

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MRI-Guided Thrombolysis in Stroke with Unknown Onset

Intravenous thrombolysis may be effective even when the time of stroke onset is not exactly known. MRI can identify patients waking up with stroke symptoms in whom thrombolysis is beneficial.

read more on PAGE 15

The High Costs of Chronic Migraine

Migraine generates a huge burden for patients and an economic loss for society, as was confirmed by a large-scale French survey. As such, the positive results of interventions to prevent or treat migraine cause quite a stir.

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MEDICOM MEDICAL PUBLISHERS

Editor Prof. Valeria Caso, University of Perugia, Italy

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Letter from the Editor

Prof. Valeria Caso

Dear Reader,

Dear Colleagues,
The 4th annual Congress of the European Academy of Neurology was held in Lisbon on June 16th – 19th this year. The scientific programme featured top speakers, stimulating discussions, and news on scientific breakthroughs. More than 6,700 participants from 104 countries attended the meeting. It covered the whole range of neurologic disorders in various formats, and offered altogether 42 scientific and 48 educational sessions. More than 2,100 abstracts had been submitted and discussed. The overarching theme of the Lisbon conference was: "Molecular and genetic therapies for neurogenetic disorders" with state of the art lectures on e.g. spinal muscular atrophy and familial amyloidosis.
The conference built on the enormous success of the previous editions and continues to be Europe's foremost forum for discussing and disseminating the latest standards, guidelines, and updates on neurology management and care. During the Late Breaking News session two papers were simultaneously released online by Lancet Neurology. One paper reported on the effects of cognitive behavioural therapy of severely fatigued patients with myotonic dystrophy type 1, while the other study reported the results of a trial on the safety and efficacy of rasagiline as an add-on therapy in patients with ALS.

This conference report summarises the main topics of the Lisbon conference.

Enjoy reading.

Best regards,
Valeria Caso

Biography

Valeria Caso is a stroke neurologist at the University of Perugia Stroke Unit, Italy and has been recently certified in the role of full professor in Neurology.
She is past president of the European Stroke Organisation (ESO) and member of the EAN Programme Committee.
She has authored and co-authored more than 200 published papers and book-chapters.
She has been involved in 20 multicentre trials serving in various positions including steering committees. She is currently actively involved in international research projects on cervical artery dissections, heart and brain, intracerebral haemorrhage, and acute stroke treatment. She has made her primary interest the treatment and prevention of stroke in women and working on stroke guidelines in women.

Neurogenetics are revolutionising diagnosis and now even treatments

Interview with EAN president
Prof. Günther Deuschl MD, FEAN
conducted on 18 June 2018 in Lisbon by Michiel Tent

Four years after the founding of the EAN and after four years of presidency, Prof. Günther Deuschl from Kiel in Germany is succeeded by Prof Franz Fazekas from Graz, Austria. Prof. Deuschl talks to Medicom about highlights of the 2018 EAN-meeting and about his successor.

What have been some of the highlights of this conference so far for you personally?
"First of all, it was the first time our conference was held in Lisbon. It is a pleasure to be in Portugal, where neurology is strongly represented. For example, it was here that functional neurological surgery was developed; also, many genetic neurological diseases were discovered in Portugal. The conference itself has neurogenetics as an overarching theme this year. We are very pleased with the response to the way we decided to treat this topic, ranging from a slightly 'philosophical' approach to diagnostic and therapeutic applications – genetic applications – in neurology, which have provided the visitors with a really interesting overview of the current field."

"But there were many more highlights. As far as teaching is concerned, we had patients on stage for the first time, who were interviewed by experts in the field in question. The participants could hear and see how the experts do their job, which I think is a very important teaching tool. Also for the first time, we did the Neuro Quiz, with two teams competing. After the presentation of four example cases or findings, the two teams, as well as the audience, could make their decisions, which is a huge learning tool. Then, of course, there was the state of the art. We have seen dramatic improvements in, for example, the field of stroke. Imaging is now implemented into therapy, which is really new. Before, you had to perform a CT scan before you could do a thrombolysis; now we can use imaging information to treat patients that we could not treat before. That is a huge improvement for patients. And there are many more such highlights."

Coming back to neurogenetics as the overarching theme of this meeting: can you please explain why this is so important?
"Neurogenetics have really revolutionised the diagnosis of neurological disorders; this is a process that has been going on for some 30 to 40 years. It started 1993 with the discovery of the Huntington gene. But what is really ground-breaking is that it is now also beginning to be applied to therapy. We have the first gene-driven therapies in neurology now, for spinal muscular atrophy. It is one of the first big successes of genetic therapy. Results were already touched upon in last year's meeting. But seeing babies who were prone to die within the next few years really recover and have an almost normal life... is truly stunning."

Your colleague overseas, Prof. Ralph Sacco, who is president of the *American Academy of Neurology* (AAN), said last April that more neurologists are needed. Is that a concern within Europe as well?
"Absolutely. However, the need for neurologists very much depends on the country. There are countries where the number of neurologists is considered relatively reasonable. In other countries, our data show that many patients with neurological diseases cannot be treated by a neurologist because there are too few available. These countries are aware of this and are now undertaking efforts to solve this issue. It is a work in progress."

You will be succeeded as EAN president by Prof. Franz Fazekas. What can you tell us about him; what do you expect of him?
"First of all, Prof. Fazekas is an excellent scientist, who is especially active in the fields of stroke and multiple sclerosis. Very few scientists can excel in two fields, but he does, his specialty being imaging. Having known him through our daily activities for about four years now, I could not possibly think of a better successor than him, deeply skilled in analysing neurological situations and the situation of neurology. He also possesses the elegancy needed to keep the EAN together: he is a very polite person and very much dedicated to the task ahead of him. He will have a very good presidency, which will move the EAN significantly forward."

You will now have some more spare time; what do you intend to do with it?
"I will spend it on working for neurology."

Multiple Sclerosis

This year the very first drug against primary progressive multiple sclerosis (PPMS), ocrelizumab was approved. It may be regarded as a 'sign of the times', since significant progress has been made in the past few years in understanding the pathogenesis of PMS. Most of the clinical trials carried out on PPMS have yielded negative results thus far, but they attribute to understanding PMS pathology and finding biomarkers to monitor its course. Also discussed at the EAN meeting were two important new treatment guidelines: the EAN/ECTRIMS guidelines on the pharmacological treatment of MS, and the EAN guidelines on palliative care of patients with severe MS.

New guidelines on pharmacological treatment

In a collaborative effort, the EAN and ECTRIMS issued new guidelines on the pharmacological treatment of MS, which was expanded on during the EAN meeting. The new guidelines were originally published in *Multiple Sclerosis* in early 2018 [1]. It supports physicians in weighing the opportunities and risks of the available treatment options when making therapy decisions. The guidelines were updated due to the availability of new treatment options, including the recently approved cladribine and ocrelizumab, providing new treatment options for relapsing MS but also for primary and secondary progressive MS (PPMS and SPMS).

The following recommendations were made regarding PPMS and SPMS, including assigned strength:

- consider treatment with mitoxantrone for patients with active SPMS, taking into account, in consultation with the patient, the efficacy, and specifically the safety and tolerability profile of this agent (weak).
- consider treatment with ocrelizumab or cladribine for patients with active SPMS (weak);
- consider treatment with ocrelizumab for patients with PPMS (weak).

"This new guideline is part of the EAN guideline programme under which all important neurological diseases are to be reappraised. About 20 of these guidelines are currently being worked on," stated EAN president Prof. Deuschl (Christian-Albrechts-University, Germany). "These efforts underscore the major significance of the EAN, providing important principles not only for medical practitioners but also for healthcare policy."

Consumer/caregiver involvement

At the EAN meeting, a new EAN guideline on palliative care of patients with severe MS was published [2]. "There were 751 MS patients and 183 caregiver relatives involved," first author Prof. Köpke (University of Lübeck, Germany) explained. They participated in an international online survey; part of the MS patients and caregiver relatives were also invited to focus group meetings. By doing so, the EAN emphasises shared decision-making as an increasingly important concept that underscores patient autonomy and promotes the individualisation of diagnosis and therapy. "It increases the reliability and relevance of the guideline for clinical practice," said Prof. Köpke.

He also noted that it was time and resource intensive to include 'consumers' in the guideline process, but also highly rewarding. "Patients and caregivers really helped us to formulate the guideline in a way that was in line with actual practice and their own needs. We were able to see clearly which of our ideas met with approval or rejection." Free comments, 569 in total, raised new aspects as well as sensitive issues that had been left out of the first draft.

A Spanish study – unrelated to the guidelines – showed that the burden of MS can also be high for caregivers [3]. The Spanish study surveyed 72 caregivers among a sample group of 201 patients with MS. "23.6% of carers had a high level of strain, according to the Caregiver Strain Index," explained first author Dr Maurino (Roche Pharmaceuticals, Spain). "The index has demonstrated its worth, proving itself to be a feasible method of determining the burden placed on family caregivers."

Slowly-evolving lesions in secondary progressive MS

Slowly evolving lesions (SELs) on MRI were recently detected and characterised in longitudinal trials of PPMS [4]. This lesion type is characterised by microglial activation and slow expansion of a pre-existing plaque. According to British scientists, SELs may also be found in SPMS [5]. These lesions, also known as 'smouldering lesions', are promising biomarkers of chronic plaque evolution in PMS, given their more destructive signature on magnetisation transfer ratio (MTR). MTR highly correlates with demyelination and axonal loss within MS lesions.

The British group included 79 SPMS patients from the MS-SMART trial, who underwent brain proton density-weighted/T2, FLAIR,

and MTR scans at week 0, 24, and 96. A total of 4,756 lesions were screened. Manually delineated lesions showing Jacobian expansion were selected as 'candidate SELs' (n=1,140), out of which 140 final SELs (2.9%) were chosen.

Baseline MTR within SEL was lower compared to the non-SELs and non-candidates (24.51, 26.26, and 28.89, respectively; P<0.001). MTR decrease between baseline and week 96 within SELs was significantly greater compared to non-SELs (P=0.02) and to non-candidates (P=0.01). The relationship between SELs and clinical disability needs to be established in future studies.

New insights in progressive MS

More recent advances in understanding the complex pathogenesis of PMS, identifying biomarkers, and refining clinical trial design were highlighted in a plenary symposium the EAN Congress. PMS may be more modifiable than previously assumed, with ocrelizumab as the first drug to have been approved for PPMS in early 2018.

Prof. Stadelmann (University of Göttingen Medical Center, Germany), discussing pathological concepts in PMS, explained that there is ongoing (pathologically detectible) inflammatory and demyelinating disease activity in PMS. The previously mentioned smouldering lesions become more abundant. Molecular pathways leading to neuroaxonal dysfunction and loss are not yet well understood.

Prof. Stadelmann argued that synaptic loss in PMS patients sometimes occurs irrespective of demyelination and may therefore also be present in non-demyelinated areas. Remyelination may occur in this disease stage, but it is observed in only about 20% of PMS patients. Even in late-stage lesions, there is evidence of remyelination. "What we do not know is how efficient this is." Thus, it is also hard to say if remyelination correlates with the disease course.

Targeting the peripheral activation of pathogenetic T-cells and B-cells or preventing their CNS penetration has had modest and contradictory effects on progression in PMS. However, ocrelizumab has shown to be effective in PPMS [6] and siponimod in SPMS [7]. Subgroup analyses suggested that the effect is larger in younger and more active patients.

Treatments and outcome measures in progressive MS

Prof. Sastre-Garriga (University Hospital Vall d'Hebron, Spain) suggested that, unlike in relapsing-remitting MS (RRMS), brain volume may not be a good response marker in PPMS. There is a need for new MRI markers to monitor PPMS and SPMS in clinical trials. Candidates for inclusion in future MRI protocols are grey matter and thalamic atrophy.

"It is challenging to define responders in PMS," Prof. Derfuss (University Hospital Basel, Switzerland) observed. "Expanded Disability Status Scale (EDSS) is not considered sensitive enough as outcome measure. We need more sophisticated outcome measures to capture the subtle disease progression. It also takes longer before you can evaluate the effect." The window of opportunity to treat PMS seems to be early in the disease course, when there is still inflammatory activity. "Siponimod, for example, seemed mostly effective in PMS patients who still had clinical or MRI inflammatory disease activity in the years before."

Prof. Derfuss stated we should consider other CNS cell types as primary targets of therapeutics in PMS, for example antigen-presenting cells such as microglia and astrocytes. Studies evaluating biotin, high-dose simvastatin, ion channel blockers, and clemastine are ongoing and seem to hold some promise. Blocking ion channels may reduce thinning of retinal nerve fibre layer, which could serve as surrogate marker in PMS trials. Moreover, there may be a role in the treatment of PMS for mesenchymal stem cell transplantation; a phase 1b study is in progress.

Long-term efficacy and safety of ocrelizumab

A large amount of long-term efficacy and safety data were presented at the EAN; the large majority of which was reassuring. Ocrelizumab significantly delayed time to wheelchair-confinement (EDSS ≥7.0) in the ORATORIO trial, including the extended controlled period: 30 (6.2%) of 488 ocrelizumab and 24 (9.8%) of 244 placebo patients reached this milestone (HR=0.54, P=0.022) [8]. The observed benefit with ocrelizumab potentially translates to a meaningful long-term benefit for PPMS patients.

In the open-label extension (OLE) of the pooled OPERA trials, RRMS patients switching from interferon-β-1a to ocrelizumab experienced a consistent and robust reduction in annualised relapse rate (ARR), which was maintained through the OLE [9]. The benefits of ocrelizumab on ARR, confirmed disability progression and confirmed disability improvement as seen in the 2-year double-blind trial, were maintained after 2 years in the OLE. The updated safety profile in the ocrelizumab MS all-exposure population (RRMS and PPMS patients) was generally consistent with the controlled-treatment period for the RRMS and PPMS populations [10].

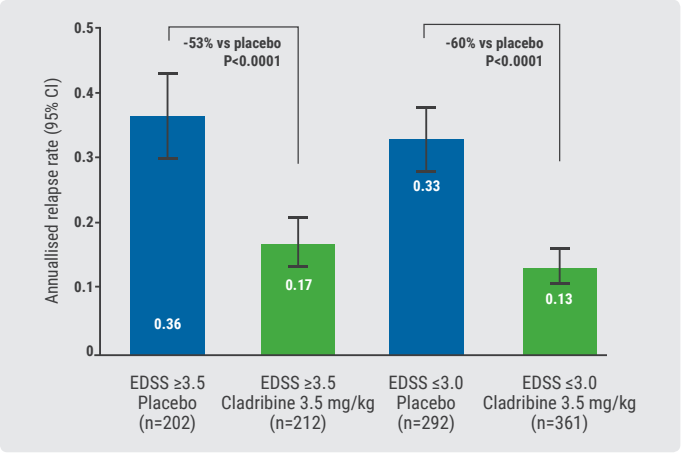
Other efficacy and safety updates in short

- No meaningful difference was observed in the ARR between EDSS subgroups of patients with RRMS who were treated with cladribine tablets [11]. Cladribine reduced relapse rate by 60% and 53% for EDSS subgroups ≤3.0 and ≥3.5,

respectively (Figure 1). This outcome supports the concept that cladribine tablets 3.5 mg/kg are also effective for RRMS patients with higher EDSS and increased risk of conversion to SPMS with relapses. Analysis of malignancy rates in a cohort that included patients with up to 8 years of follow-up confirmed that cladribine was not associated with an increased rate of malignancies vs other disease-modifying drugs [12].

- In paediatric-onset MS, fingolimod significantly reduced MRI activity and slowed brain volume loss for up to 2 years vs interferon-β-1a [13]. Fingolimod significantly reduced the annualised rate of new/newly enlarging T2 lesions (52.6%; P<0.001), number of gadolinium-positive T1 lesions per scan (66.0%; P<0.001), annualised rate of brain volume change (−0.48% vs −0.80%, P=0.014), annualised rate of number of new T1-hypointense lesions (62.8%; P<0.001), T2 lesion volume (per cent change from baseline: 18.4% vs 32.4%, P<0.001), and combined unique active lesions per scan (60.7%; P<0.001).
- Extended interval dosing of natalizumab is associated with a statistically significant, clinically meaningful lower risk of progressive multifocal leukoencephalopathy in JCV antibody-positive patients compared with standard interval dosing [14]. This was concluded from sensitivity and post-hoc analyses from the TOUCH registry in the US. Extended interval dosing's benefit-risk could not be evaluated.
- Both newly diagnosed and non-newly diagnosed patients treated with continuous peginterferon-β-1a every 2 weeks exhibited sustained yearly NEDA (i.e. no evidence of disease activity) rates over 4 years [15]. NEDA achievement in the first 2 years predicted positive long-term clinical outcomes.
- In a pooled analysis of phase 3 studies, long-term treatment with teriflunomide 14 mg was not associated with high-grade lymphopenia, while low-grade lymphopenia was uncommon [16]. Infection rates were similar in patients with or without lymphopenia, consistent with an immunomodulatory mechanism of action of teriflunomide that has limited impact on protective immunity.

Figure 1 Mean annualised relapse rates at 96 weeks [11]



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Epilepsy

The new classification of seizure types by the International League Against Epilepsy (ILAE) was extensively discussed at the EAN 2018 meeting. Seizures are divided into those of focal, generalised, and unknown onset, with subcategories of motor or non motor, and with retained or impaired awareness for focal seizures. The guiding principle of the task force was advice from Albert Einstein to "make things as simple as possible, but no simpler." Among the epilepsy research that was presented were two late-breaking abstracts, one on the long-term efficacy and safety of everolimus in tuberous sclerosis complex (TSC), the other on aggressive refractory status epilepticus (RSE) treatment after cardiac arrest.

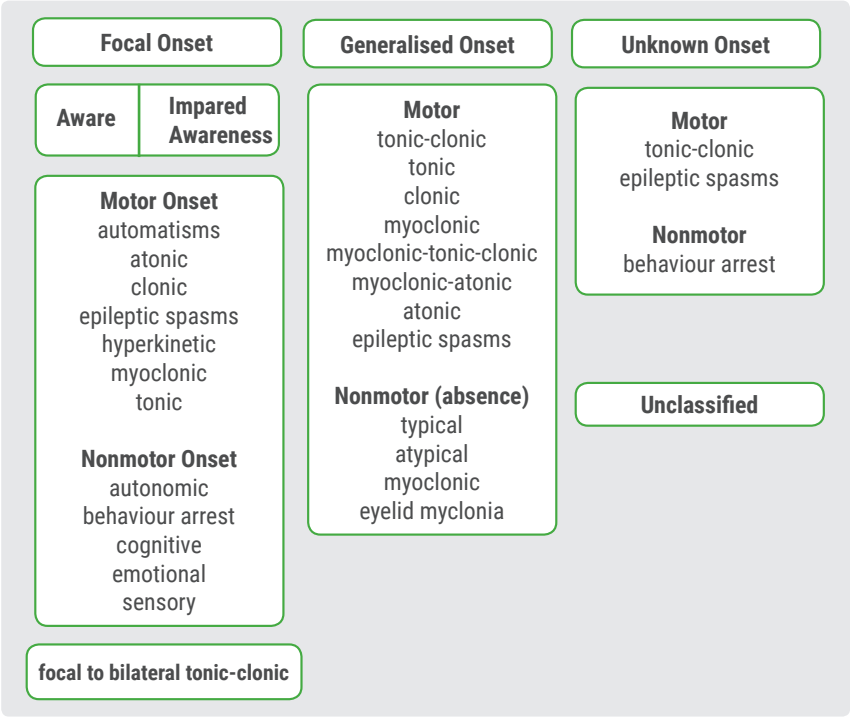
New classification of seizure types

In 2017, the ILAE presented a revised operational classification of seizure types [1]. Dr von Oertzen (St George's University of London, UK) explained the motivations for the focus group to do the revision: "We wanted to recognise that some seizure types, like spasms, can have a focal or a generalised onset. We also wanted to include some missing seizure types, as well as difficult to classify seizures with an unclear onset. Another problem was that retrospective seizure descriptions often do not specify a level of consciousness. We wanted more clarity on nomenclature." The new classification does not represent a fundamental change but allows greater flexibility and transparency in naming seizure types, also meant to enhance communication with non-experts and patients. As Dr von Oertzen put it: "We wanted words to mean what they say." Examples of expressions that have been avoided altogether are 'simple partial seizure' and 'complex partial seizure', as well as 'convulsion'. The classification is operational and not based on fundamental mechanisms. The task force chose not to develop a classification based solely on observed behaviour; instead, the 2017 classification is interpretive, allowing the use of additional data to classify seizure types.

Changes in the ILAE classification include the following (see also Figure 2):

- 'partial' becomes 'focal';
- awareness is used as a classifier of focal seizures;
- the terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalised are eliminated;
- new focal seizure types include automatisms, behaviour arrest, hyperkinetic, autonomic, cognitive, and emotional;
- atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be of either focal or generalised onset;
- focal to bilateral tonic–clonic seizure replaces secondarily generalised seizure;
- new generalised seizure types are absence with eyelid myoclonia, myoclonic absence, myoclonic–atonic, myoclonic–tonic–clonic;
- seizures of unknown onset may have features that can still be classified.

Figure 2 The expanded ILAE 2017 operational classification of seizure types [1]



Aggressive refractory status epilepticus treatment after cardiac arrest

After cardiac arrest, aggressive and prolonged treatment of non-periodic refractory status epilepticus RSE is justified in a substantial proportion of patients. Discontinuous or unreactive EEG background activity, and periodic discharges indicate a much worse prognosis than RSE after cardiac arrest.

This was concluded from a prospective cohort study of 166 consecutive patients with cardiac arrest in coma, the results of which were presented as a late-breaking abstract [2]. There were 36 participants (21.7%) with non-periodic RSE. They were treated with a standardised aggressive protocol with antiepileptic drugs and anaesthetics as long as multi-modal prognostic indicators were not unfavourable. Outcomes were compared to patients with other EEG patterns (benign; generalised periodic discharges; malignant non-epileptiform). Primary outcomes were survival and cerebral performance category at 6 months. RSE started a median of 3 days after cardiac arrest and lasted a median of 4.7 days. A benign EEG pattern was recorded in 76 patients (45.8%), a generalised periodic pattern in 13 patients (7.8%), and a malignant non-epileptiform EEG pattern in 41 patients (24.7%). The four EEG patterns were highly associated to different prognostic indicators (low flow time, clinical motor seizures, N20 responses, non-refractory status epilepticus, neuroimaging). Survival and good neurological outcome (cerebral performance category 1 or 2) at 6 months were:

- 72.4% and 71.1% for benign EEG pattern;
- 54.3% and 44.4% for non-periodic RSE;
- 15.4% and 0% for generalised periodic discharges;
- 2.4% and 0% for malignant non-epileptiform EEG pattern.

Long-term efficacy and safety of everolimus in tuberous sclerosis complex

Long-term exposure to everolimus achieved sustained reductions in TSC-associated treatment-refractory seizures over time in the phase 3 EXIST-3 study, with a tolerable safety profile. These results were also presented as a late-breaking abstract [3].

Patients completing the extension phase of the EXIST-3 trial continued receiving everolimus in the post-extension phase (PEP). Efficacy endpoints included response rate, defined as ≥50% reduction in average weekly seizure frequency from baseline, and median per cent reduction in seizure frequency until end of extension phase.

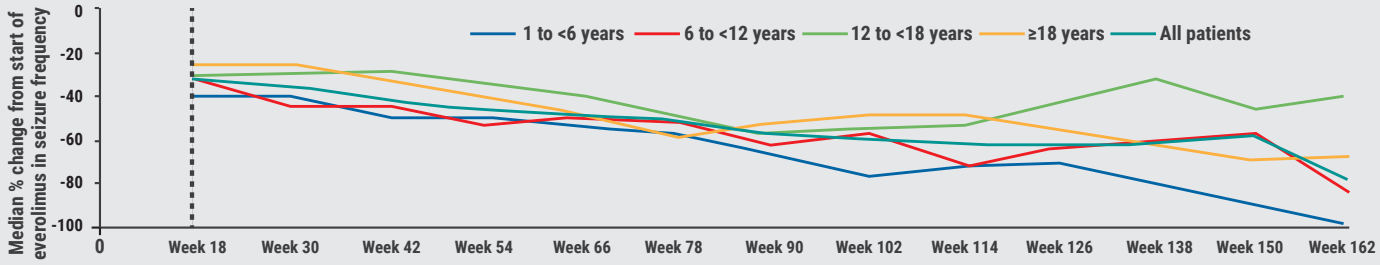
Of 361 everolimus-treated patients from the core phase, 343 (95%) entered the extension and 249 (69%) the PEP. Median duration of everolimus exposure was 30.4 months. Efficacy persisted over time with slightly greater effects in younger patients (Figure 3). Among 244 patients evaluated in the PEP, 18.9% were seizure-free since their last visit; 64.8% had stable or improved seizure status for the first 3 months of the PEP. This trend continued in subsequent 3-month intervals:

- 18.2% and 64.5% from 3-6 months;
- 17.1% and 70.1% from 6-9 months;
- 20.0% and 61.8% from 9-12 months.

Most common adverse events (>30%) were pyrexia, stomatitis, and diarrhoea; incidence decreased over time. Four deaths occurred during the study, due to sudden unexplained death in epilepsy (n=2), pneumonia (n=1), and septic shock (n=1).

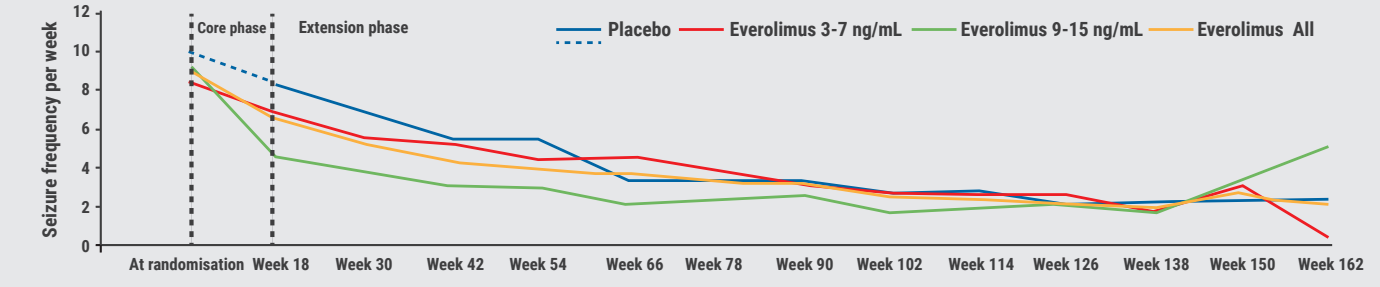
Figure 3 Efficacy of everolimus on treatment-refractory seizure frequency [3]

A Median percentage reduction in seizure frequency from the start of everolimus in overall population and by age category



Number of patients													
1 to <6 years	99	96	93	88	84	72	60	48	34	29	16	7	2
6 to <12 years	104	98	97	91	87	78	69	61	52	40	28	12	4
12 to <18 years	84	79	75	70	67	61	58	50	39	32	23	16	8
≥18 years	65	62	55	50	44	41	35	32	24	20	12	6	1
All patients	351	334	319	298	281	251	221	190	148	120	79	41	15

B Seizure frequency by 12-week interval from randomisation and by treatment group



Number of patients													
Placebo	114	114	114	109	105	100	92	83	70	57	40	32	20	8
Everolimus 3-7ng/mL	114	114	109	102	94	91	85	75	68	58	44	31	16	8
Everolimus 9-15 ng/mL	125	125	119	115	110	102	96	82	71	59	49	35	19	9
Everolimus All	353	353	342	326	309	293	273	240	209	172	133	98	55	25

After week 18, patients in the placebo arm transitioned to receive everolimus (solid line)

Epilepsy from a genetic standpoint

Recent advances in genetic techniques have led to the discovery of an increasing amount of epilepsy genes. As Dr Weckhuysen (University of Antwerp, Belgium) explained, most progress has been made in the field of severe childhood epilepsies, but several gene findings have also proven a role of genetics in the etiology of focal epilepsy syndromes with later onset age. Identifying a genetic cause has several important consequences: it will reduce the need for further (sometimes invasive) diagnostic testing, and guide counselling about prognosis and recurrence risk. Most importantly however, for a selection of genetic epilepsies, establishing a genetic diagnosis also has important treatment implications. An increasing amount of case reports and small cohort studies report on the benefits of selected treatments in specific genetic epilepsies.

Two faces of amyloid-β pathology

An Italian study has contributed new insights into the relationship between amyloid-β (Aβ) and late-onset epilepsy [4]. The results highlight a high prevalence of Aβ pathology among patients with late-onset epilepsy of unknown origin (LOEU), exposing them to higher risk of Alzheimer's disease (AD). The authors therefore think LOEU patients should be screened for cognitive impairment to avoid late diagnosis. From the fact that half of LOEU patients with pathological $A\beta_{1-42}$ experienced no cognitive decline, they conferred that Aβ may support epileptogenesis without impacting on cognition. This would point to a form of epilepsy that is Aβ-mediated.

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Parkinson's Disease and Other Movement Disorders

Deep brain stimulation (DBS) is often regarded as the second therapeutic breakthrough after L-Dopa in the history of Parkinson's disease (PD) therapies. But what impact does it have on the long-term course of the disease? That is one of the many questions regarding PD that were addressed at the EAN meeting. Also, screening for dysautonomia and blood glucose dysregulation in PD patients with moderate to advanced disease was advocated. And dementia may be predicted relatively simple in early PD.

Being a 'morning person' associated with Parkinson's disease risk

Being a 'morning person', a phenotype driven by the circadian clock, is associated with a higher risk of PD [1]. This is the outcome of a study that aimed to explore a causal relationship between chronotype (the behavioural manifestation of circadian rhythm) and risk of PD.

The researchers used Mendelian randomisation (MR), which involves the use of genetic variants to explore causal effects of exposures on outcomes (in other words, where genetic variation is a surrogate marker for the risk factor). Two-sample MR was undertaken using publicly available GWAS data. Associations between genetic instrumental variables and 'morning person' (one extreme of chronotype) consisted of the per-allele odds ratio of being a morning person for 15 independent variants. Being a morning person was found to be causally linked with the risk of PD (OR 1.27; 95% CI: 1.06-1.51; P=0.012).

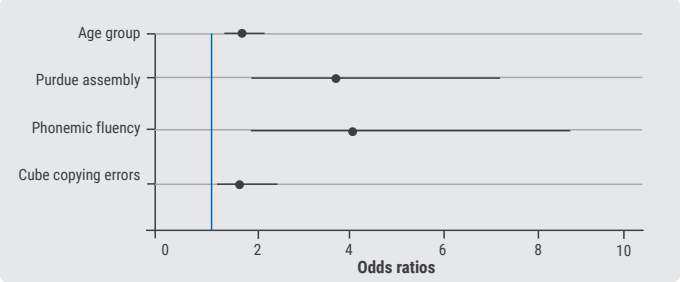
Predicting early dementia in Parkinson's disease patients

Poor performance on three simple clinical tests performed early in PD can be used to predict early dementia [2]. These tests include the Purdue assembly task, phonemic fluency, and cube copying, according to British scientists.

A total of 488 PD patients assessed within 3.5 years of diagnosis were recruited between 2010-2015 (the Discovery cohort) and then re-assessed after 18 months. The Montreal cognitive assessment (MoCA) was used to assess cognition, using a score of <23 for screen-defined dementia. A broad spectrum of other motor and non-motor symptoms were also assessed. Of the 488 included PD patients 61 developed new dementia at 18-month follow-up. Independent predictors of dementia were: older age at diagnosis with poor performance on phonemic fluency, cube copying, and the Purdue assembly task (Figure 4). The area

under the ROC curve for this model was estimated at 0.81 (95% CI: 0.74-0.89). According to the authors, these findings have implications for both clinical practice, designing clinical trials, and targeting novel treatments.

Figure 4 Odds ratios of model for factors predicting dementia, with their 95% confidence intervals [2]



Age at diagnosis was analysed as a 5-level ordinal variable, cube copying errors was analysed as a 3-level ordinal variable, and both phonemic fluency and Purdue assembly were analysed as dichotomous variables (poor performers <20th centile).

Glucose control is impaired in advanced Parkinson's disease

Glucose control is impaired in advanced nondiabetic PD patients [3]. "Dysglycemia appears to be a novel non-motor consequence of PD, which could be related to impaired adaptive insulin secretion due to dysautonomia", commented Dr Marques (University of Clermont Auvergne, France).

Dr Marques and her group aimed to detect changes in glucose regulation in PD patients compared to healthy controls in response to oral glucose intake. They compared blood glucose and insulin kinetics during a 75 g oral glucose tolerance test of 50 PD patients and 50 matched healthy controls.

Blood glucose was significantly higher after 90 (P=0.04) and 150 minutes (P=0.01) in PD patients compared to controls, as well as the total area under time curve for blood glucose. However, insulin levels were not significantly increased in PD patients. Higher blood glucose levels were associated with higher BMI (P<0.001), female gender (P<0.033), longer duration of PD (P=0.001), lower dose of dopaminergic treatment (P=0.023), and higher score of dysautonomia (P=0.017). "Dysautonomia and blood glucose dysregulation should be screened in PD patients with moderate to advanced disease in clinical practice, to help prevent the metabolic syndrome, and to prevent diabetes", said Dr Marques. "This is important because diabetes in PD is associated with a more aggressive phenotype." She added that insulin-releasing drugs may be preferable to insulin-sensitizer drugs in diabetic PD patients. Overall, the connection between PD and higher glucose levels is an extremely interesting area, but the precise underlying molecular mechanisms are still elusive and will require further research.

Different pathogenesis in Parkinson's disease with hypotension

"PD with dysautonomia perhaps does not belong in the group of PD patients, but should rather form a new group", said Dr Donadio (University of Bologna, Italy). His group studied phosphorylated α-synuclein (p-syn) deposits in skin nerves and clinical characteristics in PD patients with orthostatic hypotension (PD+OH) vs PD patients without dysautonomia (PD-OH), to clarify the peripheral nerves involvement in these two conditions [4].

The results showed a wide involvement of p-syn deposits in autonomic cholinergic and adrenergic skin nerves and higher incidence of REM sleep behaviour disorder in PD+OH compared to PD-OH. PD-OH showed a lower load of skin p-syn, which was mainly restricted to adrenergic fibres of skin vessels persisting at follow-up, despite worsening of motor performances. A slight increase of skin p-syn deposition was found over time, but still lower than PD+OH. Dr Donadio: "These data suggest PD+OH and PD-OH have a different pathogenesis and may help to identify a specific diagnostic trait for PD+OH patients."

Effects of deep brain stimulation on long-term Parkinson's disease course

Treatment with chronic subthalamic DBS was associated with longer intervals to recurrent falls and onset of psychotic symptoms [5]. There was no evidence for beneficial effects of DBS on the long-term evolution of dementia, need for nursing-home placement, or overall survival. These were the main results of a study evaluating the impact of DBS on the long-term natural history of PD in a controlled manner.

A centre in Innsbruck (Austria) collected retrospective information on key disease milestones (recurrent falls, psychosis, dementia, and nursing-home placement) and death of PD patients treated with chronic subthalamic DBS >10 years (1999–2007). A control group of PD patients was extracted from a registry study (EuroPa). A total of 54 patients with DBS and 54 patients without DBS at baseline were included. Compared to patients without DBS, patients treated with DBS were at lower risk of recurrent falls (HR=0.6; P=0.035) and of psychosis (HR=0.4; P=0.031). There was no significant difference in risk for dementia (HR=1.2, P=0.67), nursing-home placement (HR=0.6; P=0.26), or death (HR=1.1; P=0.73).

Peripheral tactile vibration as new Parkinson's disease treatment option

Preliminary data confirm that a non-invasive intervention, peripheral vibrotactile stimulation, results in less slowing and decrement in amplitude of a repetitive hand movement, and less tremor compared to baseline in PD patients [6].

British scientists assessed motor performance in a group of 16 right-handed PD patients (ON medication; 10 out of 16 were also tested OFF medication) using the 9-hole peg test and 3 drawing tasks. Each task was repeated 3 times and under 3 conditions: with no external stimulus; and when a vibratory stimulus was applied to the dominant wrist at a frequency of 200 Hz, with either a 20 or 60 bpm modulating frequency. Application of a 200 Hz vibratory stimulus with 60 bpm during trials resulted in a significant improvement in motor performance compared to application of 20 bpm ($P<0.05$) and in absence of vibration. There was no significant difference in motor performance following no vibration and 20 bpm during trials ($P>0.5$).

Other movement disorders

- Ocular motor examination can be used as a robust marker of disease progression in progressive supranuclear palsy (PSP), scientists from München (Germany) reported [7]. Variability between patients was found to be considerable. Prospective clinical and equipment-based quantification of ocular motor markers in well-characterised cohorts of PSP patients is needed.
- In a randomised, double-blind, placebo-controlled trial, deferiprone led to marked reduction of iron accumulation in the brain and showed a trend towards slowing clinical progression in pantothenate kinase-associated neurodegeneration [8]. An open-label extension trial will provide additional data on 36 months of deferiprone treatment.
- Different morphology patterns were found in two variants of functional (psychogenic) dystonia (FD) [9]. Fixed FD was related to a global white matter disconnection affecting main sensorimotor and emotional control circuits. 'Mobile' FD had alterations in grey matter structures important for sensorimotor processing, emotional, and cognitive control.

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Alzheimer's Disease and Other Dementias

Biomarkers, early diagnosis and prevention of Alzheimer's disease (AD) and other dementias have become the main focus of dementia research. In a proposed 'research framework', the diagnosis of AD is purely based on biomarker positivity, meaning symptoms do no longer define the disease. The main goal is to diagnose AD in a preclinical stage, so when drugs to prevent AD finally arrive, biomarker tests can indicate the right patients for treatment.

Is Alzheimer's disease getting a 'lab diagnosis'?

He was quick to point out his phrasing was "slightly provocative", but Prof. Schmidt (Medical University of Graz, Austria) did address an important issue in diagnosing AD: to what extent can biomarkers replace clinical diagnosis? At a plenary session on dementia, Prof. Schmidt argued AD research has focused on revisions of diagnostic criteria in the past decade. The main goal is to diagnose AD earlier, incorporate the entire clinical spectrum of the disease including atypical forms, and to prove that a pathophysiological process of AD creates the basis of symptomatology. Assessment of AD biomarkers is considered instrumental for diagnosis making.

In an update of the 2011 criteria of the National Institute on Aging and Alzheimer's Association (NIA-AA) AD diagnosis is purely based on biomarker positivity, irrespective of clinical symptoms (hence the phrasing 'lab diagnosis') [1]. Three general groups of biomarkers, based on the nature of the pathologic process that each measures are recognised (labelled ATN): Aβ deposition, pathologic tau, and neurodegeneration (see Table 1). The update was labelled a 'research framework' because its intended use is for observational and interventional research, not routine clinical care.

Table 1 ATN biomarker grouping [1]

(A)	Aggregated Aβ or associated pathologic state CSF $A\beta_{1-42}$, or $A\beta_{1-42}/A\beta_{1-40}$ ratio Amyloid PET
(T)	Aggregated tau (neurofibrillary tangles) or associated pathologic state CSF phosphorylated tau Tau PET
(N)	Neurodegeneration or neuronal injury Anatomic MRI FDG PET CSF total tau

Prof. Schmidt explained the update of the 2011 NIA-AA criteria was a result of:

- the evolving understanding of what biomarkers tell us;
- the acceptance that imaging and CSF biomarkers are valid proxies for AD pathology/pathophysiology;
- an increasing recognition of frequent mismatches between clinical diagnosis and AD pathology: AD can exist without symptoms (problem of sensitivity), while the classic clinical phenotype is too often not AD pathology (problem of specificity).

The new criteria have their advantages and shortcomings, argued Prof. Schmidt. As the authors said themselves: "We envision that defining AD as a biological construct will enable a more accurate characterisation and understanding of the sequence of events that lead to cognitive impairment that is associated with AD, as well as the multifactorial aetiology of dementia. This approach also will enable a more precise approach to interventional trials where specific pathways can be targeted in the disease process and in the appropriate people." However, even if they are only research criteria numerous questions remain, according to Prof. Schmidt. For example:

- Is evidence of biomarkers enough to define AD?
- Will interventional research be inclined to treat the proteinopathy alone but not the clinical syndrome?
- Can asymptomatic subjects who may never convert be treated with potentially harmful substances?

Prevention and treatment of vascular dementia

Preventive measures and treatment of vascular cognitive impairment (VCI) and vascular dementia (VaD) have had very limited results in controlled studies so far, argued Dr Ferro (University of Lisbon, Portugal). VCI and VaD are second to AD pathology as a cause of cognitive decline and associated dependency. A major risk factor for VCI is stroke. The risk to develop VCI/VaD after stroke depends on factors like stroke severity, early life IQ, and cognitive reserve.

Evidence of treatments is of moderate or low quality; the effect on an individual level is very limited at best for all of the following interventions:

- General management: treatment of comorbidities and complications, depression, and other psychiatric disturbances.
- Symptomatic pharmacologic treatment: galantamine, donepezil, rivastigmine, memantine, actovegin.
- Cognitive training/rehabilitation.
- Brain stimulation (low evidence).
- Acupuncture (low evidence).

For the prevention of VCI/VaD very few factors and interventions are associated with any effect:

- Lifestyle factors, vascular risk factors, multidomain interventions are associated with only very modest effects at the individual level.
- Stroke and stroke recurrence prevention is important.
- Anti-hypertensives: 9 randomised controlled trials (RCT), only 2 positive.
- Statins, antidiabetics, aspirin, and vitamins: no evidence of any preventive effect.

Dr Ferro stressed that physical activity may help prevent progression to cognitive impairment. Results of the LADIS study showed that in older people with white matter changes, physical activity was associated with a reduced risk of VaD (HR 0.42) and improved executive function and processing speed [2]. This was independent of age, education, white matter change severity, medial temporal atrophy, previous and incident stroke, and diabetes.

Frontotemporal dementia

In his talk on frontotemporal dementia (FTD) Dr Schott (University College London, UK) said the behavioural variant (bvFTD) is the most common. Core clinical features are socially inappropriate behaviour; impulsive, rash, or careless actions; early apathy and inertia; early loss of sympathy or empathy; early perseverative, stereotyped, or compulsive/ritualistic behaviour; hyperorality and dietary changes; executive deficits, relative sparing of memory/visuospatial functions. Dr Schott gave some clinical tips:

- Beware of new psychiatric disease in late middle life.
- A normal mini–mental state examination (MMSE) result does not exclude bvFTD.
- There can be overlap with primary progressive aphasia syndromes and 'frontal AD'.
- Take a careful family history exam, not only including dementia, but also ALS and atypical parkinsonism. Always look for ALS motor signs.

Progressive non-fluent aphasia is characterised by effortful speech and repetition, with difficulties retrieving words and with phonetic/phonological and grammatical errors. It may be associated with orofacial apraxia, dysphagia, fasciculations (overlap with motor neuron disease), and parkinsonism. Behavioural features and intellectual decline are seen relatively late. On MRI, subtle frontotemporal widening may be visible. Dr Schott: "The patient is worse than the scan indicates."

Semantic dementia is a disorder of semantic memory, with severe word retrieval difficulties and impaired vocabulary. Grammar and syntax are preserved; there is fluent, effortless 'empty' speech. Behavioural disturbance often occurs relatively early. In this case, the scan is worse than the patient.

Logopenic progressive aphasia is characterised by slow, hesitant speech and aphasia.

Dr Schott presented the following suggestions for the management of FTD:

- Management must be supportive, especially for carers.
- Safety issues must be addressed: driving, job, risk assessment.
- Consider acetyl-cholinesterase-inhibitor in case of AD, and sometimes neuroleptics.
- For behavioural modification, jigsaw and other puzzles may be helpful.
- Support groups (www.raredementiasupport.org/ftd)
- Information source: www.ftdtalk.org.
- Monitor for ALS, parkinsonism, dysphagia.
- Planning of the future is important, including end of life.
- Some patients (especially genetic cases) may be good candidates for treatment trials (http://genfi.org.uk).

Lewy body dementia

Dementia with Lewy bodies and PD dementia together are referred to as Lewy body dementias (DLB). Patients not only suffer from dementia but also face other challenging symptoms, such as hallucinations, parkinsonism, autonomic dysfunction, and sleep disorders. As Dr Lemstra (VUmc Amsterdam, the Netherlands) pointed out, these patients require more care than other patients with dementia; they are generally more depressed and have a lower quality of life. The impact on caregivers is also considerable. According to the recently revised recommendations of the DLB Consortium on diagnosis and management [3], core clinical DLB features are:

- visual hallucinations;
- fluctuating cognition;
- parkinsonism;
- REM sleep behaviour disorder, which may precede cognitive decline.

Indicative biomarkers are:

- reduced dopamine transporter uptake;
- reduced metaiodobenzylguanidine (MIBG) myocardial scintigraphy;
- polysomnographic confirmation of REM sleep without atonia.

New diagnostic biomarkers are proteomics, CSF α-synuclein, real-time quaking-induced conversion – which Dr Lemstra called "promising" in determining the level of α-synuclein –, skin biopsy, and perhaps α-synuclein PET scanning. Dr Lemstra said early diagnosis is crucial, but there are "issues": the clinical and pathological overlap with AD, the absence of direct biomarkers, and the diagnostic (in)accuracy of criteria and tests.

There is no disease-modifying therapy. For cognition Dr Lemstra suggested cholinesterase-inhibitors; for hallucinations rivastigmide, antipsychotics ("no haloperidol") or low-dose clozapine; for parkinsonism levodopa ("start low, go slow"); for REM sleep behaviour disorder clonazepam, melatonin; and for depression/anxiety SSRI's, mirtazapine. A general piece of advice: "Stop anticholinergic medication."

Physical activity as a moderator of Alzheimer's disease pathology

A systematic review of observational studies found no association between a physically active lifestyle and less detrimental AD-related biomarkers [4]. The number of studies was limited however, thus hampering a conclusion.

The Danish scientists included observational studies of physical activity (PA) or physical fitness (PF) in healthy subjects, patients with mild cognitive impairment and patients with AD, with AD biomarkers as outcome measures (Aβ, total tau, phosphorylated tau in CSF; 18F-FDG PET, amyloid PET, hippocampal atrophy on MRI). Of 55,114 screened studies, 50 were included. A total of 9 studies reported results on amyloid PET, 5 on CSF, 4 on 18F-FDG PET and 32 on hippocampal volume. Of these, 3 studies were longitudinal. Also, 12 studies reported a significant association between hippocampal volume and either PA or PF, 2 studies reported a significant association between total tau and phosphorylated tau and PF/PA and 1 study between Aβ and PF/PA, whereas 2 studies found an association between amyloid tracer uptake and PF/PA. Finally, 2 studies reported increased metabolism in parietal and temporal areas correlated with PF/PA.

More highlights

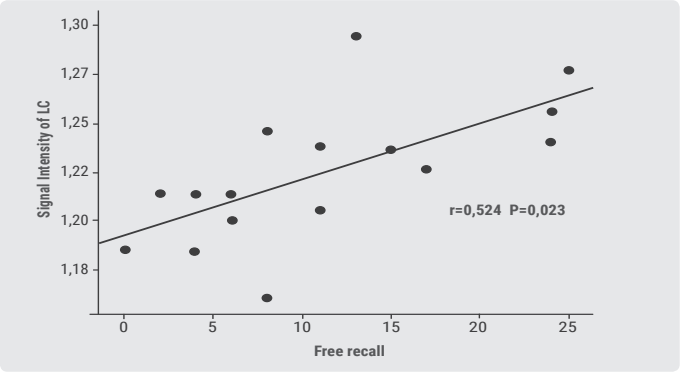
- In prodromal AD (mild cognitive impairment), neuropsychiatric symptoms are related to cognitive, functional, and biological biomarkers. Neuropsychiatric Inventory caregiver-burden emerged as an independent predictor of progression to dementia [5].
- Burden of white matter hyperintensities (WMH) seems to have an impact on AD progression only when present in large amounts [6]. There was no significant difference between WMH burden and progression status in either AD without or with cardiovascular disease (Table 2). However, there was a trend for a higher WMH burden in progressed vs stable patients diagnosed with AD with cardiovascular disease.

Table 2 Burden of white matter hyperintensities (WMH) and progression in AD without and with cardiovascular disease (CVD) [6]

	AD without CVD	AD with CVD
n	139	31
Progressed: n, (WMH mean)	85 (4.33 ml)	16 (23.02 ml)
Stable: n, (WMH mean)	54 (6.69 ml)	15 (14.82 ml)
P-Value, WMH-burden (Stable vs Progressed)	P=0.122	P=0.159

- Does the retina provide a 'window to look into the brain'? Retinal atrophy seems to be related with evolution-time of AD [7]. The amnesic variants showed a greater atrophy compared to visual forms of the disease, especially in the outer plexiform layer. Atrophy in this region correlated with CSF biomarkers of neurodegeneration.
- There is a clear decrease of locus coeruleus signal in typical and atypical AD, independently of clinical presentation [8]. A positive correlation with episodic memory scores was found (Figure 5), suggesting locus coeruleus may play a crucial role in maintaining cognitive function, probably via the norepinephrine system. Innovative therapeutic approaches targeting the noradrenergic system might therefore benefit AD patients.
- Metformin use is associated with prolonged survival in DM patients with dementia, while insulin was associated with an increased risk of heart failure [9]. Patients using insulin could benefit from more frequent check-ups regarding hypoglycaemia and cardiovascular status.

Figure 5 Correlation between locus coeruleus signal intensity and verbal episodic memory test (free recall) in typical AD patients [8]



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Migraine

The 2018 EAN meeting featured a total of 47 original presentations on headache and migraine, often presented by young researchers. "It makes me confident that this field has a promising future," said Dr Martins (University of Lisbon, Portugal). Many presentations on this burdensome condition focused on calcitonin gene-related peptide (CGRP) (receptor) inhibitors, which hold great promise in preventing migraine. The novel serotonin-1F receptor lasmiditan registered positive results in the treatment of acute migraine.

Migraine's high costs in a broad sense

Migraine generates a significant burden for patients and an economic loss for society. French researchers drew this conclusion from their study of the socio-economic impact of severe migraine in patients with at least 8 days of headaches per month [1]. These patients are affected in their professional lives but also in their social lives and personal budgets.

Of 7,720 survey participants, forming a representative sample of the general population, migraine prevalence with at least 8 days of headaches per month in patients was 3.8% (68% of them were women). "Their average age was 41 years, when people are at the peak of their careers, and have families to provide for", observed lead author Dr Leiba (Novartis, France). 63% of workers reported an impact of migraine on their work, especially on their efficiency. Absenteeism at work was estimated at 33 days a year on average, with an annual loss of 3.8 billion euros for society. More than three-quarters of patients had sleep disorders and benefited less from their free time. For 14% of patients, a relative had to adjust his working time during migraine headaches. 58% of patients needed to purchase non-reimbursed medicines for migraine (average monthly cost 32 euros) and 43% other therapies (average monthly cost 52 euros).

Erenumab in a difficult-to-treat population

Results from the phase 3b LIBERTY study confirm efficacy and safety of erenumab as preventive treatment for migraine in a difficult-to-treat population who previously failed on 2–4 prior preventive migraine treatments [2].

In this 12-week, double-blind trial, 246 patients were randomised to erenumab 140 mg or placebo. The primary endpoint was proportion of patients achieving ≥50% reduction from baseline in monthly migraine days (MMDs) during weeks 9–12. At baseline, the mean MMDs were 9.3. At week

12, the proportion of patients reaching the primary endpoint was higher in the erenumab 140 mg group vs placebo (30.3% vs 13.7; P=0.002). With erenumab 140 mg, there were also greater reductions in MMDs (mean difference: −1.61; P=0.004) as well as in monthly acute migraine-specific medication days (mean difference: −1.73; P<0.001). Safety and tolerability of erenumab were comparable to placebo; no patients in the erenumab group discontinued due to adverse events.

A subgroup analysis of the STRIVE study assessed the efficacy of erenumab in episodic migraine patients with and without self-reported aura [3]. Of 955 patients randomised, 52% had a history of aura. Erenumab induced greater reductions in MMDs in both subgroups.

Galcanezumab in patients who failed prior preventives

Galcanezumab (GMB) 120 mg/240 mg is efficacious compared with placebo in reducing MMDs in both patients who failed and did not fail ≥2 prior preventive treatments. This was the conclusion of a subgroup analysis of three phase 3 studies of GMB (EVOLVE-1, EVOLVE-2, and REGAIN), assessing possible differential treatment effects in patients who had failed ≥2 previous preventives vs who had not [4].

In both subgroups, GMB 120 mg/240 mg significantly improved overall mean reduction of MMDs vs placebo (P<0.001) in all 3 studies (Table 3). Significant treatment-by-subgroup interactions were seen for GMB 240 mg (EVOLVE studies) and GMB 120 mg (REGAIN study), suggesting better efficacy vs placebo for these doses in patients who failed prior preventives. Mean percentage of GMB-treated patients with ≥50% response was significantly higher vs placebo for both subgroups. Treatment-by-subgroup interactions may be driven by lower placebo response in patients who failed preventives previously, as the magnitude of change for GMB-treated patients was similar in both subgroups.

Table 3 Overall change from baseline in number of MMDs in patients with migraine who failed ≥2 previous preventives and who did not [4]

		Placebo	GMB 120mg	GMB 240mg
EVOLVE Studies (Intergrated set)	Failed ≥2 previous preventives	n=85 -0.81 (0.61)	n=43 -3.45 (0.73)	n=44 -3.85 (0.77)
	Did not fail ≥2 previous preventives	n=790 -2.68 (0.17)	n=393 -4.61 (0.20)	n=384 -4.36 (0.21)
REGAIN Study	Failed ≥2 previous preventives	n=161 -1.44 (0.62)	n=66 -5.91 (0.79)	n=96 -3.30 (0.71)
	Did not fail ≥2 previous preventives	n=377 -3.69 (0.43)	n=207 -4.82 (0.48)	n=178 -5.77 (0.53)

Results are least square mean change from baseline (standard error) from integrated analysis of EVOLVE-1 and EVOLVE-2 studies, and from REGAIN study.

A novel serotonin-1F receptor agonist

Next to all CGRP inhibitors, a novel serotonin-1F receptor agonist drew some attention as well. In the double-blind, phase-3 study SPARTAN, significantly more patients using lasmiditan were headache-free after 2 hours vs placebo [5]. Safety was consistent with a previous lasmiditan trial, with dizziness reported as the most frequent treatment-emergent adverse event.

Lasmiditan shows specific affinity *in vitro* for the serotonin-1F receptor, however without any vasoconstrictive action. In SPARTAN, patients with a Migraine Disability Assessment Score (MDAS) >11 were randomised 1:1:1:1 to lasmiditan (200 mg, 100 mg, or 50 mg) or placebo. Patients took their first dose within 4 hours of a migraine attack and, if needed, took a randomly assigned second dose. The primary and key secondary endpoints were the proportion of patients who were free from headache pain and free from most bothersome symptom (MBS) 2 hours after the first dose, respectively. MBS were nausea, phonophobia, or photophobia.

The proportion of patients who were headache pain-free and MBS-free at 2 hours post-first dose was significantly less with placebo (21.3%, 33.5%) than with lasmiditan:

- 200 mg (38.8%, 48.7%; both P<0.001)
- 100 mg (31.4%, 44.2%; both P<0.001)
- 50 mg (28.6%, 40.8%; both P<0.01).

The proportion of patients who experienced a treatment-emergent adverse event after the first dose of lasmiditan 200 mg, 100 mg, 50 mg, or placebo were 39.0%, 36.1%, 25.4%, and 11.6%, respectively. Dizziness, paraesthesia, and somnolence were most frequently reported.

Other news

- An area of mismatch between neuronal activation and glucose uptake was found in the visual cortex of migraine patients between attacks [6]. This observation supports the assumption that activity-induced rupture of cerebral metabolic homeostasis may be a cornerstone in migraine pathophysiology.
- Migraine with visual aura was found to be associated with a thicker visual cortex corresponding to visual areas in women [7]. The authors suggest this may be an inherent trait and thus a biomarker, rather than a consequence of repeated aura attacks.
- In an analysis of symptoms precipitating cluster headache attacks, pre- and post-ictal symptoms were found to be very frequent [8]. This indicates that a cluster headache attack is not restricted to the pain-phase alone.

- In a case series of 725 Spanish patients, factors precipitating a migraine attack were identified [9]. The most important ones were stressful life events, mentioned by 238 (32.8%), and weight gain, mentioned by 22 (3%).
- The CaMEO study sought to identify natural subgroups of migraine, based on profiles of Comorbidities and Concomitant Conditions (CCCs) [10]. Eight underlying patterns of comorbid health problems among migraine patients were identified. Each class had a distinct CCC pattern, characterised as follows: Class 1, many CCCs; Class 2, respiratory/psychiatric; Class 3, respiratory/pain; Class 4, respiratory; Class 5, psychiatric; Class 6, cardiovascular; Class 7, pain; and Class 8, few CCCs. The distribution of individuals across models was variable, with one-third of respondents in Class 8 and <10% in Class 1.

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Stroke

The field of stroke care is evolving at an impressive pace, with mechanical thrombectomy as a fast-rising star. A new study reveals it may even benefit very old (≥80 years) patients – but how to select them? In the large majority of stroke patients, thrombolysis remains the treatment of choice. Guided by MRI, thrombolysis can be effective in selected patients even when the time of stroke onset is unknown. Also, tenecteplase may be a viable alternative to alteplase in patients with ischaemic stroke and atrial fibrillation. EAN president-elect Prof. Fazekas commented on several very recent stroke studies.

Thrombolysis in stroke with unknown onset

Two recent randomised trials suggesting that the time window for mechanical thrombectomy may be further expanded in selected patients are testimony to the rapid developments in the field of stroke. Results of the DEFUSE 3 and DAWN trials implied the time window might be expanded to up to 16 hours and even up to 24 hours, respectively [1,2]. Also, the WAKE-UP study presented evidence how intravenous thrombolysis can still be effectively used even when the time of stroke onset is not exactly known [3]. Prof. Fazekas, who was co-author of the study, said: "According to European treatment guidelines, intravenous thrombolysis is only a viable option if the treatment is initiated within 4.5 hours of the attack. This means that we have to know when the stroke occurred, which is unfortunately not the case in 14 to 27 per cent of strokes. We now have clues how MRI may identify those patients in whom thrombolysis is beneficial even if we do not know the exact time of stroke onset."

The 503 participants of the WAKE-UP trial had ischaemic MRI lesions while fluid-attenuated inversion recovery (FLAIR) imaging was negative, suggesting that the stroke probably occurred not more than 4.5 hours earlier. They were 1:1 randomised to intravenous alteplase or placebo. A favourable outcome at 90 days was reported in 131 of 246 patients (53.3%) in the alteplase group and in 102 of 244 (41.8%) in the placebo group (adjusted OR 1.61; P=0.02). Functional outcomes were also significantly better in the alteplase group (Table 4).

There were 10 deaths (4.1%) in the alteplase group and 3 (1.2%) in the placebo group (OR 3.38; P=0.07), while the rate of symptomatic intracranial haemorrhage was 2.0% in the alteplase group and 0.4% in the placebo group (OR 4.95; P=0.15). Prof. Fazekas said this did not outweigh the positive effects of thrombolysis.

Other recently published stroke studies

There were various other recently published stroke studies Prof. Fazekas commented on.

- One study highlighted the importance of secondary prevention in reducing the risk of recurrent stroke [4]. It showed the 5-year risk rate of stroke and other vascular events in a selected cohort of patients who had a transient ischaemic attack (TIA) or minor stroke was 6.4% in the first year and 6.4% in the four years thereafter. The study analysed data from 3,847 patients. The primary outcome – a composite of stroke, acute coronary syndrome, or death from cardiovascular causes – occurred in 469 patients.

Table 4 Primary and secondary efficacy outcomes (intention-to-treat population) [3]

Outcome	Alteplase Group (n=254)	Placebo Group (n=249)	Effect Variable	Adjusted value (95% CI)	P-value
Primary efficacy end point					
Favorable outcome at 90 days– no./total no. (%)	131/246 (53.3)	102/244 (41.8)	Odds ratio	1.61 (1.09 to 2.36)	0.02
Secondary efficacy end points					
Median score on modified Rankin scale at 90 days (IQR)	1 (1 to 3)	2 (1 to 3)	Common odds ratio	1.62 (1.17 to 2.23)	0.003
Correlation between treatment response at 90 days and deficit level at baseline – no./total no. (%)	72/246 (29.3)	44/244 (18.0)	Odds ratio	1.88 (1.22 to 2.89)	0.004
Global Outcome Score at 90 days			Odds ratio	1.47 (1.07 to 2.04)	0.02
Median score on Beck depression Inventory at 90 days (IQR)	6.0 (2.0 to 11.0)	7.0 (2.0 to 14.0)	Mean difference (Log_e)	-0.04 (-0.22 to 0.15)	0.69
Total score on EQ-5D at 90 days	1.9±2.1	2.4±2.4	Mean difference	-0.52 (-0.88 to -0.16)	0.004
Score on visual analog scale on EQ-5D at 90 days	72.6±19.7	64.9±23.8	Mean difference	7.64 (3.75 to 11.51)	<0.001
Median infarct volume at 22-36 hr (IQR) – ml	3.0 (0.8 to 17.7)	3.3 (1.1 to 16.6)	Mean difference (Log_e)	-0.16 (-0.47 to 0.15)	0.32

"During the observation period 345 patients had strokes, 196 in the first year alone and 149 in the remaining four years," Prof. Fazekas said. The estimated cumulative rate was 9.5%.

- In patients with minor ischaemic stroke or high-risk TIA, those who received a combination of clopidogrel and aspirin had a lower risk of major ischaemic events at 90 days than those who received aspirin alone. This was the result of a large international study with 4,881 participants [5]. Prof. Fazekas: "The combination therapy was more successful than aspirin alone, but also carried a heightened risk of major bleeding. Nevertheless, in individual cases, use of this dual therapy, which prevents the aggregation of blood platelets, is justified and certainly worthwhile." In the experimental group 5.0% suffered ischaemic stroke, myocardial infarction, or death from an ischaemic vascular event. In the control group this was 6.5% (HR 0.75; P=0.02). Major haemorrhage occurred in 23 patients (0.9%) receiving clopidogrel plus aspirin and in 10 patients (0.4%) receiving aspirin plus placebo (HR 2.32; P=0.02).
- Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke and was associated with a higher risk of bleeding [6]. "This is regrettable, as we urgently need to find ways to prevent these kinds of strokes," commented Prof. Fazekas. A total of 7,213 stroke patients were randomised 1:1 to rivaroxaban 15 mg/day or aspirin 100 mg/day for an average of 11 months. Ischaemic or haemorrhagic stroke or systemic embolism occurred in 172 patients and 160 patients, respectively (HR 1.07; P=0.52). Recurrent ischaemic stroke occurred in 158 and in 156 patients. Major bleeding occurred in 62 and in 23 patients (HR 2.72; P<0.001). Around one fifth of all strokes are caused by embolisms. Prof. Fazekas: "Before initiating any anticoagulation therapy we still need to determine if there really is a cardioembolic source."

Thrombectomy in very old stroke patients

Mechanical thrombectomy is an increasingly important therapy for acute stroke that may also benefit patients ≥80 years, but a careful selection of patients and risk assessment are mandatory. This may be concluded from a Portuguese study, in which 208 patients with acute ischaemic stroke underwent mechanical thrombectomy [7]. First author Dr Lopes de Sousa (Central Lisbon Hospital Centre, Portugal) concluded: "For patients ≥80 years, thrombectomy appears to be riskier than for younger patients. But one third of the patients ≥80 years can be fully functional in their everyday lives after the procedure, so we need to identify the factors associated with favourable outcome."

Patients with a pre-stroke modified Rankin scale ≤2 and anterior circulation acute ischaemic stroke who underwent mechanical thrombectomy were reviewed. Of these participants 134 were <80 years old and 74 were ≥80. Hypertension and previous TIA were more frequent in the very old (P=0.05, and 0.005 respectively). There were no differences between both groups regarding admission NIH Stroke score (16.6 vs 16.2; P=0.65), previous intravenous thrombolysis (63.5% vs 65.7%; P=0.76), revascularisation time (267 vs 254 min; P=0,52) and haemorrhagic transformation (36.5% vs 34.3%; P=0.76). Age ≥80 years was associated with poor (modified Rankin scale >2) 3-month functional outcome compared to younger patients (67.6% vs 46.3%; P<0.01). Of the group ≥80 years, 24 patients (32,4%) were functionally independent at 3 months. No difference in death was observed between the groups (P=0.08). On logistic regression, age (P<0.01) and admission NIH Stroke score (P<0.01) were associated with a poor outcome after 3 months.

Tenecteplase in acute ischaemic stroke and atrial fibrillation

Tenecteplase (TNK) in acute ischaemic stroke in relation to atrial fibrillation was evaluated for the first time in a randomised controlled study. In a post-hoc analysis of the NOR-TEST study efficacy and safety of TNK vs alteplase (tPA) was assessed [8]. There were no major differences in outcome between the two groups, although female patients with atrial fibrillation had more serious strokes and tended to benefit less from TNK.

In NOR-TEST, patients with a suspected ischaemic stroke were randomised to either TNK 0.4 mg/kg or tPA 0.9 mg/kg. In the study population (n=1,100), 183 patients (16.6%) had atrial fibrillation. There were no major differences in outcome between the TNK and tPA group in the subgroup of patients with atrial fibrillation. Male sex, lower age, and NIH Stroke score were associated with better outcomes. Patients with atrial fibrillation were older, had more serious strokes, lower functional outcome, and higher mortality.

Other news

- Endovascular procedures allow the availability of human thrombus material for histopathologic analysis. A pilot study revealed that arterial cerebral thrombi are widely heterogeneous; their composition correlates with the density of the occluded vessel on CT scan [9]. These outcomes support the importance of thrombus composition analysis as a possible future tool for understanding the mechanisms underlying stroke.
- An easy to use 5-point prediction score was validated to predict haemorrhage expansion based on non-contrast CT findings in acute intracerebral haemorrhage [10]. This so-called BAT score can identify subjects at high risk of haemorrhage expansion. It is a tool that requires just a baseline non-contrast CT scan and may help select intracerebral haemorrhage patients for anti-expansion clinical trials.
- In patients with atrial fibrillation, direct oral anticoagulants started a median of 5 days after stroke seem to have a clinical benefit compared to treatment with vitamin-K antagonists, mainly due to a lower risk for intracerebral haemorrhage and mortality [11]. This conclusion was based on individual patient data analysis of 7 prospective studies with 4,912 participants.
- Idarucizumab proved to be a beneficial therapeutic option for patients treated with dabigatran presenting with ischemic stroke or intracranial haemorrhage in daily German stroke centre routine [12]. Outcome was favourable with a median NIH Stroke score improvement of 3.5 points and modified Rankin scale 0-3 in 63%. Overall mortality was low with 6%.

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Neuromuscular Disorders

Two important late-breaking abstracts were presented on the last day of the EAN 2018 meeting, both on neuromuscular disorders. They were truly late-breaking, as the corresponding papers were published online only minutes before in The Lancet Neurology. One study concerned an innovative trial approach in a genetic disease: a RCT of cognitive behavioural therapy in myotonic dystrophy type 1 [1]. The other study was a trial of rasagiline add-on therapy in patients with ALS [2].

Cognitive behavioural therapy in myotonic dystrophy

Cognitive behavioural therapy increased the capacity for activity and social participation in patients with myotonic dystrophy type 1 (DM1) at 10 months. It may therefore be considered in severely fatigued patients with DM1. "Despite differences in healthcare systems, favourable effects can be achieved," commented Prof. Schoser (Ludwig Maximilian University of Munich, Germany), who presented the results of the OPTIMISTIC trial. It was a multicentre, single-blind

RCT at four neuromuscular referral centres with experience in treating DM1 patients. "The design of the trial was very similar to an RCT of a drug," said Prof. Schoser. One of the important take-away messages was that it is feasible to run a large RCT of cognitive behavioural therapy in a rare genetic disease such as DM1. "We succeeded in our aims to create the necessary clinical infrastructure, validate our outcome measures, and improve patients' health status."

The 255 participants were randomly assigned (1:1) to either cognitive behavioural therapy plus standard care and optional graded exercise, or standard care alone. Cognitive behavioural therapy focused on addressing reduced patient initiative, increasing physical activity, optimising social interaction, regulating sleep–wake patterns, coping with pain, and addressing beliefs about fatigue and DM1. This therapy was delivered over a 10-month period in 10–14 sessions. Of 128 patients assigned to cognitive behavioural therapy, 33 (26%) also received the graded exercise module. The primary outcome was the 10-month change from baseline in scores on the DM1-Activ-c scale (score range 0–100). This score increased from a mean of 61.22 points at baseline to 63.92 at month 10 in the cognitive behavioural therapy group (adjusted mean difference 1.53) and decreased from 63.00 to 60.79 in the standard care group (−2.02). The mean difference between groups was 3.27 points (P=0.007). Prof. Schoser: "In the experimental group the result of the 6-minute walking test improved by 26.5 m (8%), which is very supportive of the primary outcome."

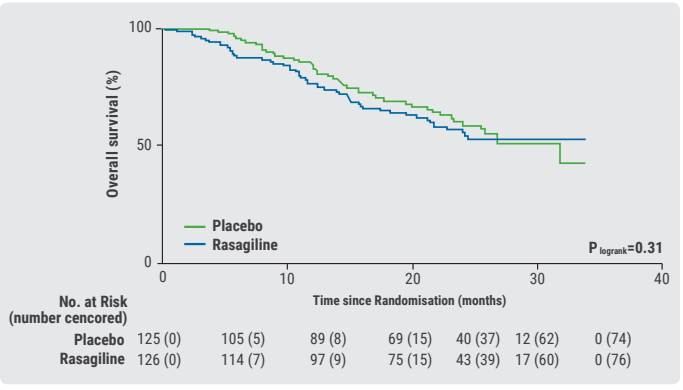
In the cognitive behavioural therapy group, 244 adverse events occurred in 65 (51%) patients, vs 155 in 63 (50%) patients in the standard care alone group. The most common were falls: 155 events in 40 patients (31%) in the cognitive behavioural therapy group and 71 in 33 patients (26%) in the standard care alone group. Serious adverse events did not differ between the two groups.

Rasagiline in ALS

In the other late-breaking trial, rasagiline 1 mg/day was found to be safe in patients with ALS also receiving riluzole. It did not prolong survival, which was the primary outcome of the trial, although a post-hoc analysis suggested that rasagiline may modify disease progression in patients with an initial slope of ALS Functional Rating Scale Revised greater than 0.5 points per month at baseline.

"Rasagiline is a monoamine oxidase B inhibitor, but it is more than that," explained the study's first author Prof. Ludolph (Ulm University, Germany). It has neuroprotective potential in PD and had shown a disease-modifying effect in a mouse model of ALS. The 252 participants of this randomised phase 2 study were randomly assigned to receive rasagiline (n=127) or placebo (n=125) in addition to riluzole (100 mg/day). The survival probability at the end of the study was 0.43 in the rasagiline group and 0.53 in the placebo group (Figure 6). The estimated effect size was 0.91 (P=0.31). Prof. Ludolph: "A post-hoc analysis revealed a positive effect on survival in fast-progressors after 6 months, but not anymore after 18 months." Rasagiline was well tolerated, and most adverse events were due to disease progression rather than treatment. Adverse event frequency was comparable between both groups. The most frequent adverse events in the rasagiline and placebo group were dysphagia (25% vs 19%) and respiratory failure (20% vs 25%). Prof. Ludolph concluded: "We have to consider different treatments in fast and in slow progressors."

Figure 6 Overall survival in the rasagiline and placebo groups [2]



Patisiran in hereditary transthyretin mediated amyloidosis

Patisiran had a favourable impact on overall nutritional status over 18 months in patients with hereditary transthyretin mediated amyloidosis (hATTR) who participated in the phase 3 APOLLO trial [3]. hATTR is a multisystemic, rapidly-progressive, life-threatening disease. Patients often have poor nutritional status and overall weight loss, due in part to severe gastrointestinal manifestations as well as cardiac disease. In the APOLLO study, patisiran 0.3 mg/kg Q3W demonstrated significant improvements in neuropathy and quality of life compared to placebo in hATTR patients with polyneuropathy (n=225) and was generally well tolerated. One of the secondary endpoints was change in modified BMI, defined as the product of BMI and albumin levels. At baseline, mBMI was similar in the patisiran and placebo groups. In the placebo group, mBMI declined by a least square mean of 119.4 kg/m^2 x g/L over 18 months relative to baseline, whereas least square mean decline was only 3.7 with patisiran. Improvement compared to placebo was seen as early as 3 months after starting treatment with patisiran.

More results in short

- In Duchenne muscular dystrophy (DMD), steroid treatment may have a benefit in delaying the time to reach important respiratory and also cardiac milestones [4]. This was concluded from a retrospective, longitudinal, single-centre study including all patients with DMD (n=312) followed up between 2000 and 2017. Mean age at baseline was 6 years. An increase in forced vital capacity was observed up to age 13, followed by relative stability. After the age of 9, forced vital capacity declined on average 6% per year. At age 16, only 5 out of 51 patients on steroids had non-invasive ventilation vs 3 out of 5 steroid-naïve patients.
- In the first ever study to apply Motor Unit Number Index (MUNIX) in FTD, lower MUNIX values were found to be present in bvFTD [5]. This outcome suggests lower motor neuron dysfunction without clinical evidence of ALS in some instances. The study aimed to identify neurophysiologic evidence of lower motor neuron system dysfunction across FTD subtypes.
- RNA-sequencing and bioinformatic analysis of human motor neurons implicate selective roles of SMN/SYNCRIP protein complex and Motif 7 in spinal muscular atrophy (SMA) [6]. This study of complementary pathways disrupted in human SMA is important to identify alternative therapeutic targets besides direct SMN protein increase. The authors claimed their findings represent a crucial step towards the discovery of efficacious therapies for all SMA subtypes.

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