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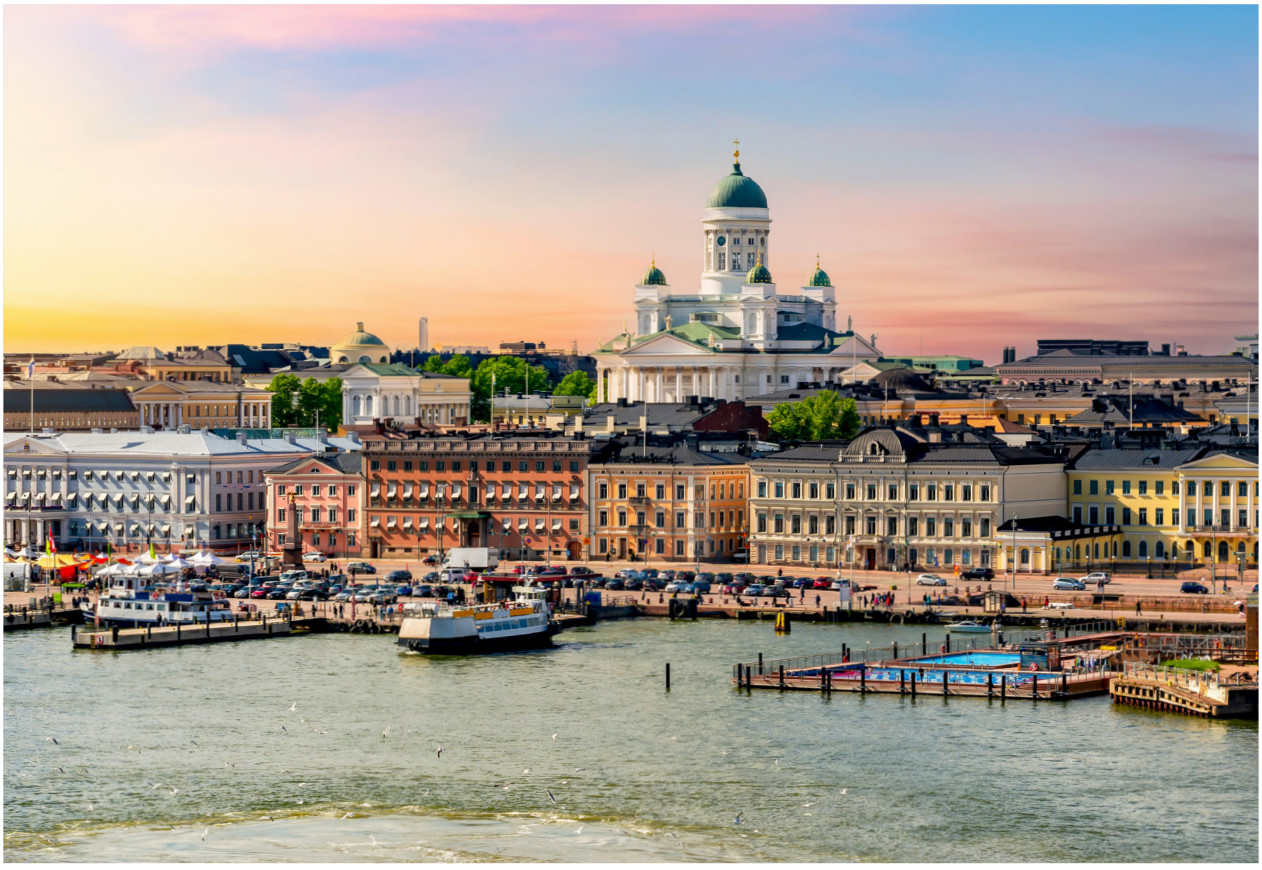
HIGHLIGHTS CONFERENCE REPORT



This Highlights report includes:

- Vagal nerve stimulation for the reduction of cognitive impairment in Alzheimer's disease
- Extended success for N-acetyl-L-leucine in Niemann-Pick disease type C
- Novel tool to predict outcomes in anti-NMDAR encephalitis
- Treatment escalation and de-escalation in late-onset MS
- Therapeutic advancement in spinal muscular atrophy
- High risk for recurrent vascular events in young stroke patients

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Advances in Neurostimulation

Spinal cord stimulation for chronic pain: state-of-affairs in 2024

Spinal cord stimulation (SCS) is an end-of-line treatment option for patients with chronic pain. However, controversies circle this topic, leading to a 'trench war' between neuromodulation practitioners and opponents. Dr Cecile de Vos (Erasmus University Medical Centre, the Netherlands) discussed the current evidence and ongoing developments in the field.

"The clinical evidence on SCS up to 2010 is based on conventional SCS, for paraesthesia, a modality for which blinded randomised-controlled trials were not possible," explained Dr de Vos [1]. Although systematic reviews showed long-term pain relief of SCS for patients with persistent spinal pain syndrome or complex regional pain syndrome [2,3], the 2016 EAN guideline on central neurostimulation therapy in chronic pain conditions only provided a 'weak recommendation' for SCS [4]. "Again, mainly due to the lack of placebo-controlled trials."

In recent years, high-frequency, paraesthesia-free paradigms of SCS have been developed. "This innovation makes it possible to conduct placebo-controlled trials," according to Dr de Vos. Although SCS appears to outperform placebo for pain relief, the studies that were included in a more recent systematic review on this topic have large methodological differences [5]. "The heterogeneity of study designs, the unknown role of the placebo effect, the balance between efficacy and complications, and heavy industry involvement in clinical trials are still controversial elements in the domain of SCS," clarified Dr de Vos. Moreover, SCS is an expensive treatment, with device costs being around $20,000.

Dr de Vos argued that with an average success rate of over 50% in a heavily pre-treated population of patients with neuropathic pain, the efficacy of SCS compares favourably versus pharmaceutical therapies [6]. "Moreover, severe complications are very uncommon [7]."

"We need well-designed, independent, multicentre, placebo-controlled studies, in 1 pain condition, with objective outcome measures, to gain a better understanding of SCS therapy and to develop personalised approaches and treatment guidelines," Dr de Vos concluded.

1. De Vos C, et al. Spinal cord stimulation for the treatment of chronic pain. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.
2. Simpson EL, et al. Health Technol Assess. 2009;13(17):iii,ix-x,1-154.
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4. Cruccu G, et al. Eur J Neurol. 2016;23(10):1489-1499.
5. Duarte RV, et al. Pain. 2020;161:24-35.
6. Finnerup NB, et al. Lancet Neurol. 2015;14(2):162-173.
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Vagal nerve stimulation for the reduction of cognitive impairment in Alzheimer's disease

Auricular vagal nerve stimulation (AVNS) may be an effective therapeutic method to reduce cognitive impairment in patients with mild cognitive impairment (MCI) due to Alzheimer's disease (AD), results of a randomised-controlled trial showed.

Dr Adam Broncel (Neuromedical, Poland) presented a randomised, double-blind study that compared AVNS with placebo in patients with MCI due to AD (n=60) [1]. Participants in the experimental arm received AVNS during their sleep for 6 months. The main outcome of the study was the Alzheimer's Disease Assessment Scale (ADAS)-Cog score change from baseline at week 12.

After 12 weeks of therapy, the authors found a significant benefit of AVNS on ADAS-Cog score as compared with placebo (P<0.0001). Participants in the experimental arm displayed a median improvement of -7.0 points whereas participants in the placebo arm did not have an improvement in their ADAS-Cog score. The changes in Verbal Memory Probing (VMP) score from baseline showed a favourable effect of AVNS as well. "After 26 weeks of treatment, we noticed that the treatment effect of AVNS on the ADAS-Cog score was even larger, with a median improvement of -9.5 points from baseline," Dr Broncel mentioned.

The study showed that AVNS may be an effective method for the treatment of cognitive impairment in patients with MCI due to AD. "Its safety and ease-of-use add to the applicability of AVNS," concluded Dr Broncel.

1. Broncel A, et al. Auricular vagal nerve stimulation in patients with mild cognitive impairment due to Alzheimer's disease. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.

Innovations in VNS and DBS for refractory epilepsy

In recent years, there have been various developments in vagal nerve stimulation (VNS) and deep brain stimulation (DBS) modalities to treat patients with refractory epilepsy. Dr Paul Boon (Ghent University, Belgium) guided the audience through the latest research results.

"Over 30% of patients with epilepsy are drug-resistant despite the development of many new anti-seizure medications," expressed Dr Boon. VNS and anterior nucleus of the thalamus (ANT)-DBS are 2 of the options that may help these refractory patients [1].

Two randomised-controlled trials showed that VNS yields a response rate between 23–31% in patients with refractory epilepsy in the short term, increasing up to 65% after over 5 years of follow-up [2,3]. The side effects of VNS are usually limited. "VNS has positive effects on alertness and mood," added Dr Boon. "On the downside, we do not yet know which patients are most likely to respond to VNS, since there are no responder-identification studies available." In recent years, innovative VNS tools have become available. So-called 'closed loop VNS' can detect ictal tachycardia and automatically deliver additional stimulation, resulting in shorter and fewer seizures, with responder rates up to 70% [4]. "The newest tools can even be pre-programmed automatically, reducing the number of visitations for the patients, increasing the ease-of-use, and taking steps towards personalised VNS," added Dr Boon. Moreover, last year a study was initiated

to assess functional MRI-guided modulation of VNS stimulation parameters [5]. "The preliminary results are promising," according to Dr Boon.

ANT-DBS resulted in a 29% greater seizure reduction compared with the control arm in the SANTE trial. The responder rate increased up to 68% at 5 years of follow-up [6]. The MORE study confirmed these findings [7]. "Patients with unifocal epilepsy and no prior epilepsy surgery appeared to respond better to ANT-DBS," mentioned Dr Boon. "We also saw a signal of depression and memory impairment with this treatment in the short term." Furthermore, correct contact positioning and site experience were predictive of improved outcomes. Combining VNS and ANT-DBS may be a promising option for the population as well, a small study (n=33) suggested [8].

A meta-analysis comparing VNS and ANT-DBS indicated that seizure reduction rates are higher with DBS than with VNS after 1 year (58% vs 33%), a difference that was mostly undone after 3 years (64% vs 54%) [9]. A head-to-head comparison of VNS and DBS is however unavailable and unlikely to be conducted in the near future. Finally, VNS is the less expensive option, reducing the cost by approximately 50% as compared with DBS [10].

"Several novel neurostimulation modalities are emerging, improving the situation for the many patients with drug-resistant epilepsy," Dr Boon ended on a positive note.

1. Boon PAJM, et al. Vagal nerve and deep brain stimulation for the treatment of refractory epilepsy. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.
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8. Parisi V, et al. Neurosurgery. 2021;89(4):686-694.
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10. Vincent T, et al. J Med Econ. 2022;25(1):1218-1230.

Genetic and Molecular Therapies

Extended success for N-acetyl-L-leucine in Niemann-Pick disease type C

The 12-month data from the IB1001-301 study revealed a marked reduction in disease progression with N-acetyl-L-leucine (NALL) compared with placebo in patients with Niemann-Pick disease type C. NALL was efficacious irrespective of background miglustat treatment and well-tolerated in the study population.

"NALL is a chemically modified amino acid which induces the normalisation of mitochondrial function with knock-on effects, including normalisation of lysosomal function, inter-ion cellular signalling, and dampening neuroinflammation," explained Dr Tatiana Bremova-Ertl (University Hospital Bern, Switzerland).

The phase 3 IB1001-301 study (NCT05163288) randomised 60 patients with Niemann-Pick disease type C to 12 weeks of therapy with NALL or a placebo, after which participants crossed over to the other arm to receive another 12 weeks of therapy. Participants could enter the extension phase of the trial after the randomised period had ended. The primary and secondary efficacy endpoints were met at 12 and 24 weeks and the agent was well-tolerated [1]. Dr Bremova-Ertl presented the findings after 12 months of follow-up in the extension period [2].

At month 12, the Niemann-Pick type C Clinical Severity Scale (NPCCSS) was slightly improved in participants receiving NALL (-0.12) whereas a historical cohort showed that the scores of patients not receiving NALL worsened over this period (+1.50). "This difference corresponds to a 108% reduction in annual disease progression," noted Dr Bremova-Ertl. Moreover, NALL was efficacious, regardless of miglustat background therapy. Finally, the improvement in the Scale for Assessment and Rating of Ataxia (SARA) score that was found after the randomised period (mean change from baseline -1.97) was maintained during the extension phase of the study (mean change from baseline -1.92).

"Based on the positive findings from IB1001-301, the extension phase is open to recruiting new patients with Niemann-Pick disease type C to further evaluate NALL," Dr Bremova-Ertl concluded.

1. Bremova-Ertl T, et al. N Engl J Med 2024;390:421-431.
2. Bremova-Ertl T, et al. Long-term findings of N-acetyl-L-leucine for Niemann-Pick disease type C. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.

Therapeutic advancement in spinal muscular atrophy

Recent advances in therapeutic approaches for spinal muscular atrophy (SMA) were highlighted by Prof. Sabrina Sacconi (Nice University Hospital, France). The focus was on genetic underpinnings, current therapies, and future perspectives for this debilitating neuromuscular disorder.

SMA pathology is predominantly due to a deletion in exon 7 of the *SMN1* gene, seen in 95% of cases. The SMN protein plays a critical role in several cellular processes, including ribonucleoprotein assembly, RNA transport, protein translation, endocytosis, autophagy, and mitochondrial homeostasis.

Three main current therapeutic strategies were discussed by Prof. Sacconi [1]. Nusinersen is an antisense oligonucleotide therapy that enhances the inclusion of exon 7 in the nearly identical paralogue paralogue *SMN2* mRNA , leading to increased production of functional SMN isoform. Clinical trials, including the ENDEAR and NURTURE studies, have shown significant motor function improvements and increased survival rates in infants treated early

[2,3]. Risdiplam, an oral *SMN2* splicing modifier, has demonstrated efficacy in increasing SMN protein levels systemically, including within the central nervous system. Clinical trials such as FIREFISH (NCT02913482) and SUNFISH (NCT02908685) indicate sustained improvements in motor milestones and functional outcomes in both pre-symptomatic and symptomatic patients [4,5]. Gene therapy with onasemnogene abeparvovec uses an adeno-associated virus (AAV) to deliver a functional copy of the *SMN* gene, dramatically altering the disease trajectory. Onasemnogene abeparvovec has been shown to improve survival and motor function in *SMA1* patients; 15 out of 15 trial participants were event-free at 13.6 months [6].

Prof. Sacconi underscored the need for early intervention, highlighting the benefits of newborn screening programs globally. Future directions include improving drug delivery systems, optimising dosing, and developing combination therapies to address multiple aspects of SMA pathology. Ongoing trials like DEVOTE (NCT04089566) and MANATEE (NCT05115110) are exploring higher doses and combination regimens to enhance therapeutic outcomes.

"We are entering a new age of molecularly targeted therapies for inherited diseases of nerve and muscle," said Prof. Sacconi. Continued research and development are essential to further refine these therapies and expand their accessibility. Comprehensive newborn screening and personalised medicine approaches remain critical components for early and effective intervention in SMA.

1. Sacconi S. From gene to RNA therapies: New treatment horizons for genetic neuromuscular disorders. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.
2. Finkel RS, et al. N Engl J Med 2017 Nov 2;377(18):1723-1732.
3. De Vivo DC, et al. Neuromuscul Disord. 2019 Nov;29(11):842-856.
4. Darras BT, et al. N Engl J Med 2021 Jul 29;385(5):427-435.
5. Mercuri E, et al. Lancet Neurol. 2022 Jan;21(1):42-52.
6. Strauss KA, et al. Nat Med. 2022 Jul;28(7):1390-1397.

Therapeutic advancement in Pompe disease

Prof. Antonio Toscano (University of Messina, Italy) gave a comprehensive overview of recent advances in therapies for hereditary myopathies, focusing on Pompe disease. The presentation included a detailed analysis of multiple clinical trials, highlighting the efficacy and safety of enzyme replacement therapies (ERT) and novel therapeutic approaches [1].

There has been a rapid evolution of therapies for hereditary myopathies, with new molecular approaches offering promising advances. Antisense oligonucleotides and ERT have already radically changed diseases such as Duchenne muscular dystrophy (DMD) and Pompe disease. Additionally, RNA toxicity reduction strategies in myotonic dystrophy type 1 and facioscapulohumeral muscular dystrophy are emerging as potential therapies.

A historical randomised study involving 90 patients with late-onset Pompe disease evaluated the impact of biweekly intravenous alglucosidase alfa (20 mg/kg) over 78 weeks [2]. Results showed significant improvements in the 6-minute walk test and stabilisation of forced vital capacity (FVC). The study concluded that alglucosidase alfa improves walking distance and maintains pulmonary function over 18 months.

More recently, the COMET trial compared the 'next-generation ERT' avalglucosidase alfa with alglucosidase alfa in 100 treatment-naïve late-onset Pompe disease (LOPD) patients [3]. The primary outcome was the change in FVC% from baseline to week 49. Avalglucosidase alfa demonstrated clinically meaningful improvements in respiratory function and ambulation, proving non-inferior to alglucosidase alfa with no safety concerns reported.

Further analysis from the COMET trial revealed sustained clinical outcomes for patients on avalglucosidase alfa, with FVC% stabilisation over 145 weeks [4]. Disease-specific and general patient-reported outcomes indicated significant improvements in daily activities, disease symptoms, respiratory function, and mobility. These long-term results have led to a new EPOC consensus paper on the use of ERT for LOPD [5].

In parallel with COMET, the PROPEL trial assessed cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in LOPD patients [6]. Despite not achieving statistical superiority in improving the 6MWT distance, cipaglucosidase alfa plus miglustat showed potential for long-term efficacy and safety, warranting further investigation.

Prof. Toscano also presented a study on safety and patient satisfaction of home-based intravenous ERT for Pompe disease and mucopolysaccharidosis type I during the COVID-19 pandemic [7]. The findings support home therapy as a viable alternative, maintaining treatment compliance and safety.

To conclude, Prof. Toscano summarised the promising developments and ongoing challenges in the treatment of myopathies. He underscored the importance of personalised and long-term treatment strategies. There is still a need for reliable biomarkers to monitor disease progression and therapeutic efficacy in clinical trials.

1. Toscano A. The landscape of new treatments in hereditary myopathies. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.
2. van der Ploeg AT, et al. N Engl J Med 2010 Apr 15;362(15):1396-406.
3. Diaz-Manera J, et al. Lancet Neurol. 2021 Dec;20(12):1012-1026.
4. Kishnani PS, et al. JAMA Neurol. 2023 Jun 1;80(6):558-567.
5. Schoser B, et al. Eur J Neurol. 2024 Jun 14:e16383.
6. Schoser B, et al. Lancet Neurol. 2021 Dec;20(12):1027-1037.
7. Toscano A, et al. Orphanet J Rare Dis. 2023 Oct 27;18(1):338.

Neurological Risk Factors and Predictive Tools

Under investigation: Opioid use and the risk for dementia

The use of opioids is associated with an increased risk for dementia, but only from a certain intake quantity, results from a Danish observational study showed. The more opioids an individual uses, the higher the risk for dementia. The investigators emphasised that these findings need to be validated through causative research.

Dr Nelsan Pourhadi (Copenhagen University Hospital Rigshospitalet, Denmark) and colleagues investigated data from 1,872,854 individuals between 60–75 years of age in the year 2000, or turning 60 between 2000 and 2020, to assess the link between opioid use and the risk for dementia [1]. Individuals with cancer, established dementia, or previous opioid use or addiction were not included in the study.

In total, 93,638 cases of all-cause dementia were identified. Incidence-density-matching per sex and age was conducted using 468,190 controls. The investigators applied a total standardised dose (TSD) to compare the quantity of opioids that was taken by an individual. One TSD was equivalent to 30 mg of oral morphine per day. Also, the authors used a default 5-year lag time window between the last opioid intake and the diagnosis of dementia to reduce reverse causation bias.

"There was an association between opioid use and dementia," said Dr Pourhadi. "But this association only appeared to exist if a patient had used 90 TSDs or more." For individuals between 60–75 years of age who had used between 31–90 TSDs, the incidence rate ratio (IRR) was 1.06 (95% CI 0.99–1.13). In the same age category, the IRRs for individuals who had used between 91–200 TSDs, between 201–500 TSDs, and over 500 TSDs were 1.28 (95% CI 1.16–1.41), 1.44 (95% CI 1.28–1.62), and 1.58 (95% CI 1.43–1.75), respectively. This trend was consistent across age categories, except for the 90+ category, in which the authors did not find an association between opioid use and the risk for dementia. Furthermore, the effect was consistent irrespective of 'weak' or 'strong' opioid use but appeared to be less pronounced in the chronic-pain subgroup of patients.

"Following these findings, it would be interesting to investigate the link between opioid use and dementia in dementia subtypes and to examine the potential causality of the observed associations," Dr Pourhadi concluded.

1. Pourhadi N, et al. Opioids and the risk of dementia. Late-breaking session 1, 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.

Novel tool to predict outcomes in anti-NMDAR encephalitis

An internationally validated, easy-to-use tool (NEOS2) can predict which patients with anti-NMDAR encephalitis will improve on first-line therapy at diagnosis.

Anti-NMDA Receptor (anti-NMDAR) encephalitis is the most common autoimmune encephalitis characterised by complex neuropsychiatric features and the presence of Immunoglobulin G antibodies against the NR1 subunit of the NMDA receptors in the central nervous system, and early diagnosis and treatment can be beneficial for the final outcome [1]. "With the NEOS score, we can adequately predict the outcome of patients with anti-NMDAR encephalitis 1 month after treatment," said Dr Juliette Brenner (Erasmus University Medical Centre, the Netherlands). It would be better if physicians could predict the outcome of first-line therapy for these patients at the time of diagnosis. "Then we would know which patients would benefit from first-line therapy and which patients need to receive more aggressive therapies," explained Dr Brenner. The research team developed the NEOS2 score to overcome these issues [2].

The NEOS2 tool was developed in a cohort of 712 patients with anti-NMDAR encephalitis from 5 countries. The original NEOS model included a 'need for ICU admission', MRI abnormalities, CSF leukocyte count >20 cells/µL, a treatment delay >4 weeks, and a lack of response to first-line therapy as independent variables. By adding age and the interaction effect between treatment delay and the number of leukocytes to the model and omitting the effect of first-line therapy, the NEOS2 score yielded the same accuracy for predicting the 1-year outcome as the original NEOS score. Furthermore, the new model successfully predicted response to first-line therapy and which patients would return to school or work after 3 years. Because of the omission of first-line therapy effect as a variable, the NEOS2 score can already be used at diagnosis.

1. Dalmau J, et al. Lancet Neurol. 2008 Dec;7(12):1091-8.
2. Brenner J, et al. Predicting outcome and improvement after first-line treatment of anti-NMDAR encephalitis at diagnosis: the NEOS2 scores. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.

Diagnostics and Disease Management in Neurology

What is the value of transcranial ultrasound for diagnosing Parkinson's disease?

Transcranial ultrasound may be a valuable tool for the diagnosis of Parkinson's disease (PD) in patients with parkinsonism, possibly sparing the use of expensive imaging techniques. Prospective studies with longer follow-up and head-to-head studies comparing transcranial ultrasound with other diagnostic modalities are needed to further assess its value.

"Although MRI, PET, and scintigraphy are useful instruments for diagnostic purposes, there is a need for a complementary, more available, and cost-effective method to differentiate between PD, atypical parkinsonism (AP), and essential tremor (ET)," explained Dr Markus Stiehm (Skåne University Hospital, Sweden). The current retrospective study aimed to evaluate the diagnostic value of a substantia nigra-positive finding through transcranial ultrasound in patients with newly diagnosed parkinsonism [1].

The study included 72 patients with suspected parkinsonism who were referred for transcranial ultrasound. The findings from the initial test were compared with the final diagnosis after a long-term follow-up; the mean follow-up duration was 95.6 months. Dr Stiehm added that all final diagnoses were reviewed by an experienced neurologist and that nuclear imaging results could be analysed for this purpose.

The observed sensitivity of transcranial ultrasound for diagnosing PD versus non-PD appeared to be limited, at 73.21%. However, the specificity (87.50%) and positive predictive value (95.35%) were promising. "Transcranial ultrasound does not appear to be suitable as a single first-line diagnostic tool, due to the limited sensitivity," argued Dr Stiehm. "It can however be regarded as a non-invasive, cost-effective, complementary diagnostic method, potentially sparing the use of expensive nuclear imaging techniques in some patients." Large prospective studies with longer follow-up time are needed to gain further insights into the usefulness and reproducibility of transcranial ultrasound.

1. Stiehm M, et al. The diagnostic value of transcranial ultrasound in Swedish Parkinsonism patients: a retrospective cohort study including a long follow-up period. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.

How to achieve goal-concordant care in severe acute brain injury?

Discussing prognostic estimates and goals of care may improve the alignment of medical decisions with the patient's wishes, a Swiss study among patients with severe acute brain injury (SABI) indicated.

"Patients with SABI lack decisional capacity," said Dr Nawfel Ben-Hamouda (Lausanne University Hospital, Switzerland). "So how can we go about the shared decision-making process?" Dr Ben-Hamouda explained that 'goal-concordant care' is to understand a patient's individual goals and values and to align medical treatment decisions with these goals. The current study compared the alignment between the patient's wishes and the level of care that was received, by analysing the patient's medical documentation, the perspective of the patient's surrogates/family members, and the perspective of the clinicians [1]. The included patients with SABI (n=110) were followed for 6 months.

Surrogates appeared to be more inclined than clinicians to think that the patient would want to receive life-prolonging care by certain measures, excluding resuscitation, whereas doctors and nurse clinicians were more inclined to think that the patient would want to receive life-prolonging care by all medically indicated measures, displaying a first discordance between perspectives. Furthermore, clinical caretakers were more frequently unsure about the goals of the patient than the family members. Finally, the study showed that 46% of the family members' decisions were influenced by prognostic scores, suggesting that prognostic scores may be valuable tools to improve goal-concordant care.

1. Behaghel G, et al. Prognostic scoring and goal-concordant care after severe acute brain injury: a mixed-method study. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.

Changing treatment landscape in myasthenia gravis

Conventional immunosuppressants are widely used to treat patients with myasthenia gravis (MG) but come with many side effects and a delayed onset of action. Novel therapies have been arriving and may improve the situation for this patient population. Prof. Kristl Claeys (University Hospital Leuven, Belgium) discussed the current treatment landscape.

"Ineffectiveness, a delayed onset of action, and serious side effects are problems we encounter with conventional therapies for MG," said Prof. Claeys. Fortunately, novel therapies are arriving, including complement C5 inhibitors, neonatal Fc receptor inhibitors, B-cell inhibitors, plasma cell inhibitors, and various cytokines and chemokines. Prof. Claeys mainly focussed on complement C5 inhibitors and neonatal Fc receptor inhibitors [1].

The neonatal Fc receptor inhibitor efgartigimod was tested among 167 patients with generalised MG in the phase 3 ADAPT trial [2]. The included participants were randomised 1:1 to receive efgartigimod

as add-on therapy or to a placebo, for 26 weeks. A significantly larger proportion of participants on efgartigimod achieved an MG-ADL response (44/65 vs 19/64; P<0.0001). Efgartigimod had a favourable safety profile and displayed superior efficacy to placebo on other endpoints as well; results that led to the EMA approval of this agent for patients with generalised MG. "Next to efgartigimod, rozanolixizumab is an approved neonatal Fc receptor inhibitor for the MG population, and nipocalimab and batoclimab are still under investigation," added Prof. Claeys.

Regarding complement C5 inhibitors, the phase 3 REGAIN trial compared eculizumab with a placebo in 125 patients with generalised MG [3]. The randomisation occurred in a 1:1 fashion and lasted for 26 weeks. "Although the primary endpoint of 'MG-ADL change from baseline at week 26' was not met, the results were good, and EMA approval was provided," said Prof. Claeys. "Also, few adverse events were seen with this agent." Ravulizumab and zilucoplan are other EMA-approved complement C5 inhibitors for the treatment of patients with generalised MG and pozelimab, cemdisiran, and gefurulimab are all being tested in phase 3 trials.

"The new biological therapies work faster, more selective, target-specific, and come with an acceptable safety profile," summarised Prof. Claeys. "Nonetheless, there are many issues to be resolved, such as deciding which position these therapies take in the treatment cascade, collecting evidence on long-term efficacy and safety, and determining the value of these therapies during myasthenic crises."

1. Claeys K, et al. Advances of treatments in myasthenia gravis. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.
2. Howard JF, et al. Lancet Neurol. 2021;20:526-536.
3. Howard JF, et al. Lancet Neurol. 2017;16(12):976-986.

Stroke and Vascular Events

High risk for recurrent vascular events in young stroke patients

The recurrence of vascular events is a considerable risk for young patients who survived an ischaemic stroke or transient ischaemic attack (TIA), results from a multicentre study indicated. The aetiology often remains the same from the first to the recurrent event.

Dr Jenna Broman (University of Helsinki, Finland) and colleagues investigated the rate of recurrent strokes, vascular events, cancer, death, and associated factors among patients who experienced an ischaemic stroke or TIA. From the 5,023 patients aged 18 to 55 who experienced an acute cerebrovascular event and were recruited for a previous study [1], 396 patients were evaluated after approximately 10 years of follow-up [2].

In total, 22.5% had experienced a recurrent vascular event, of which 15.7% were cerebrovascular events and 8.6% were classified as 'other vascular events'. Next, 6.8% of the patients had died (n=27), most frequently due to a vascular event (n=12) or because of cancer (n=7).

Atrial fibrillation at baseline was an independent risk factor for recurrent vascular events in the long term (adjusted HR 3.24; 95% CI 1.26–8.37). Dr Broman also shared that patients often retained the same cause for the recurrent vascular event as the one that was determined for the first event.

"Further studies are needed to investigate whether detailed individual risk assessment and more rigorous secondary preventive strategies and patient adherence can reduce the risk of recurrent vascular events," reasoned Dr Broman.

1. Rolfs A, et al. Stroke. 2013;44(2):340-349.
2. Broman J, et al. Long-term risk of recurrent vascular events and mortality in young stroke patients: insights from a multicenter study. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.

Anticoagulation or antiplatelet as secondary prevention for cancer-related strokes?

There was no clear difference between the use of anticoagulation or antiplatelet agents relating to the secondary prevention of cancer-related strokes, in a Swiss observational study. However, findings from a subgroup analysis suggested that patients with embolic stroke of undetermined source (ESUS) and venous thromboembolism (VTE) exclusion may benefit more from anticoagulation therapy.

"Cancer-related stroke is characterised by multi-territory infarction, specific laboratory findings, the absence of the SVS-sign, high stroke recurrence rates, and a lack of evidence for secondary prevention strategies," outlined Dr Moritz Kielkopf (University of Bern, Switzerland). The current study aimed to compare the outcomes of anticoagulation versus antiplatelet therapy in a real-world population of patients with cancer-related stroke (n=135) [1]. The main study outcome was the overall mortality within 1 year after the stroke. "Of the 135 included patients, 43% was on anticoagulation and 57% received antiplatelet therapy at time of discharge," added Dr Kielkopf.

Patients in the anticoagulation group were generally younger (69 vs 75 years; P=0.01), had more multi-territory brain infarcts (47% vs 17%; P<0.001), more frequently had ESUS (83% vs 49%; P<0.001), were more likely to have metastatic disease (72% vs 41%), and had higher D-dimer levels (median 8,536 µg/L vs 1,010 µg/L). The uncorrected comparison between these two groups of patients showed that patients on anticoagulation had a higher 1-year mortality rate than those on antiplatelet therapy (66% vs 33%; log-rank P<0.001). The adjusted analysis did not reveal a difference in 1-year mortality for anticoagulation versus antiplatelet

therapy (adjusted HR 0.76; 95% CI 0.36–1.63; P=0.47). However, there was a trend towards a benefit of anticoagulation over antiplatelet therapy concerning mortality among patients with ESUS and VTE exclusion (adjusted HR 0.38; 95% CI 0.14–1.05; P=0.06).

In conclusion, there was no clear superiority of anticoagulation over antiplatelet treatment as a secondary prevention therapy for cancer-related strokes. "Large-scale clinical trials are needed to further unravel this topic and to create evidence-based guidelines," Dr Kielkopf decided.

1. Kielkopf M, et al. Anticoagulant versus antiplatelet treatment for secondary stroke prevention in patients with active cancer. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.

Multiple Sclerosis

Treatment escalation and de-escalation in late-onset MS

Patients with late-onset multiple sclerosis (LOMS) should be managed differently than patients with adult-onset (AO) MS. Prof. Fredrik Piehl (Karolinska University Hospital, Sweden) talked about various treatment-related aspects that should be taken into consideration for the management of this specific group of patients.

"We see less inflammatory disease activity and fewer relapses in patients with LOMS than in patients with AOMS," said Prof. Piehl [1]. "However, the consequences of a relapse may be worse in patients with LOMS and LOMS is associated with more evident neurodegeneration."

Differences between older and younger patients with MS can also be seen in the benefit of disease-modifying treatments. The benefit from treatment in terms of relapse risk and disability progression appears to be less in patients over 40 years than in patients younger than 40 years [2,3]. From 53 years of age, there may be no benefit at all, a meta-analysis indicated [4]. "On the other hand, with older age, the therapeutic risk increases due to comorbidities and perhaps more severe treatment-related adverse events," added Prof. Piehl. Especially with anti-CD20 therapies, the risk of hospital-treated infections increases with longer treatment duration [5]. "Moreover, infections are more likely to have an impact on disability progression if a patient is older," according to Prof. Piehl.

Results from the DISCOMS study suggested that it is probably safe to de-escalate therapy in a population of patients with a median age of 62 years [6]. However, in patients around 50–55 years of age it may not be safe to de-escalate therapy, findings from the DOT-MS trial revealed [7]. "The authors observed a significantly increased MRI activity in patients who discontinued therapy versus those who stayed on therapy," clarified Prof. Piehl. He further explained that the de-escalation strategy depends on the disease-modifying therapy at hand. "With anti-CD20 therapies, there is no substantial risk of rebound after discontinuation, whereas natalizumab comes with an increased risk of rebound if this drug is stopped."

Prof. Piehl emphasised that the initiation of a disease-modifying treatment at an advanced age should be based on inflammatory disease activity and not just on chronological age cut-offs. Finally, he mentioned that the choice of therapy should be based on an individualised benefit-risk analysis, taking inflammatory activity and co-existing risk factors into account.

1. Piehl F, et al. Escalation and de-escalation of treatments in late-onset multiple sclerosis. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.
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How different are late onset and adult onset MS really?

Late-onset multiple sclerosis (LOMS) is different from adult-onset (AO)MS in various ways. Dr Celine Louapre (Sorbonne University, France) talked about the clinical and imaging features of LOMS to inform the audience about this condition.

"LOMS is usually defined as MS diagnosed after 50 years of age," said Dr Louapre. "It is a condition that is susceptible to misdiagnosis, due to comorbidities and differential diagnoses such as cervical myopathy, polyneuropathy, stroke, and Meniere disease."

Just as in AOMS, more women are affected by LOMS (around 64.5%) [1,2]. There is a strongly increased risk for a progressive course of the disease in LOMS [3] but there are fewer relapses in the first years of LOMS than in the first years of AOMS [4]. "The annual relapse rate is however higher in the first years of LOMS than in patients with AOMS who have longer disease duration," added Dr Louapre. Next to this, LOMS is associated with a more rapid evolvement of disability than AOMS [5]. "The time to be unable to walk is significantly shorter in patients with LOMS but still at an older age than in AOMS [6]," according to Dr Louapre. Brainstem, spinal, and supratentorial involvement at diagnosis have been associated with an increased risk for disability in LOMS [7]. "These findings were however not confirmed in other studies," Dr Louapre nuanced.

Furthermore, the symptoms at onset are somewhat different for patients with LOMS than for those with AOMS. Visual symptoms and numbness may be more common in AOMS, whereas LOMS has been associated with a higher incidence of bowel/urinary complaints, fatigue, muscle weakness, and spasms at onset [6,8]. "The imaging features we see at diagnosis in LOMS are broadly comparable to what we

observe in AOMS," said Dr Louapre. Brain lesions and spinal cord lesions are seen in 73% and 64% of the patients with LOMS, respectively [9]. Gadolinium-enhanced lesions may be somewhat less common in patients with LOMS than in those with AOMS [10]. Finally, over time, less MRI activity was observed in LOMS versus AOMS [11]. "This may be an effect of age itself more than age at onset," commented Dr Louapre.

"The different clinical and imaging features of LOMS and AOMS may be linked to the fact that AOMS is associated with more inflammation and active focal demyelination, whereas remyelination impairment and neurodegeneration are more typical elements of LOMS," Dr Louapre ended.

1. Louapre C, et al. Clinical and neuroimaging features of late-onset multiple sclerosis. 10th EAN Congress, 29 June–2 July 2024, Helsinki, Finland.
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