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NEUROLOGY

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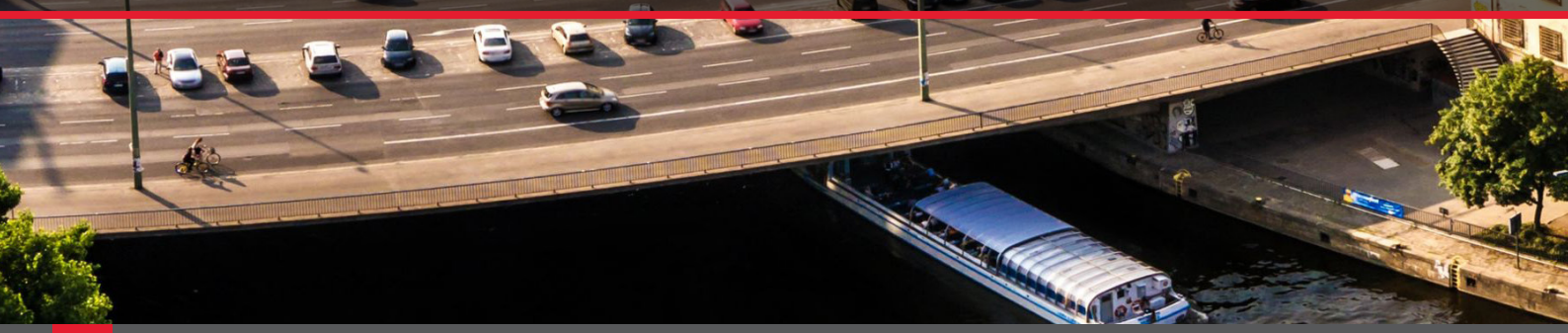

NEUROLOGY

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Neurology

EMJ GORELY NEW MEDIA

European Medical Journal
EMJ Neurology Vol 3.1
August 2015

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Welcome

Welcome to this year's edition of *EMJ Neurology*, which aims to provide readers with an in-depth look at the latest developments in this unique and complex field of medicine. The first part of our journal is devoted to reporting the main stories that emerged during the European Association of Neurology (EAN) Congress that took place on 20th-23rd June in Berlin, Germany. In the latter part of the journal, the focus shifts to a selection of topical peer-reviewed papers describing the results of extensive research by highly respected neurologists.

EAN 2015 was a seminal event showcasing research on a wide range of neurological conditions and other issues affecting the field, as well as being an opportunity for discussion and interaction with delegates from across the globe. Prominent topics featured at the congress included Alzheimer's disease, Huntington's disease, Parkinson's disease, epilepsy, and migraine to name but a few. In our coverage of EAN we have summarised a broad selection of important presentations that took place, conducted fascinating interviews with highly regarded members of the neurological community, and strived to describe everything that took place over the course of four days, including the awards given in recognition of exceptional contributions to the field.

After our report on the congress, readers will find some superb research papers contributed by preeminent neurologists. For example, Jellinger provides an update on the current state of treatment for Alzheimer's disease, a condition which is growing in significance as the size of the elderly population continues to grow. In another noteworthy contribution, Pellegrini et al. describe the available treatment options, associated side-effects, and current guideline recommendations for managing sialorrhoea, which is a frequent complication of motor neurone disease. With papers like these only representing a taster of the full selection, readers are certain to find much to hold their attention and provide new perspectives.

Here at EMJ it is our hope that this edition of *EMJ Neurology* will provide an excellent insight into the mechanisms of neurological disease and new treatment options, which we hope will help healthcare professionals in their daily work. While there is still a long way to go in this vital area of medicine, we are very encouraged by the rate of progress in recent times and we are certain that this provides grounds for optimistically believing that many of the current challenges will be overcome in the near future. We wish neurologists everywhere the very best in their future research.

Spencer Gore

Team Principal, European Medical Journal

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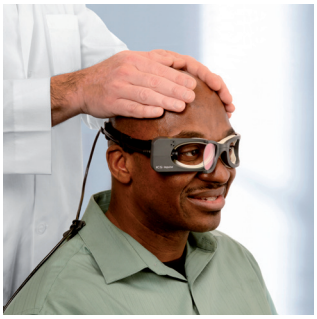

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Foreword

Prof László Vécsei

Director of the Department of Neurology, University of Szeged, Szeged, Hungary

Welcome to the third issue of *EMJ Neurology*, which I hope will enlighten you with some of the latest research developments in the field; inside you will find a plethora of fascinating articles from some of the most prominent researchers working in neurology.

Recently, clinical trial data relating to the treatment of ischaemic stroke have demonstrated the superiority of endovascular procedures. These results will change the current decision-making process in acute ischaemic stroke patients, as Cavallini et al. showcase in their review article featured in this issue. Harrison et al. describe the automated quantification of stroke damage on brain computed tomography scans (e-ASPECTS) in their paper; this can be integrated into the diagnostic pathway for acute ischaemic stroke patients in order to assist physicians with their interpretation of scan results.

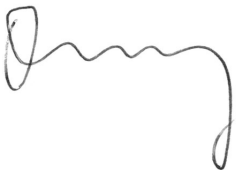
> This issue of *EMJ Neurology* brings you highlights from the 1st Congress of the European Academy of Neurology in Berlin, Germany, [...] which dedicated itself to providing the highest quality of continued medical education.

In other featured articles, Veenith and Gwyn evaluate the management of malignant middle cerebral artery infarction. The authors conclude that early decompressive craniectomies in younger patients are accompanied by an improvement in functional outcome and mortality. However, the timing, long-term survival benefits, and age thresholds of this procedure will require further investigation. In relation to the hypothalamic—pituitary alterations seen in patients with neurosarcoidosis, Tamagno et al. detail the most common endocrinological problems observed by physicians today, and why it is important to include neurosarcoidosis in the differential diagnosis of a hypothalamic—pituitary axis dysfunction.

As well as all of the above, this issue of *EMJ Neurology* brings you highlights from the 1st Congress of the European Academy of Neurology in Berlin, Germany, which was a particularly important event in the history of European neurology and which dedicated itself to providing the highest quality of continued medical education.

I hope that you enjoy reading this issue of our journal and that it inspires you to keep striving towards providing better standards of care for neurological patients. I wish you much luck in your future research and clinical endeavours.

Yours sincerely,



László Vécsei

Director of the Department of Neurology, University of Szeged, Szeged, Hungary.

the MENARINI group

MIGRAINE: THE SEVENTH DISABLER[1]

Frovatriptan in the world is:

Allegro®
Auradol®
Dorlise®
Eumitan®
Forvey®
Fromen®
Fromirex®
Frotan®
Frovamen®
Frovamig®
Frovex®
Menamig®
Menatriptan®
Migard®
Migralin®
Migrex®
Perlic®
Pitunal®
Rilamig®
Tigreat®
Triptar®

A MORE SUSTAINED EFFECT ON RELIEF OF MIGRAINE SYMPTOMS[2]

Frovatriptan is indicated for acute treatment of the headache phase of migraine with or without aura[3]

1. Steiner T.J. et al.; J Headache Pain 2013; 14:1 2. Franconi F. et al.; Neurol Sci 2014; 35(Suppl. 1): S99-S105 3. Migard-Summary of Product Characteristics

EFFICACY IN THE TREATMENT OF MIGRAINE

Migraine was ranked seventh highest among specific causes of disability globally (responsible for 2.9% of all years of life lost to disability), and in the top ten causes of disability in 14 of the 21 world regions. [1]

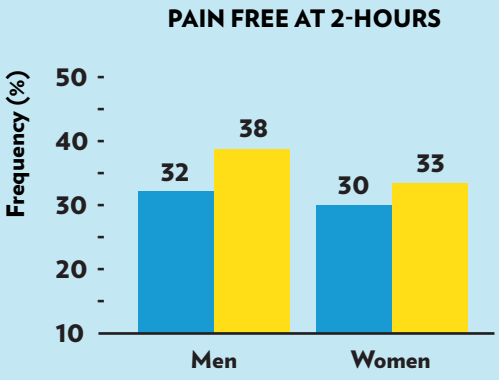
This chronic neurovascular disorder occurs in both genders, although large surveys show higher prevalence of this condition in women, with a female to male ratio in the order of 3:1. [2]

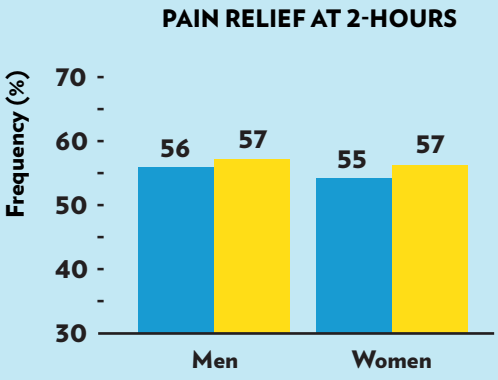
Although migraine acknowledges a complex pathophysiology, involving genetic and psychological factors, the disproportionate number of fertile women with migraine suggests that hormonal factors may indeed play an important role in the pathogenesis of migraine. [2]

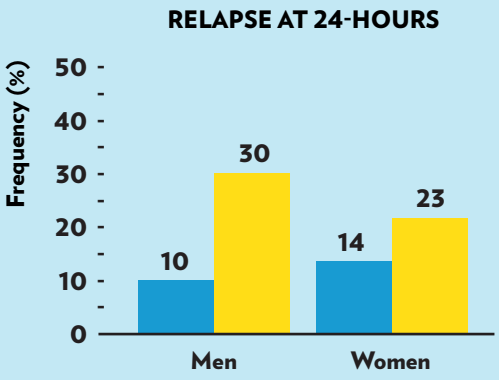
In addition, attacks are usually reported to be more severe and difficult to treat in women than in men. [2]

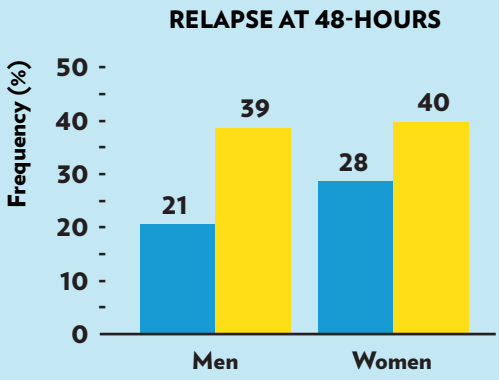
A pooled analysis of three individual randomized, multicenter, double-blind, crossover Italian studies on patients with migraine showed that frovatriptan 2.5 mg had a more sustained effect on relief of migraine symptoms than comparators. In particular, relapse at 24 h was significantly ($p < 0.05$) less likely to be reported in frovatriptan than in comparator-treated patients, with no between-gender difference. This was the case also for rate of relapse after 48 h ($p < 0.05$ between treatments). [2]

Although migraine presents in a more severe form in women, frovatriptan seems to retain its good efficacy and favorable sustained antimigraine effect regardless of the gender. [2]







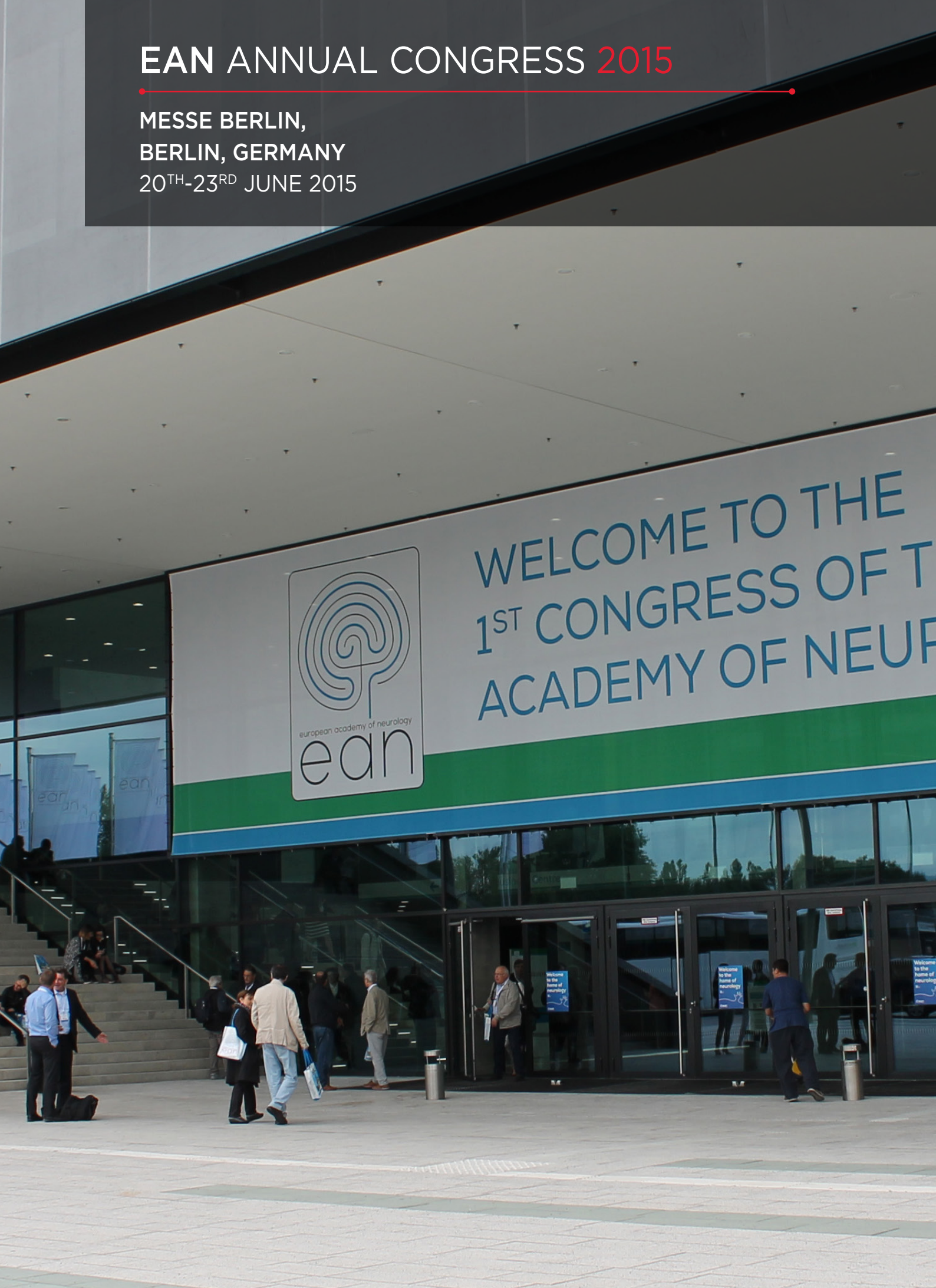


Proportion (%) of pain free at 2 h, pain relief at 2 h and relapse at 24 and 48 h in the 66 men and 280 women with migraine of the intent-to-treat population.
Data are separately shown for frovatriptan- (blue bars) and comparator-treated patients (yellow bars).
The p value refers to the statistical significance of the between-treatment difference.

Elaboration of Fig. 2 of (2)

EAN ANNUAL CONGRESS 2015

MESSE BERLIN,
BERLIN, GERMANY
20TH-23RD JUNE 2015



Welcome to the *European Medical Journal* review of the 1st European Academy of Neurology (EAN) Congress 2015

The first European Academy of Neurology (EAN) Congress since the merger of the European Federation of Neurological Societies (EFNS) and the European Neurological Society (ENS) was hosted by Berlin, Germany. As one of the world's most vibrant capitals, with an impressive cultural and scientific heritage, delegates were able to spend time relaxing and enjoying the sights and sounds of the city alongside their duties at the congress. Berlin is also heavily associated with the field of neurology, being the place where Moritz Heinrich Romberg wrote the 'Lehrbuch der Nervenkrankheiten des Menschen' – a mid-19th century textbook seen as the foundation of modern neurology, which made the city an ideal location to begin the EAN's congress journey.

A total of 6,400 participants from 106 countries descended upon Germany's capital and more than 2,000 abstracts were submitted, showing the significant interest that the event attracted. The opening ceremony was held on Saturday 20th June and welcomed visitors to both Berlin and the EAN. A series of speeches were given by leading neurologists and an additional treat came in the form of a fascinating lecture by Prof Eckart Altenmüller entitled 'What can musicians teach neurologists?'. In his address to the audience, the President of EAN Prof Günther Deuschl described the immense challenges facing neurologists today: "Neurological

diseases are becoming more and more frequent. This is simply due to the fact that the number of elderly people is increasing. [...] We are roughly at 30% of the population which is above 65 years. In 2060 this will be more than 50% in Europe."

A wide range of neurological topics were discussed throughout the congress, including ageing and dementia, cerebrovascular diseases, headache and pain, motor neurone diseases, and multiple sclerosis to name but a few. Those in attendance were provided with a rich source of new information about the field, keeping them updated on the many advances taking place. A variety of presentation formats were used, with lectures, presentations, symposia, and teaching courses all designed to enable significant engagement and interaction among the delegates.

"Neurological diseases are becoming more and more frequent. This is simply due to the fact that the number of elderly people is increasing. [...] We are roughly at 30% of the population which is above 65 years. In 2060 this will be more than 50% in Europe."

There were many noteworthy presentations at the congress, and highlights covered in this issue of *EMJ Neurology* include the results from a series of studies showing that while exercise is a major factor in slowing cognitive and functional decline in dementia patients, physical activity is ultimately unable to reduce the risk of early nursing home placement or premature mortality. Hopefully such findings will not discourage patients from undertaking more exercise in order to help improve their quality of life. In another significant study, Dr Boris Radic and his team from Croatia detail their research which found that football players suffer from slower reaction times and shorter attention spans than non-players due to the effects of the regular impact of the ball on the head. This finding could well lead to preventative measures being put in place for amateur footballers. In addition, an important session provided a thorough update on current research into new treatments for the devastating condition of Parkinson's disease. This provided some good news for Parkinson's patients, with recent trials assessing new strategies reporting promising results; it is hoped that it will not be too long before these treatments are available to patients.

EAN 2015 was undoubtedly a success and emphasised just how quickly this field of medicine is advancing. Despite this progress, neurology remains one of the most challenging areas of medicine, with neurological conditions very much on the rise in Europe's ageing population. It is therefore essential that the kind of progress detailed at EAN continues well into the future, and we aim to supplement this development with an effective and entertaining summary for our readers.

HIGHLIGHTS

Extra Resources Required to Stem the Tide of Neurological Disease

PRESSURE is mounting to secure the necessary resources for treatment and research into neurological disease in Europe, according to data presented at EAN 2015.

"The sheer scale and impact of neurological disease in Europe is underestimated and often overlooked. As a specialisation, neurology is under-resourced in many European countries. Research activities and providing care for neurological patients must be given a much higher priority at all levels," said President of EAN Prof Günther Deuschl, University Medical Center Schleswig-Holstein, Kiel, Germany, in an EAN press release from 22nd June.

Data from the European Brain Council show that 220.7 million people in Europe suffer from at least one neurological condition, and with the elderly population continuing to rise, incidence of age-related illnesses including stroke and dementia are likely to increase further. There also appears to be a shortfall in neurologists who are able to serve this demand, with just 25,000 located in EU countries.

Securing greater resources is essential, not only because of the human suffering caused by neurological diseases but also the loss of independence through disabilities and requirement for long-term care, resulting in an extremely heavy economic burden. Furthermore, 2.2 million disability-adjusted life years (a measure used to determine years lost through disease and premature death) are attributable to dementia, 1.6 million to strokes, and 640,000 to Parkinson's disease in the EU alone.

"The sheer scale and impact of neurological disease in Europe is underestimated and often overlooked. As a specialisation, neurology is under-resourced in many European countries. Research activities and providing care for neurological patients must be given a much higher priority at all levels."

Despite this, advances in modern neurology do provide some cause for optimism. "As a specialisation, neurology is moving at high speed – few other areas are moving forward so quickly. All of the subspecialties that are brought together under the umbrella of neurology are contributing to this progress," explained Prof Deuschl. "We are increasingly finding

preventative, diagnostic, therapeutic, and rehabilitative answers to the growing challenges posed by these diseases." He emphasised that the next step should be to invest a significant portion of the approximately €8 billion made available for medical research by the EU's Horizon 2020 programme into neurological research and the neurosciences.

Neurostimulatory Techniques Hold Promise for Epilepsy

NEUROSTIMULATION represents an emerging treatment modality for epilepsy, with a variety of less and non-invasive methods also currently under investigation, according to study data presented at EAN 2015. Epilepsy affects approximately 50 million people worldwide, and about 25-30% of those receiving conventional treatment do not become seizure-free and will continue to experience major adverse events (AEs).

"Despite the advent of new pharmacological treatments and the high success rate of many surgical treatments for epilepsy, a substantial number of patients do not become seizure-free or experience major AEs. This fact is an important motivation to investigate and develop novel therapeutic approaches," said Prof Paul Boon, Department of Neurology, Reference Centre for Refractory Epilepsy, Ghent University Hospital, Ghent, Belgium, in an EAN press release dated 22nd June.

Several neurostimulatory techniques are being applied or investigated in the field of epilepsy therapy: vagus nerve stimulation (VNS) is already widely available (>100,000 patients treated worldwide) and proof-of-concept has been demonstrated for trigeminal nerve stimulation (TNS).

Deep brain stimulation (DBS) has recently become available in the EU. "Several epilepsy centres around the world have initiated studies with DBS in different intracerebral structures. DBS has been shown to be efficacious in small pilot studies of patients with medically refractory epilepsy," explained Prof Boon. "The SANTE trial of bilateral DBS in the anterior nucleus of the thalamus for example has demonstrated efficacy and safety of this technology with increasing responder rates up to 40-60% after longer follow-up up to 5 years. Surgical complications and postoperative morbidity are within expectations. Reported long-term side-effects include depression and memory deficits, which require further study."

The 1st EAN Congress

Various less or non-invasive neurostimulatory techniques, such as transdermal VNS, TNS, repetitive transcranial magnetic stimulation, and transcranial direct current stimulation have been investigated or are under investigation, according to Prof Boon: "Early results for these novel approaches seem promising, but little controlled or randomised data are available. Patient responder identification also needs to be studied."

Cross-Border Cooperation is the Key to Success in Neurosurgery

LONG-TERM follow-up study has shown that more patients can be given access to neurosurgical epilepsy treatment through the use of cross-border cooperation of specialist facilities. The study, by Prof David B. Vodušek, Ljubljana University Medical Centre, Ljubljana, Slovenia, and Chairman of the EAN Liaison Committee, was presented at EAN 2015, and showed the results of a collaboration between the Ljubljana University Medical Centre and the University Hospital Erlangen, Erlangen, Germany.

"Modern medicine is developing at an amazing rate, putting new demands on both healthcare delivery and physicians' expertise. Furthermore, the modern approach to patient care relies more and more on teams consisting of a number of professionals," said Prof Vodušek, in an EAN press release dated 21st June.

Over 50 Slovenian patients underwent surgery in Germany between 2001 and 2012, demonstrating the durability of the international cooperation. "The majority of the patients - 89% - felt that the surgical treatment largely fulfilled their expectations," commented Prof Vodušek.

"In Slovenia, with two million inhabitants speaking the national language, long-term cooperation between the University Medical Centre in Ljubljana and the University Hospital Erlangen in Germany has demonstrated that even patients with epilepsy, candidates for surgical treatment, who need intraoperative neuropsychological testing in their mother tongue can be successfully treated in the framework of a transnational European Collaboration."

"Modern medicine is developing at an amazing rate, putting new demands on both healthcare delivery and physicians' expertise."

The study's success rate shows promise: 61% of the patients presented complete freedom from seizures, while 28% were free from disabling seizures. Prof Vodušek concluded: "As EAN's foremost task is improving neurological patient care in Europe, it might consider developing an 'exchange course' of high-quality

service providers of specific evidence-based treatments relying on special expertise and equipment, in non-profit academic centres, and tertiary medical centres in small countries seeking collaboration for particular patient populations mirroring the very successful EAN department to department programme facilitating exchange of young neurologists."

Thrombectomy Given Green Light in Stroke Therapy

THROMBECTOMY has been confirmed as a highly safe and efficient procedure in acute therapy, and is superior to standard thrombosis therapy in specific patient groups, according to data presented at EAN 2015.

"The procedure makes sense particularly in large thrombi which cannot be dissolved, or can only be partly dissolved with pharmacological therapy, and which occlude large brain supplying blood vessels," said EAN Vice President Prof Franz Fazekas, Head and Chair of the Department of Neurology, Medical University of Graz, Graz, Austria, in an EAN press release dated 22nd June. "The advances of the new method are indeed promising, but it is clear that mechanical thrombectomy cannot restore circulation in all affected persons either. Revascularisation is ineffective if brain tissues have already died. The challenge will be to apply the procedure specifically in those patients who can profit from it and to provide the organisational structures and workflows necessary for this complex type of treatment."

To accomplish this task, relevant European medical and scientific associations are preparing a joint recommendation on thrombectomy, which is intended to ensure that the procedure is delivered for the greatest possible benefit of patients. According to recent discussions, thrombolysis will remain the primary treatment for acute ischaemic strokes. "In occlusions of large brain vessels, however, it should be complemented by thrombectomy. If intravenous thrombolysis is contraindicated, thrombectomy undoubtedly represents the first-line treatment option in large vessel occlusions," explained Prof Fazekas.

"If intravenous thrombolysis is contraindicated, thrombectomy undoubtedly represents the first-line treatment option in large vessel occlusions."

Regarding technologies, efficacy data are primarily available for stent retrievers. The use of other systems relies on the respective situation and needs case-by-case assessment. "The time factor is important for the outcome. Thrombectomy should be performed within a maximum of 3-6 hours. However, the earlier the intervention is performed, the better the treatment results," said Prof Fazekas.

Stroke Patients with Depressive Symptoms Experience Worse Outcomes

STROKE survivors who suffer depressive symptoms experience worse outcomes regarding recovery of cognitive and functional abilities, according to the results of a study presented at EAN 2015. The meeting brought together experts on neurology from around the globe, who

witnessed the evidence suggesting that new screening methods and a more intensive treatment approach are required.

According to the study's authors, its results present a strong case for the screening of stroke and TIA patients for depressive symptoms. "These patients could benefit from closer monitoring and a more intensive treatment approach," claimed the experts. The study, which was completed by researchers from the Tel Aviv University, Tel Aviv, Israel, concluded that patients who present depressive symptoms at the time of or after a stroke or transitory ischaemic attack (TIA) have a reduced functional outcome, and are at a higher risk of cognitive impairment.

The team analysed data from 506 stroke and TIA patients from the TABASCO prospective cohort study who were admitted to an intensive care unit in Tel-Aviv between April 2008 and December 2011. The researchers found significant markers of cognitive impairment in 16.7% of these patients within 2 years of their stroke or TIA.

"The study clearly demonstrates the complexity of cerebral recovery processes after a stroke. What remains unclear, however, is the extent to which the depressive symptoms observed were the result of a pre-existing condition or a direct consequence of the stroke. Whatever the cause, the results support the case for a more holistic approach to medical surveillance and an intensive treatment approach to support recovery," said EAN vice-president Prof Franz Fazekas, Head and Chair of the Department of Neurology, Medical University of Graz, Graz, Austria.

"The study clearly demonstrates the complexity of cerebral recovery processes after a stroke. What remains unclear, however, is the extent to which the depressive symptoms observed were the result of a pre-existing condition or a direct consequence of the stroke."

Wealth Determines Age of 'Near-Stroke'

SOCIOECONOMICALLY deprived individuals suffer transient ischaemic attacks (TIAs) an average of 4 years earlier than their wealthier counterparts, according to data presented at EAN 2015.

TIAs are caused by a temporary disruption of blood flow to the brain and are often called 'near-strokes' as they can precede ischaemic strokes and display similar symptoms. Led by Prof Daniel Bereczki, Professor of Neurology, Chairman of the Department of Neurology, University of Budapest, Budapest, Hungary, the study analysed data from 4,700 TIA patients from either the poorest or the wealthiest district of Budapest and diagnosed between 2002 and 2007. The research team discovered that patients from the wealthiest district were diagnosed at an average age of 66 years, whereas those from the least wealthy district had an average age of 62 years at diagnosis.

Additional findings from the study were that only 35.4% of the 4,700 patients were hospitalised following a TIA, and there was no neurological examination carried out in 23.5% of cases despite the fact that TIA can be a warning sign of subsequent strokes. In an EAN press release dated 21st June, Prof Bereczki expressed hope that the findings of the study would encourage health systems to consider TIA victims. "Health policy is called on to take suitable actions for TIA patients especially in socioeconomically poor regions, because individuals with a low socioeconomic status are at a special risk of having a 'near stroke' due to temporarily disrupted circulation in the brain and of suffering a genuine stroke later."

6,400 participants from 106 countries

Indeed, Prof Anna Czlonkowska, Chair of the EAN Subspecialty Scientific Panel Stroke, noted that ischaemic strokes follow a TIA in 20% of cases. "Rapid diagnosis and careful clinical evaluation leading to the introduction of preventive treatment may reduce the risk of post-TIA stroke by 80%," she explained. She added that Prof Bereczki's findings "stress that prevention of stroke on the country level should definitely reach out to persons particularly vulnerable in terms of social deprivation."

"Health policy is called on to take suitable actions for TIA patients especially in socioeconomically poor regions..."

New Concepts in the Treatment of Multiple Sclerosis

NOVEL treatment approaches such as antigen-specific immunisation strategies were among the topical multiple sclerosis (MS) research areas discussed at EAN 2015, where experts urged for the development of truly individualised therapy approaches to use available drugs in a more targeted manner.

MS affects approximately 500,000 people in Europe and roughly 2-3-times as many women as men. The overall cost to European health and social-care systems is estimated at a staggering €15 billion per year. Although there are many options for treating and managing MS, more information about the pathogenesis of the disease is slowly being deciphered as new therapies become available. This should allow the ultimate goal of personalised therapy and other significant therapeutic approaches to be more readily achievable in the future.

Commenting on the vital need for personalised therapy, Prof Xavier Montalban, Director of the Unit of Clinical Neuroimmunology, Vall d'Hebron University Hospital, Barcelona, Spain, said: "Personalised medicine is one of the most unmet-needs areas we have in MS nowadays. To understand the prognosis of a specific patient, to choose the best possible treatment for that patient, and to predict the effects and side-effects that a specific drug might have in this individual are not easy exercises. But there is growing evidence, including data on biomarkers, which supports us in this task."

Prof Montalban highlighted that other emerging avenues of MS therapy will focus on the role of antigen-specific tolerance, with treatment approaches that may hinder the unwanted consequences of adaptive, pathological antibody and T cell-mediated immune responses.

Another promising therapeutic approach is the utilisation of the neuroprotective potential of vitamins and antiepileptic drugs, which is currently undergoing further investigation in two trials. "One study using biotin in progressive MS and another using phenytoin in optic neuritis both show signs of having neuroprotective effects that warrant further studies," said Prof Montalban, commenting on the initial findings.

Amyotrophic Lateral Sclerosis Remains a Mystery

STUDIES presented at EAN 2015 have discovered significant variances in the epidemiology of amyotrophic lateral sclerosis (ALS) and a link between the disease and cancer. ALS causes complete paralysis, terminal respiratory

failure, loss of speech, and severe difficulty swallowing, with experts being unsure of what triggers this rare and untreatable disease.

"Epidemiology of ALS needs to be looked at globally to identify the possible causes of these variances."

Studies conducted in Uzbekistan and Iran revealed conflicting findings. Dr Dilnoza Mirzaeva, Tashkent State Medical University, Tashkent, Uzbekistan, analysed the 2013 and 2014 national health register and discovered that 70% of cases were concentrated in one region whilst the remainder were widespread. They also found that 60% were female patients and none of the patients survived beyond 3 years.

In contrast, an Iranian study conducted by Dr Reza Boostani, Associate Professor, Department of Neurology, Mashhad University of Medical Science, Mashhad, Iran, found that 64% of the 59 patients involved were male and the mean disease duration of the 19 patients who had already died was 53 months, significantly longer than in the Uzbekistan study. "Epidemiology of ALS needs to be looked at globally to identify the possible causes of these variances," said Prof Albert C. Ludolph, Chair of the EAN Subspecialty Scientific Panel on ALS and frontotemporal dementia in an EAN press release dated 21st June.

A third study, presented by Dr Davide Bertuzzo, Department of Neuroscience, University of Turin's ALS Centre, Turin, Italy, researched the link between ALS and cancer. All 1,260 documented cases of ALS in the Piemonte and Valle d'Aosta regions between 1995 and 2004 were analysed, and revealed that both male and female ALS patients had a higher rate of cancer, particularly lung and breast cancer, compared with the general population, and these patients had worse clinical progression of ALS than those without cancer. Prof Ludolph commented on this new data: "The epidemiological study from Turin showed a higher incidence of lung and breast carcinoma among ALS patients than in the control group. A recommendation could be made to the authors to analyse the individual patients to see whether therapeutic measures to treat cancer influence the progression of ALS."

Novel Therapies Provide Hope for Sufferers of Parkinson's Disease

NOVEL therapies for the treatment and management of Parkinson's disease (PD) could soon be available, following promising recent trials that have assessed new strategies for fighting the condition, as discussed by experts at EAN 2015.

"There are a number of new treatments in the pipeline and in development that might help to improve our current management of PD. Such new therapies are aimed at reducing progressive functional worsening over time. This is a major unmet need, but most difficult to obtain, as therapeutic targets are still not clearly identified and methods to demonstrate such an effect in patients are long and complex," said Prof Olivier Rascol, Professor of Clinical Pharmacology, University Hospital Toulouse, Toulouse, France, and Chair of the EAN Subspecialty Scientific Panel Movement Disorders, in an EAN press release dated 21st June.

Prof Rascol continued to mention that new medications for the better treatment of motor symptoms of PD sufferers are in the latter stages of development. These include intrajejunal infusions, new extended-release applications, subcutaneous pump-patches, or formulations for inhalative administration, alongside new COMT inhibitors and MAO-B inhibitors which have been shown to improve 'off' problems in PD patients.

With regard to non-motor PD symptoms, new randomised controlled trials have demonstrated that dopamine and non-dopaminergic drugs can lead to improvements. For example, the dopamine agonists pramipexole and piribedil have proved effective in treating PD-related depression or apathy.

Prof Rascol explained the advances in non-pharmacological interventions: "There is an important amount of research under way in order to better understand and characterise the importance of physiotherapy or various types of physical exercise to better manage PD. However, at the moment, the quality of such trials remain usually insufficient to provide indisputable robust evidence."

Coffee Can Reduce Risk of Parkinson's Disease by One-Third

DRINKING coffee may protect you from Parkinson's disease (PD), according to results from a meta-analysis of 37 studies conducted internationally and presented at EAN 2015.

"There are a number of new treatments in the pipeline and in development that might help to improve our current management of PD. Such new therapies are aimed at reducing progressive functional worsening over time."

The analysis discovered that those who consumed coffee reduced their risk of developing the disease by 31%, and men and women appeared to benefit equally from the effects of caffeine. There may be numerous explanations why caffeine has this effect; tests on animal models have led researchers to assume that caffeine interacts with the neurotransmitter, adenosine.

"Better understanding of environmental factors which reduce or increase the risk of developing PD is crucial to safeguard against developing this disorder."

"This may have neuroprotective effects on specific brain regions which play an important role in relation to Parkinson's," explained study author Dr Filipe Brogueira Rodrigues, Instituto de Medicina Molecular, Lisbon, Portugal, as reported in an EAN press release dated 23rd June.

This is not the only study to confirm the beneficial effects of caffeine. An increasing amount of evidence is mounting to prove that caffeine can protect against other neurological disorders such as Alzheimer's disease and strokes, as well as Type 2 diabetes, depression, and liver cirrhosis/liver cancer. A suggested explanation is that all of these conditions are chronic and connected to cell degeneration in some way, although more research is required to provide conclusive reasoning.

Prof Kailash Bhatia, Professor of Clinical Neurology, Sobell Department of Movement Neuroscience, Institute of Neurology, UCL, London, UK and Chair of the EAN Subspecialty Committee on PD and Movement Disorders, emphasised: "The results of this important meta-analytic study reported at the EAN Congress confirm the finding that caffeine exposure is associated with a reduction in the risk of developing PD. Better understanding of environmental factors which reduce or increase the risk of developing PD is crucial to safeguard against developing this disorder." He added that further research is required to fully understand how and why caffeine is able to protect the way it does.

Exercise Produces Mixed Results in Dementia Patients

EXERCISE may hinder the course of dementia, assisting cognitive and functional ability in the early stage of the disease in patients. However, it cannot decrease the risk of early nursing home placement or premature mortality, according to data presented at EAN 2015.

"Physical exercise can be an effective treatment option for people suffering from mild-to-moderate dementia and

who are already on medication," said Dr Ana Capisizu, University of Bucharest, Bucharest, Romania. "Regular physical activity helps to improve patients' cognitive and functional performance. It also has a favourable bearing on mental wellbeing and can reduce depression."

"Physically active Alzheimer patients require nursing-home placement at the same stage as inactive sufferers and there is no indication that exercise extends life expectancy."

These claims are supported by the results of a study conducted by Dr Capisizu and her team, which monitored 40 patients suffering from mild-to-moderate dementia. The subjects participated in various tests at regular intervals, with some of the group following an exercise programme. After 12 weeks, the physically active patients performed significantly better in tests designed to monitor problem-solving, quality of life (QoL), and functional ability.

A recent Danish study produced similar results. Study author Dr Kristian Steen Frederiksen, Danish Dementia Research Centre, Rigshospitalet-University of Copenhagen, Copenhagen, Denmark, confirmed: "There is a clear association between exercise and QoL. Physically active patients were also a lot less likely to suffer from neuropsychiatric symptoms which may include apathy and anxiety, which frequently manifest themselves in people suffering from Alzheimer's dementia. They also performed better in activities of daily living."

However, a 3-year follow-up involving the same group showed that physical activity had no effect on two major criteria, as described by Dr Frederiksen. "Patients with Alzheimer's disease require nursing-home care placement and institutionalised care at an earlier stage than non-dementia sufferers of the same age. Although we did find a small difference with regard to nursing home placement, our data do not confirm that physical activity influences these developments. Physically active Alzheimer patients require nursing-home placement at the same stage as inactive sufferers and there is no indication that exercise extends life expectancy."

Football Players' Memories at Risk from Heading the Ball

FOOTBALL players suffer from lower reaction times and attention spans than other people, due to the impact that heading the ball has on the brain. These findings could lead to preventative measures being put in place for amateur football players, according to study data presented at EAN 2015.

Dr Boris Radic, Medical Faculty, University of Zagreb, Zagreb, Croatia and colleagues suggest that when football players' heads are exposed to these types of blows too frequently, these slight but recurring concussions result in long-term attention deficit. The researchers examined 70 individuals with no experience of playing football, and compared them with an equally large control group of amateur football players who played in a veteran league.

"Non-soccer players did significantly better in those cognitive tests which required a high reaction speed and longer attention. Soccer players also lagged behind in all other cognitive tests, with one exception: they did better when the objective was to make rapid decisions," said Dr Radic in an EAN press release dated 23rd June.

The results of this study confirm previous research that investigated the deleterious effects on cognition of head injuries sustained by heading the ball. The exposure of this problem could lead to preventative measures being introduced to protect amateur football players.

"Non-soccer players did significantly better in those cognitive tests which required a high reaction speed and longer attention. Soccer players also lagged behind in all other cognitive tests, with one exception: they did better when the objective was to make rapid decisions."

Commenting on the data, Prof David B. Vodušek, Chair of the EAN Liaison Committee, said: "Although many uncertainties remain, given the large number of amateur soccer players in the world, starting from childhood, simple preventive measures like education on the potential danger of ball heading and possibly using appropriate protective gear should be seriously considered. Neurology should help, with additional and more detailed studies, to further elucidate the details of the problem and help make the extremely popular soccer a safer sport in the future."

Symposia, teaching courses, focussed workshops, hands-on courses, interactive sessions, special sessions

AWARD WINNERS AT EAN 2015

The outstanding research efforts of young investigators were acknowledged at EAN 2015 via the EAN Tournament for Young Neurologists, which awarded prizes to the best clinical and best basic science abstracts submitted by delegates <35 years of age. A total of 12 candidate abstracts (6 focussing on clinical sciences and 6 focussing on basic sciences) were selected by the EAN Programme Committee from all those submitted to the congress and eligible to participate. The lead authors of the 12 candidate abstracts were then invited to present their work at the congress and answer questions from the audience prior to the jury, which comprised members of the EAN's Programme, Scientific, and Teaching Course Committees, choosing a winner to receive free registration, accommodation, and a travel grant to attend EAN's next annual congress in Copenhagen, Denmark, as well as a cash prize. The abstracts considered to be the second-best in both the clinical and basic science groups also received a cash prize and a certificate. The prizes awarded for clinical science both went to delegates from Iberia, with the winner hailing from Barcelona, Spain, and the runner-up from Lisbon, Portugal, while the overall and runner-up prizes for basic science went to delegates from Würzburg, Germany, and Milan, Italy, respectively.

The clinical science tournament was won by Alvaro Cobo, who investigated the presence of anti-myelin oligodendrocyte glycoprotein autoantibodies (anti-MOG) in patients experiencing a first episode of longitudinally extensive transverse myelitis (LETM). Using data from four European centres, the study analysed epidemiological, clinical, laboratory, and imaging findings from 56 patients presenting with a first episode of anti-aquaporin 4 (AQP-4)-seronegative LETM in order to explore the frequency and clinical implications of anti-MOG. A total of 13 patients (23%) tested positive for anti-MOG, with anti-MOG-positive patients being significantly younger (median age: 32.5 versus 44.1 years; p=0.007) and having a better clinical outcome as assessed by comparing Expanded Disability Status Scale scores (median: 2.0, interquartile range [IQR]: 0-2.5 versus 3.0, IQR: 2.0-5.5; p=0.04) after a median follow-up of 3.5 years (IQR: 2.1-6.6). There was no gender bias in the patients that were anti-MOG-positive or anti-MOG-negative.

These findings suggest that anti-MOG-positivity in anti-AQP-4-seronegative LETM patients identifies a subgroup who have an elevated risk of ON relapse and conversion to NMO compared with those who are negative for anti-MOG.

Data describing the prognosis of pregnancies occurring after CVT [...] are scarce despite pregnancy being associated with an increased risk of venous thrombotic events.

In the entire cohort, 6 patients (11%) converted to neuromyelitis optica (NMO), 1 patient (2%) converted to multiple sclerosis (MS), 9 patients (16%) had recurrent LETM, and 40 patients (71%) remained as monophasic LETM at final follow-up (p=0.057). Compared with anti-MOG-negative patients, a higher proportion of anti-MOG-positive patients displayed pleocytosis within the cerebrospinal fluid (92.3% versus 45.2%; p=0.003), and anti-MOG-positive patients displayed an increased risk of relapse of optic neuritis and, therefore, a higher cumulative probability of conversion to NMO (hazard ratio: 8.99, 95% confidence interval [CI]: 1.60-50.59; p=0.01). These findings suggest that anti-MOG-positivity in anti-AQP-4-seronegative LETM patients identifies a subgroup who have an elevated risk of ON relapse and conversion to NMO compared with those who are negative for anti-MOG.

The runner-up prize in the clinical science group was awarded to Diana de Aguiar dias de Sousa for her abstract describing the safety of pregnancy in women who have experienced previous cerebral venous thrombosis (CVT). Data describing the prognosis of pregnancies occurring after CVT, and the most appropriate preventive strategies, are scarce despite pregnancy being associated with an increased risk of venous thrombotic events (VTEs), including CVT. The new study interviewed women who were <45 years of age and had previously participated in the International Study of Cerebral Vein and Dural Sinus Thrombosis (ISCVT) trial, which ran from 1998 to 2001, in order to assess the rate of VTE recurrence, outcomes of subsequent pregnancies, and antithrombotic prophylaxis regimens. Follow-up data were obtained from 108 of the 185 women who participated in ISCVT (median follow-up: 169±10 months), with patients coming from 30 of the 75 original study sites. There was a total of 76 new pregnancies in 44 women and, in the third trimester, 70% of these women received low-molecular-weight heparin (LMWH; 52% at prophylactic dosage and 18% at therapeutic dosage). There were 4 incidences of VTE recurrence (including 1 CVT), which occurred in 3 of the 76 pregnancies; 2 of the 3 women were receiving prophylactic LMWH at the time of the event. Women with CVT associated with only transient risk factors displayed a lower rate of abortion compared

with women in whom a predisposing condition for CVT was identified (11% versus 24%). The conclusion from the study is that the absolute risk of pregnancy-related VTE in women with previous CVT is low, and the rate of miscarriage in women with previous CVT associated with transient risk factors is similar to that expected in the general population.

The prize for best abstract in the basic science group was received by Kathrin Doppler for her study describing the detection of phosphorylated alpha-synuclein (pαS) in the dermal nerve fibres of patients with the neurodegenerative disorder multiple system atrophy (MSA). The diagnosis of MSA is often challenging as it is characterised by the deposition of pαS within oligodendrocytes and neurons of the central nervous system. In contrast, pαS can be detected in the dermal nerve fibres of skin biopsies taken from patients with idiopathic Parkinson's disease (iPD), and therefore the study aimed to investigate whether detection of pαS within easily obtainable skin biopsies could provide a potential diagnostic tool capable of allowing differentiation of MSA patients from those with other forms of parkinsonism, such as corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP). The investigators compared the distribution of pαS within the dermal nerve fibres of skin biopsies taken from 11 patients with MSA, 30 patients with iPD, 15 patients with tauopathies (CBD, PSP), and 39 healthy controls. There was no detectable pαS within the dermal nerve fibres of the healthy controls or patients with tauopathies, whereas 64% of patients with MSA and 67% of iPD patients displayed pαS within the dermal nerve fibres of their skin biopsies.

In iPD, pαS was found mainly within autonomic nerve fibres, whereas in MSA it was mainly somatosensory nerve fibres of the subepidermal plexus that were affected. This difference in pαS deposition may allow the clinical differentiation of these two conditions.

The study aimed to investigate whether detection of pαS within easily obtainable skin biopsies could provide a potential diagnostic tool capable of allowing differentiation of MSA patients from those with other forms of parkinsonism...

The runner-up prize for basic science was awarded to Paolo Preziosa for his abstract describing the results of a functional magnetic resonance imaging (fMRI) study of fatigue MS patients. Motor fMRI was obtained from 79 MS patients (50 with fatigue [MS+F] and 29 without fatigue [MS−F]) and 26 matched healthy

controls. Compared with controls, MS+F and MS−F patients both had increased activations of the right precentral gyrus, right inferior temporal gyrus, and cerebellum. Compared with controls and MS−F patients, MS+F patients had reduced activation of the left middle temporal gyrus, left supplementary motor area (SMA), bilateral superior frontal gyrus, left postcentral gyrus, left putamen, and caudate nuclei; these patients also showed increased activation of the right middle frontal gyrus, an effect which was mainly driven by MS+F patients with a disease duration >5 years. Over time, healthy controls showed a reduced activity of the SMA and right precentral gyrus, and an increased activity of the basal ganglia; this behaviour was significantly impaired in MS+F patients. In conclusion, the study was able to demonstrate abnormalities of activation and impaired timing of communication distributed between different areas of the motor network in fatigued MS patients.

The study was able to demonstrate abnormalities of activation and impaired timing of communication distributed between different areas of the motor network in fatigued MS patients.

Nils Erik Gilhus

Professor of Neurology and Head of Department, Department of Clinical Medicine, University of Bergen, Bergen, Norway.

Q: What or who inspired you to pursue a career in neurology?

A: There were three main reasons for me choosing neurology. Number one was the need of patients with severe disease to have optimal treatment after a correct diagnosis. Number two was the challenges in research: all the unmet needs and unknown disease mechanisms and causes. Number three was the excellent neurology department in Bergen and its highly stimulating working environment.

Q: How has our understanding of neurological disorders developed since you began your career?

A: Most important is the marked improvement in patient treatment. This is true for nearly all disorders: cerebrovascular disease, multiple sclerosis (MS), immune-mediated disorders, migraine, and movement disorders are leading examples. Another key aspect is that neurology now represents one of the emergency disciplines. Furthermore, magnetic resonance, computed tomography, positron emission tomography, and ultrasound technology have made the brain and brain pathology visible in detail, and in a dynamic way. Active interventions influencing brain and nervous system functions have dramatically increased through a range of various techniques and procedures.

Q: You have co-authored several articles focussing on the relationship between epilepsy and pregnancy. What made you choose to research this particular topic?

> "Epilepsy is a treatable condition and more than two-thirds of patients become seizure-free."

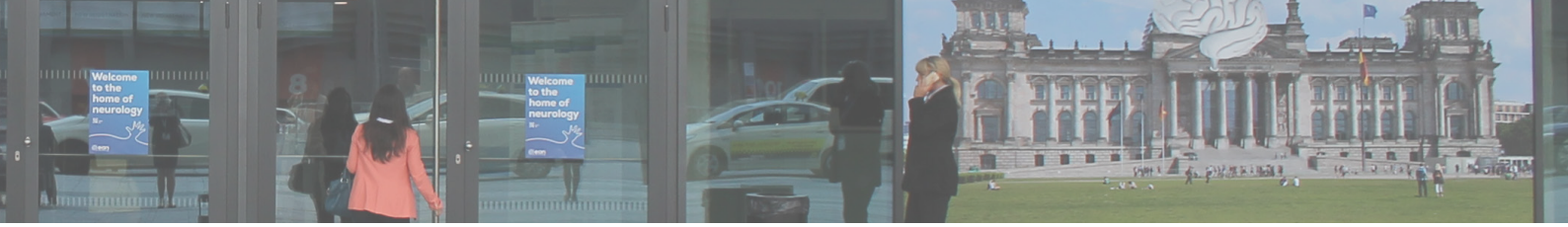
A: The health and well-being of children and young people is crucial. This can be influenced by diseases of mothers and their treatment during pregnancy. In neurology, epilepsy is one of the highly relevant conditions, but we have also examined mothers with myasthenia gravis (MG) or MS. National health registries in Norway represent an excellent source of information regarding which factors influence the outcome for both child and mother. Clinicians should lead the interdisciplinary research in this field in order to ensure that the relevant questions are asked and that the conclusions drawn are valid.

Q: To what extent does pregnancy limit the treatments available for epilepsy patients?

A: Our clear recommendation is that a diagnosis of epilepsy and ongoing antiepileptic treatment should not prevent patients from becoming pregnant. Epilepsy is a treatable condition and more than two-thirds of patients become seizure-free. Preventive drugs are the cornerstone of this treatment, which is also true during pregnancy. Young women with epilepsy should be actively treated with a definite aim of becoming seizure-free. However, drugs that are known to increase the risk of a negative influence on the child's development should be avoided if possible. The drug dose and its concentration in the mother's serum should be as low as possible. Additional risk factors such as smoking should be avoided, and folate is thought to be beneficial. Patients should be advised before becoming pregnant, and they should have a well-organised follow-up during pregnancy.

Q: Tell us a little about the work you do for the NevroNor programme in the Norwegian Research Council. What are the aims of this programme?

A: NevroNor was established as a neuroscience programme in the Norwegian Research Council more than 10 years ago. The initiative came from the universities together with the hospitals, and it was actively supported by the council and the



government. The main reason for initiating this programme was the obvious need for more and better research in neuroscience in order to improve the treatment of brain disease, as well as serving to acknowledge the excellent research groups in Norway involved in both clinical and basic neuroscience. Furthermore, public activities such as Year of the Brain, Brain Exhibitions, and the Norwegian Brain Council have been helpful.

NevroNor had an aim to be a financial instrument for securing improved large-scale funding for Norwegian neuroscience projects. In this regard, the programme has failed because the resources available have been rather limited. However, it has been able to provide 'seed money' with strategic influence, especially in supporting national network research and international cooperation. Aims regarding scientific success and relevance for patient treatment are difficult to assess. The Nobel Prize to May-Britt and Edvard Moser in 2014 did not depend on NevroNor, but shows that Norway is able to contribute significantly in neuroscience.

Q: You have also been involved in several EU research projects. Can you explain how this came about and what the outcomes of these were?

A: I have been lucky to be part of the European research network on MG. Groups with complementary research interests have joined forces, with the cooperation between basic and clinical neuroscience being especially important. Patient representatives have also been involved in some of these projects. Furthermore, we obtained financial EU support when we established the European School of Neuroimmunology (ESNI), a successful initiative promoting interaction between young clinicians and scientists at the European level. ESNI has also received valuable support from the European Federation of Neurological Societies (EFNS). The European Academy of Neurology (EAN), and previously the EFNS and ENS, should represent powerful tools for research networks, especially through the Subspecialty Scientific Panels.

Q: How do annual congresses such as EAN assist healthcare professionals? Is there anything in particular you are looking forward to from this year's congress?

"A major challenge is to find the optimal way of interacting with all the subspecialty interest groups within neurology."

A: The EAN congress is an annual highlight. The combination of a broad update in clinical neurology and specialised research news is excellent. Meeting new and old colleagues from all over the world is also valuable and stimulating. EAN is in its infancy and discussions during the congress this year will be especially important in deciding how our joint organisation should develop and what should be the major priorities. The EAN congress should become the meeting that is impossible to miss for active European neurologists. A major challenge is to find the optimal way of interacting with all the subspecialty interest groups within neurology.

Q: What advice would you give to somebody considering a research or medical career specialising in neuroscience/neurology?

A: I would give my full support and congratulate their excellent choice of going into neuroscience/neurology. This is the most interesting of all clinical fields, with a lot of challenges and where marked improvement in patient treatment, diagnosis, and general insight will be obtained during the next few years. The field is expanding and funding possibilities are increasing because of the high relevance for society. Hard and dedicated work is needed and international participation and cooperation is important, not least for the young professionals who should travel and find their active place within international professional networks. For clinicians, I would strongly advise them to combine their clinical work with research projects, and to join a good research group.

Q: In your opinion, what are the three biggest obstacles facing neurologists today and how can they be overcome?

A: The biggest obstacle is always the insufficient treatments available for many of our patients.

In European countries, that is most often because the disorder is not yet curable or treatable. The answer to this insufficiency is more and better research. However, it is a challenge for everyone to keep up with best available standards and treatment. Guidelines should be made, and they should be followed. Quality control in the daily work with patients is necessary. Finally, I would point to organisation, resources, and funding; this is the dominating aspect in some countries. My three main challenges would therefore be: more and better research; more and better quality control; and improved organisation and funding. Neurologists and neurology organisations can influence all three aspects, and we have an obligation to do so. Therefore, we should cooperate and interact with society in the broadest sense.

Q: What are the next stages for your own research?

A: My background is in the clinic but I also have experience from laboratory-based research, and neuroimmunology in particular. We are now trying to combine our clinical and biomarker data and knowledge with large patient registries, sometimes covering full national cohorts. Such registries represent an asset for Norwegian biomedical research. Comparisons with cohorts from other populations can give insights into disease mechanisms and causes, and also point to optimal treatment regimes.

Marco Feligioni

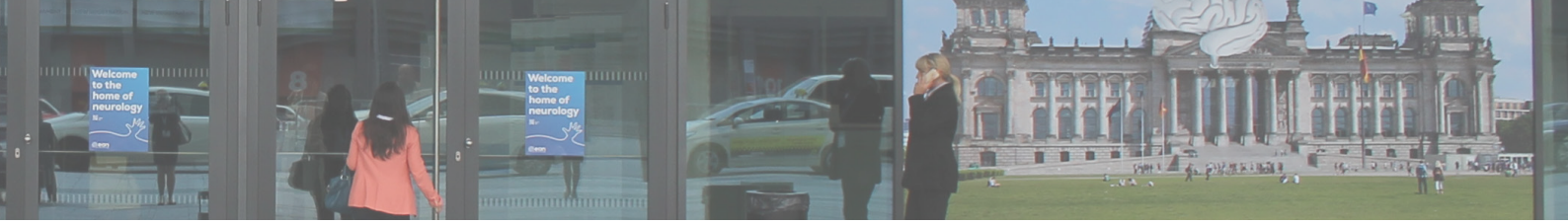
Scientific Researcher, Laboratory of Synaptic Plasticity,
European Brain Research Institute (EBRI) 'Rita Levi-Montalcini' Foundation, Rome, Italy.

Q: Who or what inspired you to take up a career in neuroscience?

A: I was a student in the Faculty of Pharmacy at the University of Genoa and I had to decide where to apply for my master's degree thesis. The choices were either pharmaceutical technology, medicinal chemistry, or pharmacology. The university courses in pharmacology were the most interesting to me and they were mostly in the area of neuroscience. In fact, the pharmacology professors were a group of bright scientists working on synaptic transmission and, therefore, my choice was to join this group of nice people who introduced me to neuroscience research.

Q: A lot of your research focusses on pathological mechanisms in Alzheimer's disease (AD). How complete is our understanding of the causes of this type of neurodegenerative disease?

A: My research is focussed on the mechanisms that contribute to the onset and development of the pathology. Today, our knowledge regarding the causes of AD is advanced and we know what causes the pathology. The two hallmarks of this neurodegenerative disease are the accumulation of amyloid-β (Aβ) aggregates and the formation of neurofibrillary tangles due to the hyperphosphorylation of Tau protein. Research at the molecular level has revealed many aspects of these mechanisms: we know how (Aβ) is produced and how Tau is hyperphosphorylated. We also know which intracellular binding partners are the ones that participate in the misprocessing of these proteins, and where all these mechanisms take place within neuronal cells. What we still need to discover is the timing of the onset of AD: we still don't know when the molecular changes that lead to accumulation of these misprocessed proteins begin in the brain. It is currently thought that the onset of this pathology occurs many years before we can measure any symptoms. Unfortunately, we still have very little knowledge of how to detect the molecular changes that take place during the onset of the pathology. That is why researchers are searching for biomarkers for use in the Alzheimer's field. Another important aspect is what causes this pathology. Some of the many hypotheses include: 'oxidative stress', diet, air pollution, and lifestyle. We already know that oxidative stress plays an important role in the onset and progression of the pathology, and recent experiments have also highlighted the importance of diet, with mouse models of AD showing delayed



development of pathology when fed with a low-calorie diet.

Q: How close are we to developing medicines that can stop, slow, or even reverse the progress of neurodegenerative diseases?

A: Research into the development of new drugs for neurodegenerative diseases is very active, although most research is directed towards finding drugs capable of reducing cognitive dysfunction because it is difficult to detect when a person starts to be affected by these pathologies. It should also be mentioned that there are many efforts to find compounds able to reduce the accumulation of Aβ or Tau hyperphosphorylation in the context of AD; I think we could benefit from this research in the future.

Q: There is a lot of media coverage of how we should expect a large increase in the incidence and prevalence of neurodegenerative diseases due to the ageing population present in many countries. Are there any preventative measures that can be taken earlier in life in order to avoid this type of disease?

A: This is a very difficult question and we still do not have an answer for it. What I can say is that for AD we know that oxidative stress and diet play a fundamental role. Therefore, a good lifestyle that reduces cells' possible exposure to oxidative stress could help. For example, it is better to avoid smoking, diets should be low in calorie content, exposure to air pollution should be reduced, and physical activity is also important.

Essentially, a healthy lifestyle serves as a good prevention for neurodegenerative diseases.

Q: What will be the next stages of your research at the EBRI Foundation, and what do you feel will be the 'next big thing' in neuroscience in general?

A: My research at the EBRI Foundation will be focussed on understanding the involvement of an emerging intracellular mechanism, protein SUMOylation, in the onset and progression of AD. We have already shown that this post-translational protein modification is enhanced in the cortex and hippocampus of a mouse model of AD during the onset and progression of the pathology. We are now investigating how this increase in SUMOylation affects synaptic transmission, and have obtained some very interesting data that we hope to be able to publish this year. I think the future of drug discovery in neuroscience lies in finding new biochemical markers that will allow us to predict pathologies at the onset, and some drugs may be able to be developed by targeting intracellular proteins involved in important pathways.

Q: Are there any areas of neuroscience that you would have liked the opportunity to explore but have not yet had the chance to do so?

A: My research to date has focussed on understanding how protein SUMOylation is involved in protein aggregation, and therefore in the future I think I would like to have the possibility to work in other areas of neuroscience and study other pathologies due to protein aggregation, such as amyloid lateral sclerosis, Parkinson's disease, and Huntington's disease.

Q: How important are international congresses to neuroscientists? Are there any specific congresses that you look forward to each year?

A: International congresses are really important for scientists because they only last for a short period, normally a few days, but are very intense in terms of scientific discussion. It is of fundamental importance to meet other scientists and listen to what they have done because these opportunities make it very easy to find new collaborations and set up new research networks. Most of the time, listening to the work of others can also help us to better understand our own research or to find answers to our scientific questions. I am looking forward to several congresses and every year I check for Alzheimer's-specific meetings, oxidative stress meetings, as well as Forum of Neuroscience and International Brain Research Organization meetings.

Q: Is there a particular area of neuroscience that you feel requires greater research and funding?

A: I think the areas of neuroscience that need more funding are those that study the basic mechanisms of cell physiology. This is fundamental for our understanding of how pathologies can

develop, but, unfortunately, we hear more and more today that science should be translational to human pathologies.

Q: What do you feel is the biggest challenge currently facing the field of neuroscience, and what is being done to tackle this?

A: I think the biggest challenge is to find out how the brain is able to store information and how our memory functions. Something more difficult to understand is how the brain uses this information in order to allow thinking and thoughts. There is something special in our brain that is able to interpret the changes in molecular machinery, modification of protein activity, and neurotransmission, and transform this biological information into something more ethereal that we experience as thinking and thoughts. Very little has currently been done in this field because it is quite complicated, although technology such as functional magnetic resonance imaging may be able to help us to study these aspects in the future.

Q: What advice would you give to someone who is considering a career in neuroscience research?

A: Every day I have to advise my students or collaborators on the best way to be successful in neuroscience. I think the first important piece of advice I can give is to be sure that research is the field you want to pursue. In science we have a very small salary compared with other jobs and this can be frustrating whilst you are doing your experiments. If you have the dedication to live this life then you are ready to work in science. Moreover, I think that having experiences in different laboratories is fundamental for the development of a good scientist.

László Vécsei

Director, Department of Neurology, Faculty of Medicine, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary.

Q: What originally inspired you to begin a career in neurology?

A: As a young medical student I started my research activities at the Department of Pathophysiology. We investigated the effects of vasopressin, oxytocin, and other neuropeptides on various behavioural pharmacology tests and neurochemical parameters. Since I planned to pursue a career in clinical sciences, it was logical to choose neurology.

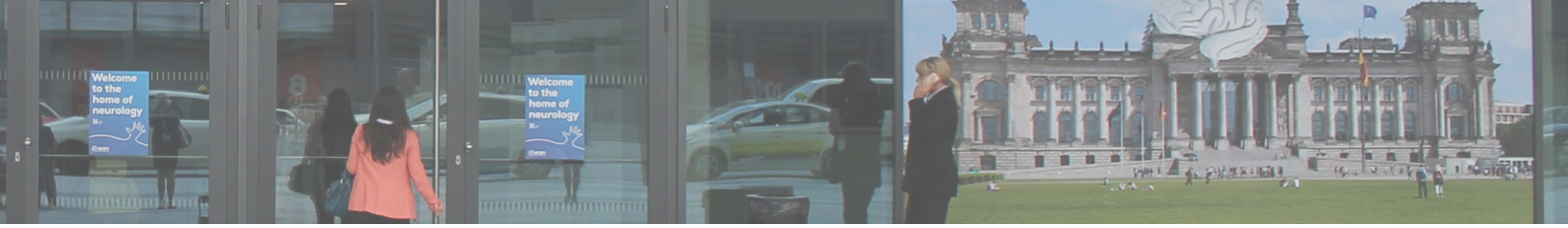
Q: How important are large congresses, such as EAN 2015, to neurologists and neuroscientists?

A: Large congresses, and in particular EAN, are very important to neurologists because most of them cover several disciplines of the entire field of neurology. As Regional Vice-President of the European Federation of Neurological Societies (EFNS), I was happy to help with the organisation of the EFNS congresses. Furthermore, congresses represent a very good opportunity to meet with other neurologists and build up collaborations around the world.

Q: How would you describe the overall rate of progress in neurology/neuroscience research in recent times?

A: I started my career in neurology more than 30 years ago. During the last couple of years there has been very significant progress in the diagnosis of neurological disorders (diffusion and perfusion magnetic resonance imaging [MRI], MRI-spectroscopy, positron emission tomography, receptor-specific single-photon emission computed tomography investigations, analysis of cerebrospinal fluid samples with high-performance liquid chromatography, and other sophisticated neurochemical methods). We have many new drugs available to treat multiple sclerosis, Parkinson's disease, epilepsy, and migraine. Thrombolysis, and recently thrombectomy, have become important in the treatment of stroke. Today, personalised medicine is getting closer and closer to our everyday clinical practice.

Q: How far has our understanding of the pathomechanisms of neurodegenerative diseases



progressed since you first began research into this area?

A: When I started my scientific work, neuropeptides were in the front line of research: Yalow, Guillemin, and Schally received the Nobel Prize in 1977 for the isolation of several neuropeptides/neurohormones; endorphins and enkephalins were subsequently characterised. An important development occurred when it was discovered that excitotoxins, such as glutamate, aspartate, and quinolinic acid, are important players in the pathomechanism. Insufficient mitochondrial function and consequent intracellular energy deficiency have been shown to be important factors involved in damage to brain tissue. Neurogenetics, proteomics, and biomarkers are in the front line of investigations today.

Q: Do the public require greater education about how to detect the onset of neurological diseases?

A: The public absolutely require education regarding this topic: if neurological disorders are diagnosed early then the treatment is more successful.

Q: Has there been any noticeable change in the types or prevalences of neurological conditions that affect patients in Hungary, or has this remained fairly similar since you started your career?

A: We have had some success in the field of stroke: thanks to our National Stroke Program the number of stroke cases is now lower. Thanks to the introduction of MRI, the diagnosis of multiple sclerosis is now much more accurate than it was 30 years ago. The classification system of the International Headache Society is a big help for the correct diagnosis of different types of headache; and the same is true for other classification systems in other types of neurological disorders.

"During the last couple of years there has been very significant progress in the diagnosis of neurological disorders..."

Q: How effective are current therapies for neurodegenerative disorders with regard to preventing disease progression and even reversing neurological damage?

A: According to evidence-based medicine, there is, unfortunately, no clear evidence of neuroprotective therapies today. We have many preclinical data, but the effects in the clinic are questionable. In our clinical research, we focus on the kynurenine system because kynurenic acid is protective while quinolinic acid is an excitotoxic substance. However, some of the drugs used in the treatment of multiple sclerosis may have beneficial effects, not only on relapses but on progression too. We need more and more clinical data.

Q: How similar is the treatment of neurological diseases in different European countries?

A: The treatments for neurological disorders should be based on data from clinical trials and on the professional guidelines from various international societies. Therefore, the treatment strategies should be similar between countries. However, in some countries it may be difficult to get financial support for some of the more expensive treatment strategies.

Q: In your view, what are the main challenges facing neurologists today?

A: Neurology today is practised according to evidence-based medicine. However, personalised medicine, which is based on the genome and proteome of individual patients, is based on very specific biomarker measurements taken from individuals, and therefore we must learn as much as possible about neurochemistry, molecular biology, genetics, and bioinformatics.

Q: What advice would you give to young medical professionals about to begin a career in neurology?

A: They should be very well-educated in basic medical sciences and should keep track of the tremendous development of clinical neurology. However, the most important part of our profession is the patient: never forget about the importance of a good case history and a thorough neurological investigation.

EDITORIAL BOARD INTERVIEWS

Giuseppe Lanza

Department of Neurology, Oasi Institute for Research on Mental Retardation and Brain Ageing (I.R.C.C.S.), Troina, Italy; and Department G.F. Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy.

Q: Your work with the Oasi Institute is highly specialised, what attracted you to this particular branch of neurology?

A: The possibility to combine clinical practice and scientific research in the field of neurodegenerative diseases and sleep disorders; this research may have crucial clinical implications for the management and treatment of these patients.

Q: Are neurodegenerative diseases such as dementia becoming more prevalent, and is there anything that people can do to lower their risk?

A: Neurodegenerative diseases are becoming more and more prevalent, even considering the longer life expectancy of the general population. A healthy lifestyle and adequate management of vascular risk factors are necessary in order to prevent these disorders.

Q: How effective are current therapies for neurodegenerative diseases, and are there more in development?

A: Current therapies do not change the course of dementing processes or Parkinsonian syndromes, but they do manage to slow down their progression. Promising evidence has come from investigations of new neuroprotective agents and disease-modifying drugs.

Q: What do you hope to achieve in your research in the next couple of years?

A: To provide further insights into the neurophysiological mechanisms and neurochemical basis of vascular-related cognitive impairment. These insights may have practical implications for the design of novel therapeutic approaches.

Q: Are there any areas of neurology/neuroscience that you would like to study but have not yet had the opportunity to? Are there any subjects that you feel deserve more attention than they currently receive?

A: Neuropaediatrics, cognitive rehabilitation, and non-invasive brain stimulation.

Q: How would you describe the overall rate of progress in neurology/neuroscience research in recent years?

A: I think that the overall amount of scientific research in neuroscience has increased recently, with its focus being on providing a greater understanding of neurodegenerative diseases.

Q: In your view, what are the main challenges facing neurologists today?

A: The prevention of stroke and minimising its consequences, the design of new disease-modifying drugs for multiple sclerosis and motor neuron disease, and enhancing cognitive rehabilitation and other non-pharmacological therapeutic interventions.

Q: How important are events such as EAN 2015 to the field of neurology/neuroscience?

A: They are extremely important and exciting, especially for young doctors and specialists. Sharing ideas and resources is the future for neuroscientists.

Q: What advice would you give to young doctors interested in a career in neurology/neuroscience?

A: Keep studying to learn and ask 'why?' of the neurobiological phenomena, attend different laboratories and institutes to share ideas with other colleagues with different areas of interest, never give up your scientific goals, and always look for cultural growth.

"Promising evidence has come from investigations of new neuroprotective agents and disease-modifying drugs."

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NON-ORAL DRUG DELIVERY STRATEGIES: FROM EARLY DIAGNOSIS TO ADVANCED TREATMENTS

Summary of presentations from the Britannia-sponsored symposium held at the 1st Congress of the European Academy of Neurology (EAN), Berlin, Germany, on 21st June

Chairpersons

Claudia Trenkwalder,[1] Werner Poewe[2]

Speakers

Werner Poewe,[2] Fabrizio Stocchi,[3] Stuart H. Isaacson[4]

1. University Medical Centre of Göttingen, Göttingen;
and Paracelsus Elena Klinik, Center of Parkinsonism and Movement Disorders, Kassel, Germany
2. Department of Neurology, Innsbruck Medical University, Innsbruck, Austria
3. Institute of Research and Medical Care, IRCCS San Raffaele, Rome, Italy
4. Florida International University, Herbert Wertheim College School of Medicine, Miami;
Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton;
and Marcus Neuroscience Institute, Boca Raton Regional Hospital, Boca Raton, Florida, USA

Disclosure: C. Trenkwalder has received personal fees for advisory boards from Mundipharma, UCB, Vifor Pharma, Britannia Pharmaceuticals, and Novartis; she has also received payments for lectures from UCB, AstraZeneca, and Desitin; and has received royalties from Schattauer Verlag. W. Poewe has received personal fees from Britannia for consultancy and lecture fees in relation to clinical drug development programmes for Parkinson's disease (PD); he has also received personal fees from AbbVie, AstraZeneca, Britannia, Lundbeck, Teva, Novartis, GSK, Boehringer-Ingelheim, UCB, Orion Pharma, Zambon, and Merz Pharmaceuticals for consultancy and lecture fees in relation to clinical drug development programmes for PD, outside of the submitted work; and has received royalties from Thieme, Wiley Blackwell, and Oxford University Press. F. Stocchi has received honoraria for participation in scientific advisory boards for GSK, Teva, Boehringer Ingelheim, Newron, Merck Serono, Novartis, Lundbeck, Impax, Schering-Plough, MSD, and UCB; and has received speaker fees for educational lectures for GSK, Teva, Boehringer Ingelheim, Merck Serono, Novartis, Lundbeck, UCB, and Britannia. S. H. Isaacson has received honoraria for CME activities, research grants and/or consultant and promotional speaker fees from AbbVie, Acadia, Adamas, Addex, Allergan, Allon, AstraZeneca, Biotie, Britannia, Chelsea, Civitas, Eisai, GE, GSK, Impax, Ipsen, Kyowa, Lilly, Merck Schering-Plough, Medtronics, Merz, Michael J. Fox Foundation, Novartis, Neurocrine, National Institutes of Health (NIH), Novartis, Orion, Parkinson Study Group, Phytopharm, Purdue, Roche, Santhera, Serono, Shire, Teva, UCB, and US World Meds.
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MEETING SUMMARY

This educational symposium, sponsored by Britannia Pharmaceuticals Limited, was held during the 1st Congress of the European Academy of Neurology (EAN), which took place from 20th-23rd June 2015 in Berlin, Germany. The symposium reviewed the role of non-oral drug delivery strategies in patients with Parkinson's disease (PD) and how they can overcome problems that occur with the gastrointestinal (GI) route of administration in many patients. GI dysfunction is recognised as a common problem in PD and may in fact be a preclinical marker of the disease. It can affect the absorption of oral medication resulting in OFF periods and unreliable control of motor symptoms, which in turn can have a negative impact on quality of life (QoL). Delayed time-to-ON (TTO) after an oral levodopa dose and dose failures are known to be significant contributors to total OFF time. Results of the recently completed

AM-IMPAKT trial in patients with morning akinesia due to a delay in the onset of oral levodopa effect demonstrate that apomorphine intermittent injection (penject) is able to provide rapid and effective resolution of such complications, restoring patients to the ON state quickly and allowing them to get on with their daily activities.

Gastrointestinal Dysfunction in Parkinson's Disease

Professor Werner Poewe

Prof Poewe reminded delegates that while PD is traditionally considered to be primarily a movement disorder, it is in fact a multi-system disease and affects areas of the brain that are not directly involved in motor control, for example the hypothalamus, locus coeruleus, and raphe nuclei of the brainstem.[1-3] PD pathology also extends into the peripheral autonomic nervous system involving sympathetic ganglia, cardiac sympathetic efferents, and the enteric nervous system (ENS).

The PRIAMO study[4] was a multicentre survey that interviewed 1,072 consecutive PD patients at different stages of disease (treatment-naïve, stable, and complex) over a period of 12 months at 55 centres in Italy to assess the prevalence of non-motor symptoms (NMS) in PD and their impact on QoL. The results found that 98.6% of patients with PD reported the presence of NMS. They occurred across all disease stages and many patients experienced multiple symptoms – the mean number of NMS per patient in the survey was 7.8. Notably, GI symptoms were present in 45% of newly diagnosed, untreated patients, 60% of those with stable disease, and 72% of those with complex disease (Figure 1).

Prof Poewe commented that, in many cases, if patients were not specifically asked about these symptoms, they might be overlooked. He highlighted the results of a study of 89 PD patients who undertook a validated NMS questionnaire (NMSQ), which was compared with standard neurology clinic reporting in case notes.[5] Results of NMSQ found a mean of 11 different NMS per patient. In contrast, chart review showed a mean of 4.8 NMS per patient, suggesting that some symptoms remain under-reported by patients unless questioned. In this study, constipation was reported by 48%, highlighting that GI problems are a frequent non-motor issue in PD.

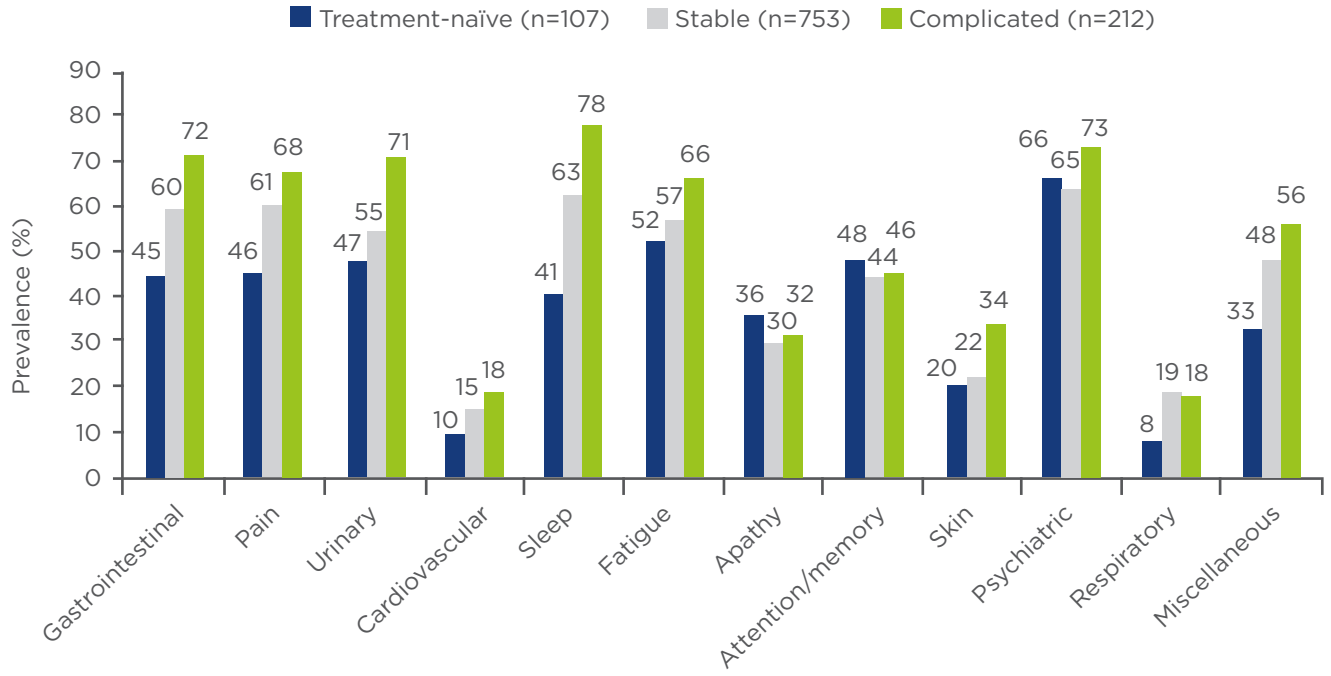

Figure 1: Prevalence of non-motor Parkinson's disease symptoms in patients with treatment-naïve, stable, and complex disease: results of the PRIAMO study.[4]
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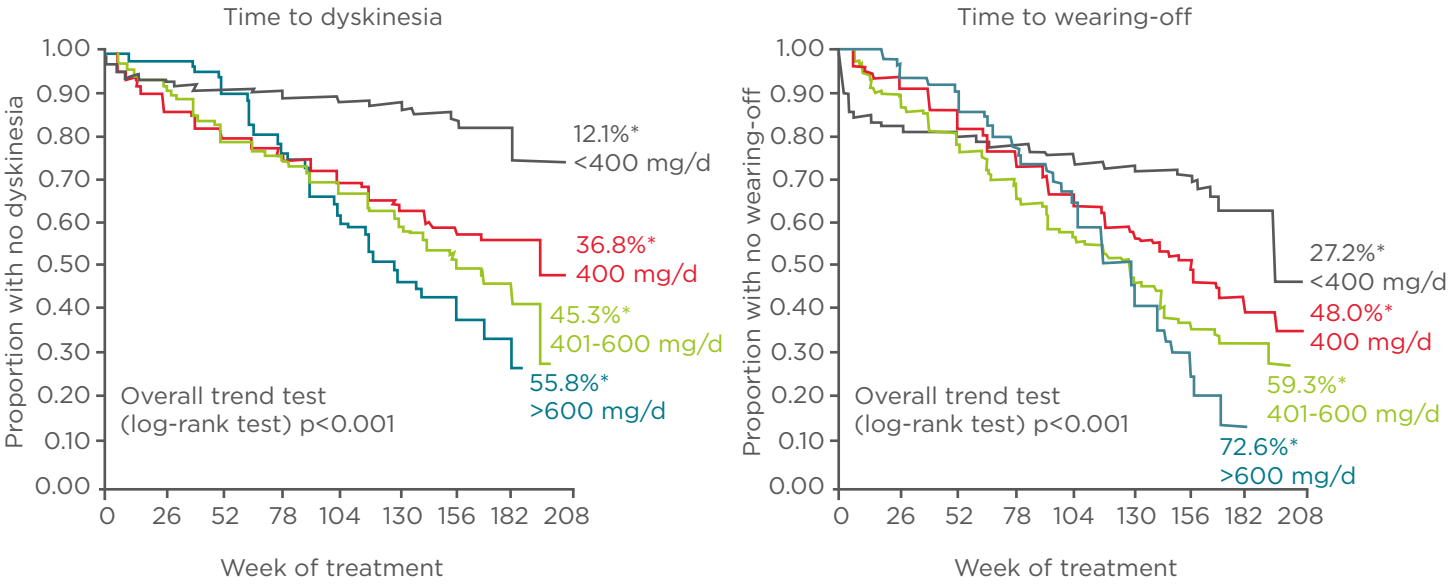

Figure 2: Levodopa dose is predictive of the development of dyskinesia and wearing-off: results of the STRIDE-PD study.[17]

*Rates at study termination.

Reproduced with permission of Movement Disorders.

GI dysfunction in PD patients is now known to occur at all levels of the GI tract.[6,7] Common clinical features include sialorrhoea (drooling), dysphagia, gastroparesis, colonic dysmotility (constipation), and anorectal dysfunction. These symptoms have a range of clinical consequences for patients, and in some cases can be a burden for their caregivers too, resulting in social embarrassment, reduced appetite, weight loss, aspiration of food, and impact on effective absorption of oral PD medication.

It is now recognised that development of NMS can precede the onset of motor symptoms in PD. A recent study was undertaken to investigate the timing of onset of NMS in PD and the possible association with motor phenotype using a custom-made questionnaire in 109 newly diagnosed, untreated PD patients and 107 age and sex-matched healthy controls from 11 centres in Spain and Austria.[8] Seventeen of 31 different NMS were found to be more common in PD patients than in controls ($p<0.05$). Notably, in >50% of PD patients, NMS preceded the onset of motor symptoms. The symptoms reported more frequently in the 2-10-year premotor period were smell loss, mood disturbances, taste loss, excessive sweating, fatigue, and pain. Constipation, dream-enacting behaviour, excessive daytime sleepiness, and postprandial fullness were frequently perceived more than 10 years before motor symptoms occurred.

The natural history of PD is characterised by a gradual decline in striatal dopamine through the preclinical and prodromal stages, eventually reaching an 80% deficit which is indicative of a diagnosis of PD and represents a 50% loss of neurons in the substantia nigra. The identification and characterisation of prodromal NMS of PD is the subject of considerable research. In the case of GI dysfunction, studies by Abbott and colleagues[9] found that constipation and infrequent bowel movements were associated with a significantly elevated risk of future PD ($p=0.005$). Further studies by this group found evidence that constipation can predate the extrapyramidal signs of PD and could be one of the earliest markers of the beginning of the PD process. The preclinical phase of PD is often characterised by the presence of incidental Lewy bodies (ILB). Assessment of bowel movement frequency in 245 men, aged 71-93 years without clinical evidence of PD who later received post-mortem examinations, found that the percentage of brains with ILB declined with increasing bowel movement frequency ($p=0.013$).[10]

There is a substantial need for an accurate early diagnostic test for PD, and with this in mind, researchers have been focussing on the potential link between ENS pathology and preclinical or prodromal PD. Alpha-synuclein is the primary structural component of Lewy bodies and its aggregation is thought to play a critical role in the

development of PD. Alpha-synuclein pathology has been found in body tissues outside of the brain not usually associated with PD. A recent study has suggested that alpha-synuclein may be present in colonic biopsy tissue in early or even prodromal PD before the development of characteristic PD motor symptoms, and may therefore be a potential diagnostic biomarker for pre-motor PD.[11] Archival colon biopsy samples obtained 2-5 years before PD onset were analysed for three patients with PD. All patients showed immunostaining for alpha-synuclein at least 2 years before the first motor PD symptom occurred. In contrast, no corresponding alpha-synuclein immunostaining was seen in 23 healthy controls.

Prof Poewe concluded by highlighting that many aspects of GI dysfunction in PD are now recognised to have a significant potential impact on oral drug delivery and hence clinical efficacy.[12] Difficulties in swallowing can lead to adherence problems in patients receiving oral medication. Delayed gastric emptying (gastroparesis) can lead to a reduction in the speed of oral levodopa delivery to its site of absorption in the small intestine, resulting in a 'delayed ON' or even dose failure. Competition between levodopa and proteins for transport across the GI mucosa can result in unpredictable drug responses. The OFF periods that the patient experiences will result in motor and non-motor fluctuations that have a negative impact on their QoL, and so Prof Poewe considered that it was important that alternative therapeutic interventions were sought in such cases.

Wearing OFF and Delayed ON – Motor and Non-Motor Fluctuations

Professor Fabrizio Stocchi

Prof Stocchi described how 'ON–OFF' fluctuations in PD patients receiving chronic oral levodopa therapy were first described by Marsden and Parkes in 1976.[13] Motor complications include both motor fluctuations and dyskinesias. Motor fluctuations can include predictable end-of-dose 'wearing-off' phenomena, peripheral problems such as delayed ON (for example morning akinesia) or 'no ON' (dose failure), and unpredictable ON–OFF periods. Dyskinesias may be peak-dose effects, distressing and painful diphasic dyskinesias, or painful OFF-period dystonia. He highlighted how debilitating and distressing these different motor complications can be in the real-life setting with a series of patient videos. In addition to classical motor fluctuations, many PD patients also experience non-motor fluctuations, such as anxiety, panic attacks, pain, fatigue, mood changes, urinary urgency, and swallowing difficulties.[14]

Wearing-off is commonly associated with the later stages of PD. However, a review of preclinical and clinical data suggest that fluctuations in the response to levodopa may appear much earlier than previously thought, and can be present in patients with early disease.[15] Prof Stocchi presented the results of the DEEP study (Early DEtection of wEaring off in Parkinson disease),[16] which was undertaken to assess the frequency of wearing-off in PD patients and its impact on QoL using a validated screening tool, WOQ-19. These results showed that the frequency of wearing-off increased with duration of disease such that, after 10 years, around 80% of PD patients experienced wearing-off phenomena.

Prof Stocchi went on to highlight some of the risk factors underlying complications in PD. He reviewed a secondary analysis of the STalevo Reduction In Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) study that had investigated the effect of levodopa dose and other risk factors on the development of dyskinesias and wearing-off. The results demonstrated that time to development of dyskinesias and time to wearing-off both correlated with the dose of oral levodopa (Figure 2).[17] Multivariate analyses showed that factors predictive of dyskinesia included young age at onset, higher levodopa dose, low body weight, female gender, and more severe Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores. Predictors of wearing-off included higher baseline UPDRS scores, higher levodopa dose, and the female gender.

Motor complications in PD patients are recognised to have a significant impact on QoL.[18] This was investigated in 143 patients with PD who were evaluated using the Hoehn and Yahr scale and the motor part of the UPDRS. In addition, a specific PD QoL questionnaire (39-item version, PDQ-39) was used. Motor complications, including early morning akinesia, nocturnal akinesia, end-of-dose fluctuations, paradoxical fluctuations, and unpredictable OFFs, were found to significantly worsen the PDQ-39 Summary Index of patients with PD. The dimensions of mobility, activities of daily living, stigma, and communication were most strongly affected.

Prof Stocchi described an ongoing study, the Time to ON Questionnaire in PD (TOQ-PD), which is a survey being undertaken in PD patients attending a routine clinical appointment to help characterise their early morning OFF problems (unpublished data). This pilot study is a non-interventional, outpatient study being conducted in 90 consecutive patients treated in movement disorders centres. As part of the inclusion criteria, patients, in the opinion of the prescribing physician, had to be able to understand and describe the changes in ON and OFF clinical status. A total of 25% of patients felt that their medication was taking >1 hour to work. Almost 52% of patients found it troublesome when their first daily dose of levodopa took longer than usual to work (delayed ON), did not work well (suboptimal ON), or did not work at all (dose failure). In the case of the mealtime dose of levodopa, this figure was 56%. Patients also described a range of problematic symptoms that occurred while waiting for their levodopa to work, including slowness, stiffness, and difficulty walking.

Prof Stocchi also recognised the contribution of peripheral factors to delayed ON and dose failure with oral levodopa, for example swallowing difficulties which he clearly illustrated with a series of endoscopic videos. Swallowing abnormalities in PD patients include abnormal lingual control of swallowing, lingual festination, delayed swallowing reflex (a tendency of parkinsonian patients to swallow during the inspiration phase increasing the possibility of aspiration), and repetitive or involuntary reflux from the vallecula and piriform sinuses into the oral cavity. These troublesome symptoms need careful management and might require a change in the type of food and diet consumed. Dopaminergic drugs may improve swallowing; however, alternative routes of administration such as transdermal therapy, subcutaneous infusion, or intraduodenal infusion should be considered.

Gastroparesis, or delayed gastric emptying, is common in PD, resulting in postprandial fullness, nausea, vomiting, and impaired drug absorption that in turn leads to delayed ON or no ON.[19] Recently, delayed TTO and dose failures have been recognised as a significant proportion of total OFF time, comprising more than twice the duration of wearing-off in PD patients.[20] This was illustrated clearly in a pharmacokinetic study of levodopa given every 4 hours undertaken by Prof Stocchi, which revealed a substantial proportion of OFF time over the day, and particularly delayed ON (unpublished data).

In view of the high prevalence of GI dysfunction in PD patients and its impact on the efficacy of oral medication, a range of alternative PD medication formulations and routes of administration have been investigated in this setting with varying degrees of success. These include liquid levodopa, transdermal dopamine agonists, subcutaneous apomorphine, and intraduodenal levodopa infusion.

Prof Stocchi also reviewed the strategies that had been investigated to tackle the phenomenon of wearing-off.[21] Standard oral formulations of levodopa result in pulsatile dopaminergic stimulation and are not able to maintain steady plasma levels throughout the day. Therefore, continuous dopaminergic stimulation (CDS) has been proposed to more closely mimic the physiological situation and help overcome the motor complications that occur with standard oral therapy.[22-25] Other options include modifying the timing or formulation of levodopa, modifying the actions of levodopa by using catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone), the use of longer-acting dopamine agonists (such as pramipexole, ropinirole, rotigotine, apomorphine, or pergolide), or by modifying the actions of dopamine at the synaptic level by using a monoamine oxidase B (MAO-B) inhibitor (rasagiline).

One option for CDS that is backed by considerable clinical experience is continuous apomorphine infusion: it has proven efficacy for PD patients with motor fluctuations that are uncontrolled by conventional oral or transdermal medication and is well tolerated. In a recent review, the data for 390 patients from 21 open-label uncontrolled studies were pooled.[26] The results showed a 58.2% average OFF time reduction (range 38-80%) and a levodopa-sparing effect with a 45.9% reduction in levodopa-equivalent dose during an observation period of 24.8 months (6-57 months). In the case of dyskinesias, 6 of 11 long-term studies showed ~50% reduction in duration and ~45% reduction in severity of dyskinesias with continuous apomorphine infusion.[27] Biphasic and peak-dose dyskinesias showed the best response to therapy. A study by Prof Stocchi's own research group showed a significant and sustained reduction in the severity of dyskinesias with long-term use of continuous apomorphine infusion over a period of 5 years.[28]

As with all therapeutic interventions, Prof Stocchi noted that it was important to select the right patient in order to maximise the success of treatment. He advised that continuous apomorphine infusion should be considered in all PD patients who develop features of complicated disease irrespective of their age or disease duration. This should include patients who have become progressively disabled, those who experience increasing or long OFF periods, those who have moderate-to-severe dyskinesias, and those who are already suffering with motor complications or who have developed levodopa-induced dyskinesias. PD patients who might not be suitable for this treatment option include those with a poor response to levodopa; those with severe cognitive impairment; patients with contraindications such as hepatic insufficiency, pregnancy, or lactation; patients without support to help them manage the infusion device; and those with excessive skin problems.

Prof Stocchi concluded his presentation by noting that continuous apomorphine infusion has several advantages over other CDS options for PD patients who experience motor fluctuations despite optimised oral medication. Importantly, it is the least invasive of the three advanced therapies (apomorphine infusion, intrajejunal levodopa infusion, and deep brain stimulation) and is completely reversible. Apomorphine infusion is practical to use – it can be initiated during inpatient hospitalisation or in a day-hospital setting – and does not induce tolerance.[28]

Apomorphine Penject – AM-IMPAKT Trial Results and Best Clinical Practice

Professor Stuart Isaacson

Prof Isaacson noted that over the past two decades the issue of motor fluctuations and OFF periods in PD patients had focussed very much on end-of-dose wearing-off of oral PD medication. However, it is now becoming increasingly recognised that in addition to end-of-dose wearing off there are many other contributors to total OFF time, including nocturnal akinesia, morning akinesia, postprandial akinesia, delayed TTO, and dose failure (no ON). Studies have now shown that delayed TTO is in fact a major contributor to OFF time, being more than twice the duration of wearing-off.[20] He acknowledged that when oral levodopa is first used to treat PD patients, the clinical effect of each levodopa dose is rapid, reliable, and sustained with an onset of around 20 mins and a long-duration response. However, with chronic treatment, the long-duration response is replaced by a short-duration response and OFF periods, such as wearing-off and delayed TTO, become more frequent.

Levodopa has been the recognised 'gold standard' treatment for PD for the past 50 years but it is an oral treatment that must be swallowed and therefore its efficacy may be affected if the patient also suffers from GI tract dysfunction. The GI tract is known to be dysfunctional in many PD patients and this can occur almost a decade or more before PD is clinically diagnosed. In addition, medications used to treat PD may also contribute to GI dysfunction, including levodopa, dopamine agonists, anticholinergics, amantadine, and inhibitors of MAO-B and COMT. GI symptoms, such as gastroparesis, can impact on the effectiveness of oral levodopa by delaying its delivery to, and absorption in, the small intestine,[19,29] resulting in delayed ON or even dose failure.[30] Absorption of levodopa can be affected by competition with ingested protein for the amino acid transporter. In addition, recent studies have confirmed a high prevalence of small intestinal bacterial overgrowth in PD, which may also affect levodopa absorption, and have reported an association with poor motor function, longer daily OFF time, and more episodes of delayed ON and no ON.[31,32]

An investigation of the prevalence of delayed gastric emptying of solids in PD was undertaken in 22 healthy subjects and 36 patients at different clinical stages of PD using a ^{13}C-sodium octanoate breath test (OBT).[29] The OBT was able to detect a significant delay in gastric emptying of a solid test meal in patients with PD that was associated with disease severity, illustrating how common gastroparesis is across all disease stages. While liquids are able to empty from the stomach quicker than solids, in PD patients there may still be a delay in gastric emptying. In the case of oral levodopa, Doi and colleagues[19] demonstrated a significant relationship between levodopa pharmacokinetics and gastric emptying in PD patients, suggesting that delayed gastric emptying is a causative factor for producing the delayed ON.

The high prevalence of early morning OFF (EMO) periods has been demonstrated in the results of the international, multicentre EUROPAR study.[33] EMO periods occur when the first morning dose

of oral levodopa has a delayed onset of action and were found in this study to be present in 59.7% of the 320 patients, occurring throughout the course of PD in mild, moderate, and severe disease. Prof Isaacson highlighted that EMO periods are often an early sign of emerging motor fluctuations and the loss of the long-duration levodopa response, and can occur despite attempts to optimise oral therapy and the use of multiple medications. During episodes of morning akinesia the patient can experience impaired mobility and function until the oral levodopa takes effect, and this is known to have a negative effect on patient QoL.[18] Although morning akinesia represents the motor component of EMO periods, both motor and NMS are frequent in PD patients at these times.

A range of treatment strategies have been employed in an attempt to resolve the issue of morning akinesia, for example the use of long-acting dopamine agonists or MAO-B inhibitors, or by aiming to improve delivery of levodopa to the proximal small intestine by using liquid, dispersible, modified, or higher-dose levodopa. However, none of these approaches addressed the problem of PD patients who have gastroparesis where emptying of both solids and liquids may be impaired,[29] and in whom a delayed onset of levodopa effect may still occur. This has been illustrated in a study by Chaná and colleagues,[30] who assessed the pharmacokinetics of levodopa in 19 patients with advanced PD with and without a delayed onset of first levodopa dose in the morning. The results confirmed that the difference in plasma concentrations of levodopa between the two groups was most likely due to delayed gastric emptying, and this phenomenon probably underlies the delayed clinical response to oral levodopa in many PD patients.[30]

Figure 3: Apomorphine pen injection.

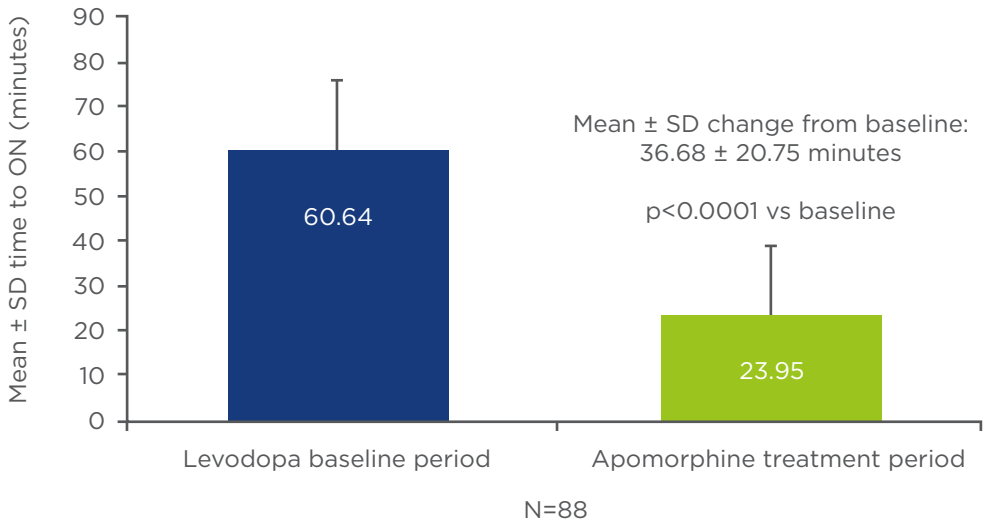

Figure 4: Change from baseline in time-to-ON following apomorphine injection: results of AM-IMPAKT [unpublished data].
SD: standard deviation; vs: versus.

These problems highlight the need to consider non-oral therapies to manage motor symptoms in this setting. The potent dopamine agonist apomorphine administered subcutaneously has provided clinicians with an effective option for the rapid resolution of the parkinsonian symptoms for over 25 years. Prof Isaacson considered that subcutaneous apomorphine intermittent injection offered an easy and practical therapeutic option for managing EMO as it avoided the oral route of administration that could be affected by delayed gastric emptying or impaired intestinal absorption. The clinical efficacy of apomorphine infusion has been confirmed in a range of randomised, controlled clinical trials undertaken in the USA. In the APO202 study of 29 PD patients with motor fluctuations and prolonged OFF time despite aggressive oral therapy, apomorphine injection was able to reverse 95% of OFF episodes over a 4-week period when used as needed.[34] The APO302 study undertaken in 62 patients at 26 USA centres demonstrated that apomorphine injection was able to achieve rapid and reliable improvements in UPDRS motor scores compared with placebo.[35]

These significant improvements in mean UPDRS motor scores were seen 20 mins after administration of apomorphine injection. In addition, apomorphine injection significantly and rapidly improved mobility as early as 7.5 mins after dosing, and this effect persisted for at least 40 mins after dosing. Apomorphine injection was found to be effective over the long term, with efficacy being maintained in patients with an average therapy duration of 14.5 months. The APO303 study of 56 apomorphine-naïve patients with advanced PD at 17 USA centres provided further confirmationof the ability of apomorphine injection to provide rapid, effective relief of OFF episodes in PD patients already receiving optimised oral medication.[36] Mean changes from pre-dose in UPDRS motor were significantly improved following apomorphine injection (4 mg) versus placebo at 20 mins (p=0.0002), 40 mins (p<0.0001; maximum improvement), and 90 mins (p=0.0229) post-administration.

Prof Isaacson described how the use of apomorphine pen injection (Figure 3) has been investigated in the recently completed Phase IV, 10-centre, open-label, efficacy and safety study – AM-IMPAKT (Apokyn for Motor IMProvement of morning AKinesia Trial).[37-39] AM-IMPAKT aimed to investigate whether subcutaneous apomorphine injection given upon awakening was able to provide rapid and reliable improvement in motor symptoms in PD patients with morning akinesia due to delayed onset of the first oral levodopa dose. During the 7-day baseline study period, each morning following their first oral levodopa dose, patients recorded their TTO in a diary every 5 mins for up to 60 mins by checking boxes either 'yes' or 'no' until onset of ON. Patients subsequently initiated treatment with the apomorphine pen and used this for another 7 days upon awakening, completing the same TTO diary each morning. The primary endpoint was a comparison of TTO between the levodopa study period and the apomorphine injection period.

Morning akinesia was found to be common in the study population and occurred throughout the course of PD, even at relatively early stages. Over half of the PD patients who entered the study were in the first decade of their disease and, despite a range of oral therapies, had experienced persistent morning akinesia for an average of 4 years. The final analysis of data for 88 patients found that apomorphine pen injection significantly improved the primary endpoint of TTO: mean baseline TTO with levodopa averaged 60.64 mins, which reduced significantly to a mean of 23.95 mins with apomorphine injection (p<0.0001; Figure 4), representing a mean change from baseline of 36.7 mins. UPDRS motor scores were also significantly reduced within 15 mins of apomorphine compared with baseline (35.5 versus 17.3; p<0.0001), representing a mean change in UPDRS score of 18.2.

Analysis of individual data for each patient was very revealing and demonstrated the reliability of the response to apomorphine injection. Approximately 98% of patients experienced a rapid and robust clinical improvement in TTO with apomorphine injection. Dose failures were found to be common during the levodopa baseline period; however, most of these patients achieved an ON state with apomorphine injection, the majority within 20 mins.

Significant improvements were also found for the secondary patient-reported outcomes following treatment with apomorphine injection. Patients and investigators were asked to rate their global impression of severity of illness relative to akinesia/motor function before and after apomorphine therapy, measured on a 7-point scale from 'normal' to 'extremely ill'. In both cases significant improvements were recorded (p<0.0001). Measures of health-related QoL also showed improvement

with apomorphine injection. EQ-5D-3L is a patient-reported health outcome scale related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and each dimension is ranked from 1 (no problem) to 5 (extreme problem), so lower scores indicate a more favourable rating. EQ-5D-3L index scores were significantly reduced from a mean of 3.30 at baseline to a mean of 2.18 at the end of the 1-week apomorphine treatment period ($p<0.0001$). Using the EQ-5D Visual Analogue Scale, subjects rate their health state relative to akinesia on a scale of 0 (worst imaginable) to 100 (best imaginable), so higher scores indicate a more favourable rating. In AM-IMPAKT, scores also showed significant improvement from a mean of 50.38 at baseline to 65.67 at the end of the apomorphine treatment period ($p=0.0001$). An exploratory analysis of the number of patients who had at least one dose failure (failure to turn ON within 60 mins) found a total of 46% of patients during the levodopa baseline period compared with 7% during apomorphine injection period.

Prof Isaacson concluded by highlighting the importance of addressing not only end-of-dose wearing-off but also delayed TTO in PD patients, since this comprises the majority of total OFF time. Commonly, oral levodopa onset is impaired or absent due to GI dysfunction and therefore there is a need for effective non-oral PD medication to return patients to the ON state quickly. Results from the AM-IMPAKT study confirm that morning akinesia is a common but under-recognised symptom of PD and that subcutaneous apomorphine pen injection meets the need for an effective, rapid, and reliable solution to this problem. Notably, the observed reduction in TTO in the study is clinically relevant since there were significant improvements across a range of subjective measures, including UPDRS motor scores, QoL, and clinician and patient global impression of severity.

Summary

Prof Trenkwalder concluded the symposium by noting that an Expert Consensus Group Report on the use of subcutaneously administered apomorphine for the management of PD had just been accepted for publication in *Parkinsonism & Related Disorders*. The publication provided both a review of the published literature on the use of apomorphine and also consensus recommendations prepared by 26 advisors from 13 countries to help guide healthcare professionals in the optimal application of apomorphine therapy in clinical practice.

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Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. 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Neuropyschiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. 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HYPOTHALAMIC–PITUITARY ALTERATIONS IN PATIENTS WITH NEUROSARCOIDOSIS

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ABSTRACT

Sarcoidosis is a non-caseating, granulomatous inflammatory disorder that can affect the central nervous system (CNS), including the hypothalamic–pituitary region, although rarely. The clinical manifestations of hypothalamic–pituitary neurosarcoidosis are heterogeneous and require a prompt diagnosis to ensure the most appropriate treatment. We have reviewed the cases of neurosarcoidosis affecting the hypothalamic–pituitary axis published since 2002 and compared them with the cases reported in the literature up to 2002, which were previously meta-analysed by our research group. Since 2002, 64 cases were identified in the literature: 37 cases presented with diabetes insipidus, 36 were found to have secondary amenorrhoea, 30 with hypogonadotropic hypogonadism, 17 with hyperprolactinaemia, 15 with thyroid-stimulating hormone deficiency, and 8 cases of panhypopituitarism. Uncommon manifestations included hyperphagia, sudden death, and thermodysregulation. We confirm that neurosarcoidosis affecting the hypothalamic–pituitary axis is an uncommon manifestation of sarcoidosis. Neither changes in the clinical manifestations and diagnosis nor significantly novel management options have appeared in the last decade. While it is a rare disorder, the involvement of the CNS is an indication to treat sarcoidosis and as the symptoms of CNS involvement, including hypothalamic–pituitary alterations, may precede the diagnosis of sarcoidosis, it is important to include neurosarcoidosis in the differential diagnosis of hypothalamic–pituitary axis dysfunction in order to facilitate prompt and appropriate treatment.

Keywords: Sarcoidosis, neurosarcoidosis, hypothalamus, pituitary.

INTRODUCTION

Sarcoidosis is a multisystem, non-caseating, granulomatous inflammatory disorder, the aetiology of which is not fully understood.[1] The term was first used by a Norwegian dermatologist describing skin lesions in 1899, but these lesions can affect almost any organ, including the nervous system.[2] It is most prevalent among Northern European and African-American populations, more common in females, and more than two-thirds of cases present between the ages of 25 and 45 years.[3] In Japanese and Northern European populations, there is a second peak of incidence in female patients over 50 years and extrapulmonary manifestations are more common in this subset.[3] It is typically a sporadic phenomenon, but familial links have been reported in 3.6-9.6% of cases, with the siblings of the index case at higher risk than parents.[4]

Sarcoidosis is thought to be caused by a combination of environmental factors in genetically susceptible individuals, possibly as an exaggerated response to an unknown antigen.[3] This theory is suggested by clusters of increased incidence reported in relation to an identifiable exposure, as demonstrated recently by the high incidence in emergency responders who worked in the aftermath of the World Trade Center attack in 2001.[5]

The most common clinical manifestations of sarcoidosis include persistent cough, fatigue, and incidental findings on chest radiograph, with

over 90% of cases affecting intrathoracic lymph nodes, lungs, skin, or eyes.[2] A clinically evident neurological involvement is less common, while there is evidence of central nervous system (CNS) involvement at post-mortem in up to 25% of cases who underwent autopsy.[2] Only approximately 5-10% of patients with a diagnosis of sarcoidosis will present with neurological symptoms.[6] However, neurosarcoidosis in isolation is very uncommon, making up approximately 1% of cases.[7] The CNS manifestations of sarcoidosis can range from cranial nerve palsy, which occurs in over 50% of cases, to more unusual clinical presentations such as leptomeningitis, neuropsychiatric symptoms, spinal cord disease, and neuroendocrine alterations in the form of hypothalamic–pituitary dysfunction.[7] These symptoms may precede the diagnosis of sarcoidosis in a relevant number of cases.[2] This point further highlights the importance of including neurosarcoidosis in the differential diagnosis of hypothalamic–pituitary disorders, especially if an infiltrative disease is suspected.

ENDOCRINE MANIFESTATIONS OF NEUROSARCOIDOSIS

Hypothalamic–pituitary sarcoidosis is often asymptomatic, at least in some stages of the disease, and may be incidentally discovered on dynamic endocrine testing after the detection of unexplained, abnormal hormone levels, or can present clinically in the form of endocrine dysfunction secondary to the hypothalamic and/or pituitary infiltration. Occasionally, the disease has been reported as mimicking a pituitary mass, although this is a much less common event.[8] Endocrine disturbances occur in 2-26% of neurosarcoidosis cases,[7] most commonly causing diabetes insipidus, galactorrhoea, and amenorrhoea.[7,9] Based on post-mortem findings from patients with hypothalamic–pituitary failure, it was initially thought that the sarcoid infiltration of the hypothalamus and/or the pituitary gland can lead to the partial or total destruction of the tissues.[10] However, later studies using neuroimaging and dynamic functional testing of the hypothalamic–pituitary hormonal axis showed that neurosarcoidosis-related hypopituitarism is mostly secondary to the infiltration of the hypothalamus.[9] Although rare, the hypothalamus is the endocrine gland most frequently involved in sarcoidosis.[11]

A review article published by our research group in 2002 described the endocrine effects of neurosarcoidosis in 91 reported cases from 1943-2002, which represented all published cases to date.[12] The range of age of presentation, distribution across different age intervals, and female-to-male ratio were similar between systemic sarcoidosis and neurosarcoidosis. Hypogonadotropic hypogonadism, diabetes insipidus, polydipsia, amenorrhoea, and anterior pituitary failure were the most common endocrine manifestations. Changes in thirst without evidence of diabetes insipidus and altered thermoregulation, appetite, and body weight were the hypothalamic disturbances more frequently reported.

Table 1: Reported cases of neurosarcoidosis with endocrine dysfunction from 2002 to 2014.

Clinical manifestation	Frequency, n (N=64)[1,18,19,23-44]	Incidence, % (previously reported incidence, %)[12]
Diabetes insipidus	37	57 (37.3)
Amenorrhoea	36	56% of females (58.7% of females)
Hypogonadotropic hypogonadism	30	46 (38.5)
Hyperprolactinaemia	17	27
Thyroid-stimulating hormone deficiency	15	24
Panhypopituitarism	8	13
Adrenal insufficiency	2	3 (2.2)
Sudden death	2	3
Hyperphagia	2	3 (2.2)
Thermodysregulation	1	2 (4.4)

The anterior pituitary failure can be associated with hypothalamic sarcoid lesions or, less frequently, with the direct infiltration of the pituitary gland itself by granulomatous lesions.[13] It has also been occasionally reported as a result of an intrasellar mass.[8] In this instance, biopsy and histological confirmation may be required. The hypothalamic involvement frequently presents with polyuria and polydipsia. This can occur as a result of diabetes insipidus or a disturbance in thirst control.[9] Hyperprolactinaemia is also seen relatively often in hypothalamic–pituitary sarcoidosis, occurring in up to one-third of cases and being due to the infiltration of the pituitary stalk, which leads to the loss of the dopaminergic control of prolactin secretion.[12] However, other manifestations, including hypothyroidism, adrenal insufficiency, growth hormone deficiency, impaired response to hypoglycaemia,[14] and hypothalamic features such as weight change due to disruption of the satiety centres, increased somnolence, personality changes, and thermodysregulation are rarer features of neurosarcoidosis.[9]

We have reviewed the literature since 2002 for case reports and case series of neurosarcoidosis causing endocrine dysfunction. In total, we identified 64 cases of neurosarcoidosis affecting the hypothalamic–pituitary axis, the details of which are summarised in Table 1. We reviewed the cases with reported changes in hypothalamic–pituitary function in a similar fashion to the previous work done by our group.[12] A total of 155 cases were identified by the two reviews, which used similar selection methods. Comparing the findings with the former data,[12] diabetes insipidus is still the most common endocrine manifestation of neurosarcoidosis and presents in more than half of the reported cases. Amenorrhoea, hyperprolactinaemia, and hypogonadotropic hypogonadism are commonly seen, whereas other manifestations such as thyroid or adrenal dysfunction and impaired thermoregulation are much less frequent. This pattern of involvement is consistent with smaller retrospective studies.

DIAGNOSIS

Three criteria necessary to make a diagnosis of sarcoidosis were set down in 1999 by the American Thoracic Society, European Respiratory Society, and the World Association of Sarcoidosis and other Granulomatous Disorders.[15] Firstly, the clinical and radiological manifestation; secondly, the histological evidence of non-caseating granulomata; and thirdly, the absence of other conditions that have the potential to cause granulomatous lesions. As per the proposed diagnostic algorithm, the biopsy site is determined by the most easily accessible involved area, ideally peripheral nodes or cutaneous lesion.[6] If no superficial skin lesion, peripheral node, or conjunctival deposit is present or suitable for biopsy, ultrasound-guided endobronchial or transbronchial biopsy combined with bronchoalveolar lavage are suggested.[6] In some cases, the use of fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) can help to localise occult sites amenable to biopsy, in addition to its use in assessing disease activity.[6]

Histological confirmation of the diagnosis presents a challenge in the case of neurosarcoidosis because a biopsy is not always practical or sufficiently safe. Zajicek and colleagues proposed a classification system for the diagnosis of neurosarcoidosis, dividing it into 'definite', 'probable', and 'possible'.[16] The diagnosis of neurosarcoidosis is therefore often based on the presence of supporting evidence other than histological factors, such as cerebrospinal fluid or magnetic resonance imaging (MRI) findings.[6,16] A less invasive method for establishing a probable diagnosis may be preferred and a biopsy is rarely performed in the case of neurosarcoidosis, with cerebrospinal fluid analysis, MRI, electromyography, and assessment of the hypothalamic–pituitary axis representing the preferred diagnostic investigations.[6] However, nervous system biopsy may be pursued in cases requiring a definite diagnosis and in the absence of a systemic positive biopsy result.[17] Lumbar puncture commonly reveals elevated cerebrospinal fluid protein, a mild-to-moderate lymphocytic pleocytosis, and sometimes shows the presence of oligoclonal bands. Cerebrospinal fluid angiotensin-converting enzyme (ACE) levels have a high overall specificity, although they have poor sensitivity and can be elevated during infectious and malignant processes, which limits their usefulness.[17] While the combination of these findings is suggestive of neurosarcoidosis, lumbar puncture to obtain cerebrospinal fluid for analysis is most useful for excluding infections or malignancy, rather than confirming the presence of neurosarcoidosis.[17]

Other investigations include measurement of serum ACE levels and Kveim testing. However, despite low false-positive rates, Kveim testing remains predominantly a research tool for

logistical reasons and due to risk of infection transmission.[18] Serum ACE is elevated in a relatively small proportion of neurosarcoidosis cases in the absence of systemic involvement, and is therefore of limited use for its diagnosis.[17] Indeed, serum ACE levels have been described in the literature as not accurate enough for the purpose of diagnosis or monitoring sarcoidosis activity due to poor sensitivity and specificity.[2,6] One retrospective study of 24 patients with hypothalamic–pituitary neurosarcoidosis noted a normal serum ACE level in two-thirds of cases, compared with only 27% of controls represented by sarcoidosis patients without hypothalamic–pituitary manifestation.[18] It has been reported that chest X-ray looking for the presence of bihilar lymphadenopathy in cases of suspected neurosarcoidosis has a superior diagnostic yield to the measurement of serum ACE levels.[17] In one review of 30 cases of neurosarcoidosis published in 2009, 48% of patients had abnormal chest X-ray scans at presentation, with over half presenting with the classical finding of hilar adenopathy, and the same review found no consistent biochemical changes in the patients reviewed with specific reference to serum ACE and calcium.[19] Hypercalcaemia in sarcoidosis is related to hydroxylation of 1,25-dihydroxyvitamin D_3 by sarcoidal macrophages, and can be reinforced by sunlight exposure.[2] One study of 24 sarcoidosis patients with hypothalamic–pituitary involvement noted hypercalcaemia in only 12% of cases.[18] While the follow-up for patients with sarcoidosis includes monitoring of serum calcium on a 6-monthly-to-annual basis,[6] we do not currently find any evidence to suggest a specific correlation between hypercalcaemia and neurosarcoidosis.

MRI with gadolinium is currently the most commonly employed imaging modality and is superior to computed tomography for assessing hypothalamic involvement, which is typically reported as a cystic or enhancing mass, or thickening of the infundibulum with or without basilar leptomeningeal involvement.[19] While contrast-enhanced MRI is a sensitive method of diagnosing neurosarcoidosis, it is not specific and the differential diagnosis includes tuberculosis, lymphoma, Langerhans cell histiocytosis, and metastatic deposit.[19] It is important to note that MRI of the brain can be normal, especially in patients who have already received corticosteroid treatment.[20] In one case series of neurosarcoidosis, 11% of patients had a normal MRI scan of the brain.[1] Up to 50% of patients with hypothalamic–pituitary sarcoidosis can be radiologically normal.[17] In this scenario, 18F-FDG PET may also prove useful for visualising areas of neurological involvement not seen by MRI.[21]

MANAGEMENT

The natural history of sarcoidosis is variable. About 50% of patients experience spontaneous remission within 2 years and the incidence of relapse in this population group is quite rare.[6] There have been a number of attempts to devise a scoring system to guide which patients will require treatment and for how long. However, none of these scoring systems are internationally validated to date. A correlation between radiographic stage at diagnosis and likelihood of progressing to chronic sarcoidosis has been proposed. Broadly speaking, systemic therapy is warranted in cases with a risk of permanent damage to major organs or disabling systemic symptoms, which extends to cardiac, renal, or neurological involvement, symptomatic hypercalcaemia, or ocular involvement which fails to respond to topical therapy.[6]

The involvement of the CNS is certainly an indication for commencing treatment. Corticosteroids, namely prednisone, are the first line of therapy for severe sarcoidosis of any organ system.[6,11,22] In the case of neurosarcoidosis, higher initial doses of prednisone are warranted (1 mg/kg once daily).[6,22] Occasionally, intravenous high-dose pulse methylprednisolone can be administered.[22] Corticosteroid therapy should be maintained at high dose for 6-8 weeks before slowly tapering the dose as tolerated.[17] It is generally recommended that the treatment continues for a minimum of 12 months in order to reduce the risk of relapse, although this time course varies depending on the clinical evolution,[6] and sometimes it can be difficult to wean patients with neurosarcoidosis off corticosteroids completely.[17] In these cases, or cases of relapse occurring during weaning, second-line cytotoxic or biologic agents may be considered.[17] Relapse is more common in neurosarcoidosis than in cases where sarcoid affects other sites, with reports of relapse rates of 20-50%.[7]

A case series of 54 patients with neurosarcoidosis published in 2009 reported that over two-thirds required maintenance immunosuppression.[1] Methotrexate is currently the preferred second-line option for steroid-resistant sarcoidosis, or can be used as a steroid-sparing agent.[6] Tumour necrosis

factor alpha (TNFα) plays an important role in the formation of granulomata.[2] Data from retrospective studies have suggested that TNFα antagonists, in particular infliximab, may have an increasing role in the management of neurosarcoidosis, in addition to their role in the management of steroid-refractory pulmonary sarcoidosis. Their use is limited, however, by an increased risk of infection, in particular reactivation of tuberculosis, and an increased risk of malignancy.[6] A case series published in 2007 advocated using a combination of corticosteroids with a second immunomodulatory agent in cases deemed to be at high risk of permanent disability from the initiation of therapy.[22] Unfortunately, in the majority of cases of hypothalamic–pituitary sarcoidosis, the immunosuppressive therapy does not appear to restore the compromised endocrine functions or improve diabetes insipidus,[18] and therefore hormone replacement regimes often need to be implemented. Dopamine agonists can be required for the treatment of hyperprolactinaemia.[18]

CONCLUSION

Endocrine dysfunction is a relatively rare manifestation of neurosarcoidosis, which is an uncommon clinical condition. Altogether, a total of 155 cases of neurosarcoidosis with hypothalamic–pituitary involvement have been described in the literature. Diabetes insipidus, hyperprolactinaemia, hypogonadotropic hypogonadism, and amenorrhoea represent the most frequently observed endocrine manifestations of neurosarcoidosis. For the most part, the endocrine changes occur in previously undiagnosed cases of neurosarcoidosis, which highlights the importance of the inclusion of this condition in the differential diagnosis when investigating hypothalamic–pituitary dysfunction, especially if an inflammatory and/or infiltrative disorder is suspected. Although, in the majority of cases, treating hypothalamic–pituitary neurosarcoidosis does not result in endocrine functions returning to normal, the involvement of the CNS remains an indication for treatment and, therefore, a correct and timely diagnosis should be ensured.

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MANAGEMENT OF MALIGNANT MIDDLE CEREBRAL ARTERY INFARCTION

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ABSTRACT

Malignant middle cerebral artery (MCA) infarcts occur in a small subset of patients with ischaemic strokes and lead to high levels of disability and mortality. Over the last 10 years, surgical interventions, in the form of decompressive craniectomies, have become more popular. There is insufficient evidence to support current medical treatments including mannitol, glycerol, steroids, hypertonic saline, and therapeutic hypothermia. Several randomised controlled trials of early decompressive craniectomies in younger patients have shown a significant improvement in functional outcomes and mortality. Questions still need answering regarding the timing of this surgery, long-term survival benefits, and age thresholds. In this review article we will discuss the evidence and uncertainties surrounding the management of malignant MCA infarcts.

Keywords: Malignant cerebral infarction, decompressive craniectomy, imaging, outcomes.

INTRODUCTION

Malignant middle cerebral artery (MCA) infarcts occur in about 8% of ischaemic strokes.[1] They are the most devastating form of acute stroke and lead to a mortality of around 80%.[2,3] This is due to the complete infarction of the MCA leading to acute brain swelling, elevated intracranial pressure (ICP), and brain herniation over 5 days.[2] It constitutes a distinct clinical picture also referred to as 'brain oedema in stroke',[4] 'cerebral infarction with swelling',[5] 'massive MCA infarction',[6] and 'space-occupying MCA infarction'.[7] Severe neurological deficits are seen more commonly than in other types of infarcts, including hemiplegia, hemisensory loss, hemianopia, global aphasia, pupillary abnormalities, and a decreased level of consciousness over 24-48 hours.[1]

Imaging is used for diagnosis and, along with the clinical presentation, can help in predicting the malignant course of the disease.[8] Risk factors for developing fatal brain swelling include a National Institutes of Health Stroke Scale (NIHSS) score ≥20 for left hemisphere infarcts or ≥15 for right hemisphere infarcts, nausea and vomiting, and >50% MCA territory hypodensity on computed tomography (CT) images.[8] Other CT parameters that have been shown to predict a fatal outcome are anteroseptal shift >5 mm, pineal shift >2 mm, and hydrocephalus.[9] Magnetic resonance imaging (MRI) with diffusion weighting (lesion volume >82 cm^3), perfusion imaging, and angiography within 6 hours of symptom onset have also been demonstrated to predict a malignant course.[10,11] Proton emission tomography, used to calculate cerebral blood flow (CBF) and the volume of ischaemic core, and neuromonitoring are new approaches that may be beneficial but which require more investigation.[12]

Over the last few years there has been uncertainty over the optimal management of patients presenting with brain swelling after a cerebral infarction.[5] Despite optimal medical management, outcomes have remained poor.[2,13] Between 2007 and 2009, three prospective randomised controlled trials (RCTs) showed an improvement in functional outcome and mortality with surgical decompression compared with medical management.[14-16] This has led to updated Scottish Intercollegiate Guidelines Network (Guideline

No. 108 December 2008) and National Institute for Health and Care Excellence (CG68 July 2008) guidelines recommending surgical intervention in certain patient groups. In this review article we discuss the evidence behind different treatment strategies used in the management of malignant MCA infarcts and where the future lies.

MEDICAL MANAGEMENT

Patients with large MCA infarcts should be cared for in a specialist neuro-intensive care unit.[7] Elective intubation may be needed to facilitate monitoring and treatment. In one case series from 2000, 24% of patients needed mechanical ventilation due to a decreased level of consciousness, heart insufficiency, and pneumonia, particularly if the infarct exceeded two-thirds of the MCA territory.[17] A cohort study evaluated the use of ICP monitoring in 48 patients with acute ischaemic stroke and elevated ICP.[18] They concluded that ICP monitoring can predict clinical outcomes in large hemispheric infarctions, but it was not useful in guiding management and they felt it did not have a positive influence on outcomes.

Mannitol

Mannitol is an osmotic diuretic that pulls water across the blood—brain barrier (BBB) out of the interstitium and intercellular spaces. It also causes a reduction in cerebral blood volume due to vasoconstriction. These effects lead to a consequent reduction in ICP and are therefore used to control cerebral oedema.[19] There are worries that if the BBB is not intact then mannitol can cross and lead to a 'rebound' intracranial hypertension when water is drawn back into the cerebral tissue.[20] In an observational study of 805 stroke patients, no effect or harm could be attributed to mannitol.[21] Other observational studies have shown that mannitol causes a reduction in ICP over 4 hours, but they do not comment on long-term outcomes.[22] A Cochrane review in 2007 identified only three small RCTs with 226 participants comparing mannitol with placebo or open control.[23] They concluded that there is not enough evidence to support the routine use of mannitol in acute strokes.

Hypertonic Saline

Hypertonic saline has been used as an alternative to mannitol to reduce cerebral oedema. It is thought to be more favourable as it is completely excluded from the BBB and expands the intravascular volume, which increases the cerebral perfusion pressure (CPP).[24] There are fears that unrestricted use may lead to severe hypernatraemia, but this has rarely been seen in clinical practice.[24] Only small case series evaluating the use of hypertonic saline in acute strokes exist. One included eight patients and showed that it led to a reduction of elevated ICP over 4 hours in 22 episodes.[25] Another case series evaluated nine patients and showed that hypertonic saline decreased ICP more rapidly than mannitol but was not as effective at increasing CPP.[22] There is no clinical trial that addresses the effect of hypertonic saline on functional outcomes.

Glycerol

Glycerol is a sugar that has also been used as an osmotic agent in large MCA infarcts. It has been shown to increase CBF and can be used as an alternative source of energy in the ischaemic brain.[26] Due to this metabolism, there is thought to be less risk of glycerol causing a rebound intracranial hypertension once it crosses the BBB.[27] Zuliani et al.[28] published a cohort study of 442 patients over 65 years of age with severe ischaemic strokes and showed there was no reduction in short-term mortality risk when they received intravenous (IV) glycerol. In 2004, a Cochrane review identified 11 randomised trials reviewing the use of IV glycerol in acute strokes.[29] They concluded that there was a lack of evidence of any improvement in long-term survival and that they would not support its routine use.

Corticosteroids

Theoretically, steroids have been shown to have a role in decreasing cytotoxic and vasogenic oedema.[30] However, there are multiple well-known adverse effects including hyperglycaemia and increased risk of infections.[27] One cohort study found concurrent treatment with steroids plus mannitol or glycerol worsened the short-term mortality risk from acute strokes in older patients.[28] A Cochrane review from 2002 identified seven randomised trials comparing corticosteroids with placebo or control in ischaemic strokes.[31] Treatment did not improve functional outcomes and they did not recommend its routine use.

Glyburide

Glyburide, a sulphonylurea used in diabetes management, is a new IV anti-oedema therapy that has undergone case—control trials.[32] It is

showing potential to improve clinical outcomes in malignant infarcts and further research is awaited.

Body Positioning

Moderate head elevation at 15-30° is routine practice in the management of elevated ICP due to the positive results of studies performed in patients with traumatic brain injuries.[33] Schwarz et al.[34] prospectively evaluated 43 ICP monitoring sessions in 18 patients with MCA infarcts without an ICP crisis. They found that CPP was maximal in the horizontal position despite the ICP being highest at this point. A systematic review and meta-analysis of observational studies published in 2014 included four studies and 57 patients.[35] The authors concluded that cerebral blood mean flow velocity was significantly increased on the side affected when in a horizontal or 15° position compared with 30°. This is currently undergoing randomised evaluation as to its effect on clinical outcomes (the HeadPoST study).

Hypothermia

Hypothermia is thought to have a neuroprotective effect by reducing cerebral metabolic rate, stabilising the BBB, reducing free radical formation, and decreasing brain oedema.[36] There are concerns regarding rebound intracranial hypertension during the re-warming period leading to cerebral herniation and death.[37] The evidence supporting its use in malignant MCA infarcts is restricted to observational studies at temperatures <33°C.[37,38] These studies have also shown high numbers of pulmonary infections and clinically relevant side-effects such as shivering. The number of patients involved and the quality of the trials available means that there is insufficient evidence to recommend its use. A randomised trial is awaited to assess the optimum timing, depth, incidence of complications, and method of cooling for therapeutic hypothermia in acute ischaemic strokes.[39]

SURGICAL MANAGEMENT

Prior to 2002 there were no RCTs comparing the surgical and medical management of malignant MCA infarcts. A Cochrane review published over this period identified only observational studies, case series, and single case reports.[40] The authors felt there was not enough significant evidence to support the use of decompressive surgery and further trials needed to be conducted. In 2007, Vahedi et al.[16] published the results of the first of three multicentre RCTs involving patients with malignant MCA infarcts (DECIMAL trial, Table 1). They compared functional outcomes with and without decompressive surgery using the modified Rankin Scale (mRS). Patients recruited were 18-55 years of age and with an infarct volume of >145 cm^3 on diffusion-weighted MRI. Surgery had to be carried out no later than 30 hours after treatment onset (range was 7-43 hours) and all patients received standard medical therapy according to published guidelines. The trial was prematurely stopped after the enrolment of 38 patients because the interim data showed a considerable difference in mortality between the two groups. The proportion of patients with an mRS score ≤3 at 1-year follow-up was 50% in the surgery group compared with 22.2% in the group receiving medical management alone (p=0.1). In a subgroup analysis, younger patients had a more favourable outcome. There was a 52.8% reduction of death in the surgical group (p<0.0001).

Another multicentre RCT included patients aged 18-60 years with malignant MCA infarcts (DESTINY trial, Table 1).[14] The infarcts were confirmed as more than two-thirds of the MCA territory on CT and with an NIHSS score >20 for lesions on the dominant hemisphere and >18 for lesions on the non-dominant hemisphere. The study randomised patients to either surgical and conservative treatment or conservative management alone. Surgery was conducted within the first 36 hours after symptom onset. The trial was stopped after 32 patients were recruited due to a statistically significant reduction in mortality in the surgical group (p=0.02). There was an improvement in the number of patients with an mRS score ≤3 after 12 months in the surgical arm but this was not statistically significant (p=0.23).

The third significant multicentre RCT in this area was published in 2009 by Hofmeijer et al. (HAMLET trial, Table 1).[15] Patients were aged 18-60 years and within 4 days of symptom onset from a large MCA infarct. This was confirmed as more than two-thirds of the MCA territory on CT and an NIHSS score ≥16 for right-sided lesions and ≥21 for left-sided lesions. They received either medical management alone, given at the discretion of the treating physician, or medical management and surgical treatment. The trial was ended after 64 patients were recruited because it was unlikely to show a statistically significant result in the primary outcome (mRS score). It did, however, show a reduction in case fatality with the surgical intervention.

Table 1: Summary of the three pooled randomised controlled trials comparing conservative management with medical management in patients with malignant middle cerebral artery infarcts.

Trial	Age range, years	Number of patients	Imaging criteria	Eligibility	Primary outcome	Secondary outcome
DECIMAL	18-55	38	CT: >50% MCA territory MRI DWI: >145 cm^3	Symptom onset <30 h	mRS score ≤3 at 6 months: p=0.18	Mortality at 1 year: p<0.0001
DESTINY	18-60	32	CT: ≥66% MCA territory	Symptom onset <36 h	mRS score ≤3 at 6 months: p=0.23	Mortality at 1 year: p=0.03
HAMLET	18-60	64	CT: ≥66% MCA territory	Symptom onset <96 h	mRS score ≤3 at 6 months: p=0.13	Mortality at 1 year: p=0.002

CT: computed tomography; MRI: magnetic resonance imaging; MCA: middle cerebral artery; DWI: diffusion-weighted imaging; mRS: modified Rankin Scale.

To obtain sufficient data to reliably estimate the effect of surgical decompression, the results of these three trials were pooled.[41] The main difference between the studies was the time allowed from the onset of symptoms to surgery, and so the pooled analysis adopted a maximum time window of 48 hours. This resulted in a total of 93 patients, with 51 randomised to surgical treatment and 42 to conservative management. At 12 months, more patients in the surgical group had an mRS score ≤4 (absolute risk reduction [ARR]: 51%, number needed to treat [NNT]: 2), an mRS score ≤3 (ARR: 23%, NNT: 4), and survived (ARR: 50%, NNT: 2). The probability of survival was shown to increase from 28-80%. The authors concluded that, in patients aged <60 years with malignant MCA infarcts, decompressive surgery undertaken within the first 48 hours reduces mortality and increases the number of patients with a favourable functional outcome.

In 2012, a Cochrane review aimed to examine the effects of decompressive surgery on survival and long-term disability in patients with massive acute ischaemic strokes.[42] They found only the three mentioned RCTs including 134 patients aged <60 years. Their analysis revealed that surgical decompression resulted in a reduced risk of death or severe disability (mRS score >4) at 12 months but there was no difference when using an mRS score >3. They felt that survival may be at the expense of substantial disability and that surgery should only be offered when it can be assumed that it is in the best interests of the patient. In addition, all of the trials were stopped early and an overestimation of the size of the effect could not be excluded. A 2014 meta-analysis with a total of 14 studies and 747 patients also concluded that early surgery (<48 hours) significantly decreased mortality.[43] This included a larger number of studies than previously analysed and found that there was a significant improvement in functional outcomes with mRS scores ≤3, which contradicted previous publications.

Older Patients

The results from the studies described above leave a large degree of uncertainty regarding how to manage patients >60 years of age and with a malignant MCA infarct. In 2009, Arac et al.[44] published a review of the available evidence involving outcomes in older patients receiving a decompressive craniectomy after a large MCA infarct. They included 19 studies totalling 273 patients, of which 73 were >60 years of age. The mortality rate was significantly worse for the older patients (51.2% versus 20.8%, p<0.0001). Furthermore, the older patients who survived had significantly higher rates of poor outcomes using an mRS score >3 and Barthel Index of <60. They concluded that age should be an important factor in patient selection for surgery. However, the data they obtained were largely from case series and retrospective studies, therefore requiring cautious interpretation of the results.

In 2014, an RCT enrolled 112 patients >60 years of age to receive either conservative or surgical management within 48 hours.[45] They found that hemicraniectomies resulted in a significantly greater proportion of patients surviving without a severe disability after 6 months (mRS score ≤4, p=0.004). However, there were no patients with an mRS score

of 0-2, with the majority having an mRS score of 4-5. They concluded that surgical management in older patients increases survival without a severe disability, but a majority of the patients will require assistance with most bodily needs.

An RCT recruiting patients up to 80 years of age was terminated after 47 patients were enrolled due to a significant reduction in poor outcomes (mRS score >4) in the surgical group.[46] They found a similar trend in a subgroup analysis of patients aged >60 years. However, such patients seemed to be at higher risk of developing a moderately severe disability (mRS score of 4). They felt that age should not be a contraindication to surgery and that the decision should be made on an individualised basis. In the 2014 meta-analysis described above, the authors investigated the association between age and functional outcome.[43] They found that surgery significantly reduces mortality in adults >60 years of age. However, the proportion of patients who had a poor functional outcome was significantly greater than the proportion in the younger patient group.

CONCLUSIONS AND THE FUTURE

Evidence supporting the medical management of patients with large MCA infarcts is clearly lacking. There are no convincing data regarding the use of mannitol, hypertonic saline, or glycerol in improving long-term outcomes, and there is the possibility that steroids may worsen mortality. The monitoring of ICP can guide management but has not been shown to have a positive impact on patient outcomes. Horizontal or 15° body positioning may increase CBF, but we are unsure if this has a beneficial effect regarding morbidity and await the results of further trials. The use of therapeutic hypothermia is not recommended and high-quality evidence is still needed, but there are promising results from observational studies.

In contrast, there is a growing library of evidence to support the surgical management of these patients. A pooling of three RCTs and a recent meta-analysis have shown both a significant reduction in mortality and improved functional outcomes (mRS score ≤4) when patients <60 years of age are treated with a decompressive craniectomy within 48 hours of symptom onset.[41,43] An mRS score of 4 means that a patient is unable to attend to their own needs without assistance, or walk unaided. The 2012 Cochrane review highlighted concerns regarding increased survival of these patients at the expense of disability.[42]

There is still uncertainty regarding how to manage older patients, and although surgery does reduce mortality in those aged 60 years and over it appears to be a predictor of a worse neurological outcome. Larger RCTs are needed to reach a consensus on management in this group. However, the future still holds many questions that need answering. There are considerable gaps in our knowledge regarding medical management strategies, including temperature modulation and head positioning. There may be the possibility of new drugs, such as glyburide, to reduce brain oedema, which will make surgical interventions redundant. Decompressive craniectomies appear to be the way forward but more clarity is needed regarding the timing, long-term outcomes in survivors, and potential age limits, so that we can answer whether we are saving the lives of patients who are then left with a significant disability, high caregiver burden, and a poor quality of life.

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CLINICAL RELEVANCE OF CEREBRAL AUTOREGULATION FOLLOWING SPONTANEOUS INTRACEREBRAL HAEMORRHAGE

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ABSTRACT

Hypertensive intracranial haemorrhage is a common neurological emergency in clinical practice. The presence of an intracranial lesion of expansive focal nature can compress vascular structures and cause ischaemic effects. It is very common for these patients to have hypertensive peaks at admission, which may progress to rebleeding and neurological worsening. The safety of blood pressure reduction in patients with hypertension and intracranial haematomas is still a debatable subject due to lack of studies on cerebral autoregulation in this situation. The aim of this study is to discuss cerebral autoregulation in patients with spontaneous intracerebral haemorrhage based on scientific and personal evidence.

Keywords: Intracranial haemorrhage, hypertensive, cerebral haemorrhage, cerebral autoregulation.

INTRODUCTION

Spontaneous intracerebral haemorrhage (SICH) accounts for 10-15% of cerebrovascular events, with a mortality rate of 35-52%; half of these deaths occur within the first 2 days after the event[1-3] and the haematoma volume is an independent prognostic variable.[4] Acute haematomas with volume >150 ml can reduce cerebral perfusion pressure to zero, leading to death. If the haematoma volume is <140 ml, most patients will survive the initial stroke.[5,6] According to the International Surgical Trial in Intracerebral Haemorrhage (STICH) there are a number of situations with little chance of a positive outcome: poor neurological condition e.g. coma or Glasgow Coma Scale (GCS) ≤5/15; age of >75 years; massive haemorrhage with significant neuronal destruction (>60 cc with GCS <8/15; >85 cc or diameter of haematoma 5.5 cm independent of GCS); large haemorrhage in dominant hemisphere; basal ganglion (putaminal) or thalamic haemorrhage.[7] Cerebral autoregulation impairment is one of the important mechanisms in the physiopathology of SICH, both from the prognostic and therapeutic points of view. Therefore, the understanding of SICH functionality at the bedside represents an improvement in terms of neurological intensive care.

Cerebral autoregulation is defined by the intrinsic capacity of the cerebral vasculature to maintain a constant cerebral blood flow (CBF) (50 ml/100 g/min), considering variations in mean arterial blood pressure within the range of 60-150 mmHg in healthy subjects.[8] These limits are not accurate in clinical practice and represent points of inflection where the association between pressure gradient and flow change significantly.[9] Above or below the autoregulation limits, CBF has a passive behaviour in relation to mean arterial pressure (MAP) and intracranial pressure (ICP). Several mechanisms have been attributed to cerebral autoregulation, which are myogenic, neurogenic, and metabolic. However, recent studies have suggested the presence of more than one mechanism.[10] Patients with chronic arterial hypertension shift the thresholds of autoregulation upward.[11]

Cerebral autoregulation consists of fast and slow components, in terms of changes in cerebrovascular resistance, in response to pulsatility pressure and mean cerebral perfusion pressure (CPP), respectively. Quantifying the cerebral autoregulation phenomenon is a complex process, as there are many physiological variables that can interfere with CBF, either directly or through metabolic coupling.[12] Static autoregulation is considered a 'gold standard' test for the assessment of cerebral autoregulation, as it measures changes in CBF arising from CPP variations. It therefore represents the slow components of autoregulation. Dynamic autoregulation evaluates fast autoregulation components and tends to be impaired early in relation to static autoregulation.[13] Therefore, there are technical limits for each methodology that require appropriate interpretations.[14,15]

The concept of cerebrovascular pressure reactivity index (PRx) was introduced by Czosnyka et al.[16] in 1997, based on the principle that, in the presence of mean blood pressure elevations, there would be cerebral vasoconstriction with reduced cerebral blood volume and, consequently, ICP. PRx indirectly reflects cerebral autoregulation, being used to optimise CPP.

PRx reflects the smooth muscle tone of cerebral arteries and arterioles, as well as changes in transmural pressure, being part of a more elaborate phenomenon called cerebral autoregulation. Expansive lesions alter the CPP and can decompensate the cerebral autoregulation mechanism responsible for maintaining adequate CBF. With the reduction in CPP, vasodilation occurs as a compensatory measure to keep the CBF. However, this vasodilating cascade culminates with a significant increase in cerebral blood volume and vascular collapse, due to increased cranial pressure.

The cerebrovascular PRx[16,17] consists of 40 measurements (every 5-15 seconds) of mean blood pressure and ICP, establishing a Pearson's correlation between these variables. Values <-0.2 represent good cerebrovascular reactivity, while values >0.2 reflect an impaired cerebrovascular reactivity. The presence of a positive correlation between MAP and ICP means impairment of cerebrovascular reactivity, and values >0.3 are correlated with a worse prognosis (increased mortality rate from 20% to 70%).[18] When the range of values between MAP and ICP are independent, cerebrovascular reactivity is adequate and thus, there is a better functional outcome. After applying it in clinical studies, Czosnyka et al. stated that a PRx >0.2 for more than 6 hours is associated with a poor prognosis.[18]

CASE REPORT

A female patient of 57 years suffered an acute stroke in 2013. On examination: Glasgow 4 with spontaneous breath and not intubated on admission, isochoric pupils, intracerebral haemorrhage (ICH) Score 3. Skull computed tomography (CT) showed a left frontal lobe haematoma. The calculated volume was 81 cm^3 (12×4.5×3 cm) with septal deviation and signs of intracranial hypertension.

Surgical removal of intracranial haematoma was performed and the patient underwent multimodal neuromonitoring in the intensive care unit. Postoperative control skull CT on first operative day showed radical haematoma removal, but persistence of septal deviation. The patient remained in deep sedation without any changes in ICP (Figure 1).

Two days after onset of stroke, the cerebrovascular PRx was preserved with a CPP between 80-90 mmHg suggesting preserved cerebral autoregulation. The optimal perfusion pressure was determined at 85 mmHg with a PRx of -0.6. However, 5 days after stroke onset, the PRx was impaired, with a CPP between 60-80 mmHg, suggesting impaired cerebral autoregulation (Figure 2).

Six days from stroke onset, the patient started to show worsening in ventilatory status that led to worsening of cranial homeostasis, which developed into intracranial hypertension escapes with no radiological alteration. This deterioration was caused by positive water balance and associated low pulmonary exchange of oxygen. Other causes of brain oedema were ruled out. Nine days from stroke onset, the patient developed refractory intracranial hypertension, pupillary alterations, and fixed mydriasis, and underwent a decompressive craniectomy (Figure 3).

DISCUSSION

This case report shows that despite the haematoma volume and tomographic signs of intracranial hypertension, there was no loss of cerebrovascular reactivity in the initial phase, implying that cerebral autoregulation was preserved. Loss of

cerebrovascular reactivity occurred days later, implying impairment of cerebral autoregulation. The pathophysiological mechanisms of brain injury by SICH are analysed by the primary effect of vascular rupture and tissue destruction, and the side-effects of haematoma growth, intracranial hypertension, oedema formation, and toxic effects of clot substances. Despite occuring in a simultaneous and interrelated manner, these can be divided into the following steps:[19,20]

I. Vascular rupture and haematoma formation: arterial rupture leads to rapid accumulation of blood in the cerebral tissue and an increase in local tissue pressure. The degree of tissue destruction is justified and explained by the sheer force of the expanding haematoma. In addition to the effect on mass, haematoma, by itself, induces three perilesional early pathophysiological changes in brain tissue: (a) neuronal and glial cell death due to apoptosis, and inflammation, (b) vasogenic oedema, and (c) breaking of blood—brain barrier.

II. Expansion of the haematoma: the ICH is not an event, rebleeding has been documented with the realisation of serial scans within the first 24 hours of the event. The incidence of haematoma increase decreases with the passage of time, 33-38% in 1-3 hours; 16% from 3-6 hours, and 14% within 24 hours of the initial event. The theory is in agreement resulting from persistent and recurrent bleeding from the rupture of a single arteriole.

III. Oedema formation: the perilesional hypoperfusion is probably due to reduced metabolic demand instead of ischaemia. Once ischaemia does not justify the neurological dysfunction after stroke, neurotoxic and inflammatory mechanisms have been proposed to explain the perilesional tissue injury: (a) local inflammation by cell mediators, humoural and cytotoxic associated with the leakage of osmotically active proteins and electrolytes; (b) induction of proteases such as thrombin, fibrinogen, and tissue plasminogen activator; (c) the clot factors associated with its degradation products.

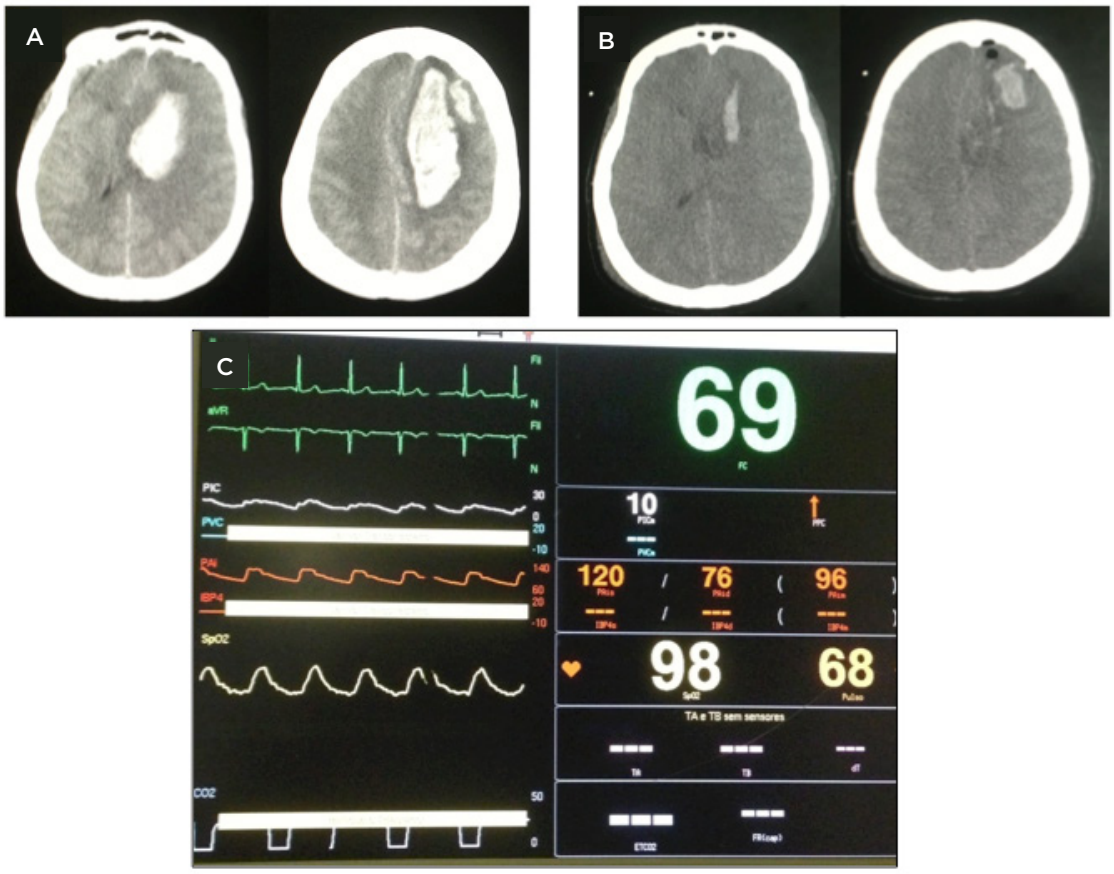

Figure 1: A: Left frontal lobe haematoma with intracranial hypertension signs; B: Postoperative control still showing septal deviation; C: Monitoring of intracranial pressure at 10 mmHg with cerebral perfusion pressure at 86 mmHg. One can also observe loss of intracranial complacency through the morphology of the intracranial pressure curve, P2>P1.

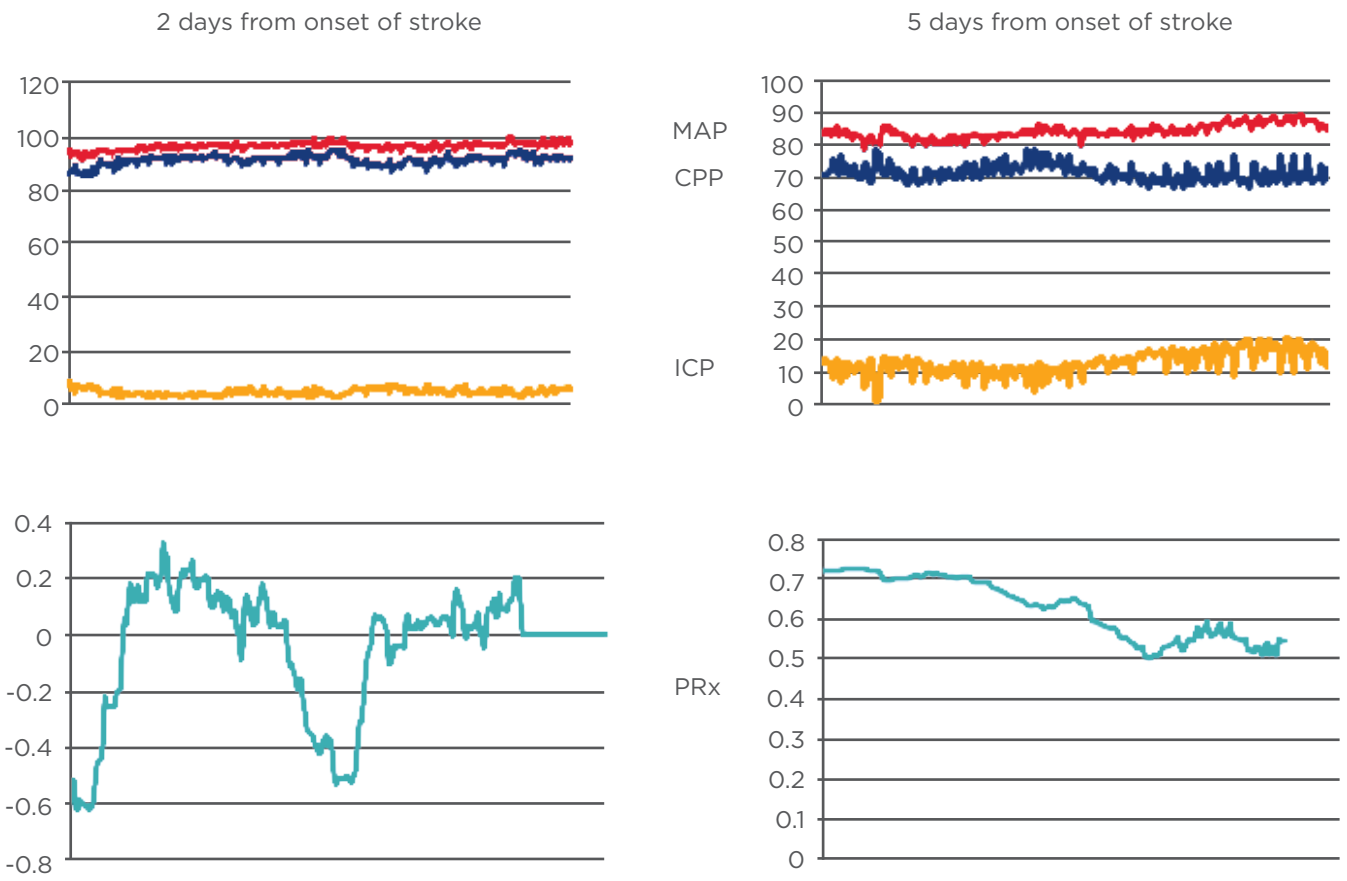

Figure 2: On the left, 1-hour multiparametric neuromonitoring performed 2 days after the onset of stroke showing a preserved cerebrovascular pressure reactivity index (PRx) with a cerebral perfusion pressure (CPP) between 80-90 mmHg. On the right, 1-hour multiparametric neuromonitoring performed 5 days from the onset of stroke, showing impaired cerebrovascular PRx, with the CPP being adjusted between 60-80 mmHg.

MAP: mean arterial pressure; ICP: intracranial pressure.

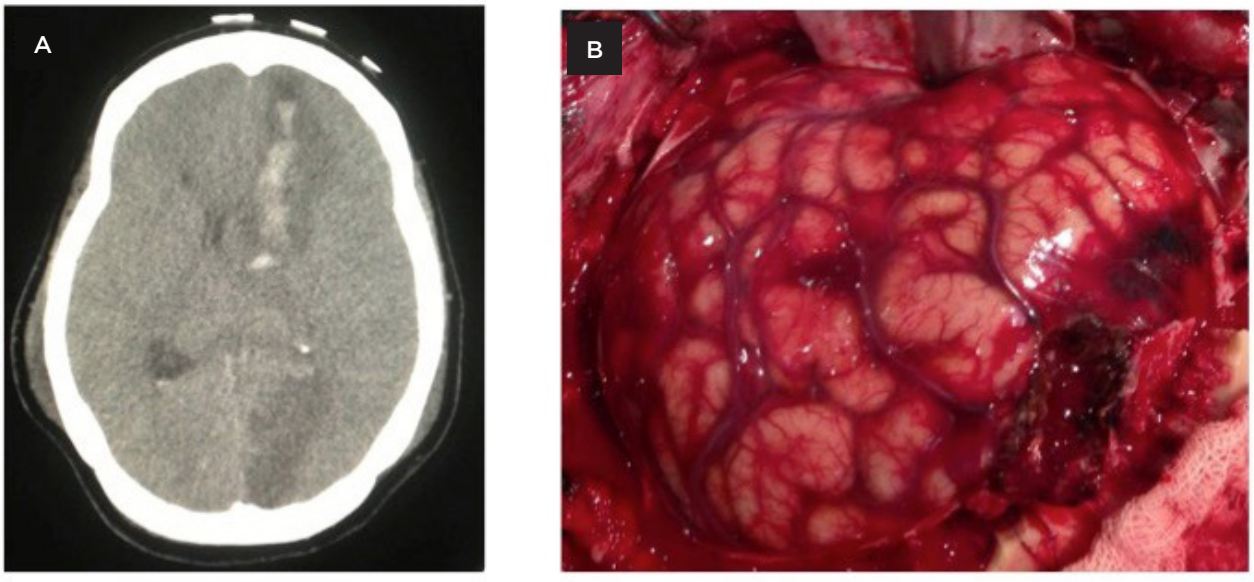

Figure 3: A: skull computed tomography performed 9 days after the onset of stroke, showing indirect signs of herniation with ischaemia in the anterior cerebral artery and left posterior artery territory. B: Brain swelling aspect after decompressive craniectomy.

Thus, the monitoring of cerebral auto-regulation is necessary, as it has a dynamic behaviour. Studies that have analysed cerebral autoregulation in patients with SICH are scarce and use different methodologies (static or dynamic):

- Zazulia et al.[21] and Powers et al.[22] studied cerebral autoregulation in 19 patients by positron emission tomography, and observed that patients with small and medium haematomas (1-45 ml) evaluated within hours after the neurological stroke (6-22 h) had preserved cerebral autoregulation in the peri-haematoma region.
- Diedler et al.[23] evaluated dynamic cerebral autoregulation in 20 patients with SICH through the cerebrovascular PRx (correlation between the ICP and MAP), observing impairment of the dynamic cerebral autoregulation, justifying it due to CPP fluctuations.
- Diedler et al.[24] assessed dynamic cerebral autoregulation in 5 patients with ganglionic intracerebral haemorrhage, observing that the perilesional region showed regional autoregulation involvement (PRx, correlation between $P_{br}O_2$ and CPP) whereas the overall autoregulation impairment (PRx, correlation between ICP and MAP) only occurred in one patient. In spite of the few cases, the hypothesis that PRx represents overall cerebrovascular reactivity (macrovasculature) was raised, but the authors were not able to assess local cerebrovascular reactivity (microvasculature) located in the perilesional region.
- Reinhard et al.[25] assessed dynamic cerebral autoregulation in 26 patients with SICH, observing that cerebral autoregulation is preserved initially; however, worsening that is ipsilateral to the haematoma can occur secondarily (between 3-5 days post-neurological stroke), being associated with a severe clinical outlook, intraventricular haemorrhage, low CPP, and poor functional outcome.
- Nakagawa et al.[26] evaluated dynamic cerebral autoregulation (Doppler) in 21 patients with early (<72 hours) lobar or basal ganglia ICH, observing that patients with ICH had higher gains in a wide range of frequency ranges compared with controls. These findings suggest that dynamic cerebral autoregulation may be less effective in the early days after ICH.
- Oeinck et al.[27] and Aries et al.[28] evaluated dynamic cerebral autoregulation (Doppler) in 26 patients with SICH on Days 1, 3, and 5 post-neurological stroke, and showed that cerebral autoregulation is usually preserved, but its impairment is associated with large haematoma volumes, arterial hypotension, and poor functional prognosis.
- Jaeger et al.[29] evaluated optimal CPP in 38 patients after head injury, observing that below the level of optimal CPP, brain tissue oxygen decreased in parallel to CPP, whereas brain tissue oxygen reached a plateau above optimal CPP. Optimal CPP correlated significantly with the CPP level, where brain tissue oxygen reached its plateau.
- Andrade et al.[30] described a new experimental porcine model designed to simulate expansive brain haematoma causing intracranial hypertension (IH). Under anaesthesia, IH was simulated with a balloon insufflation. The IH variables were measured with ICP parenchymal monitoring, epidural, cerebral oximetry, and transcranial Doppler. The ICP epidural showed a slower rise compared with parenchymal ICP. A correlation between ICP and cerebral oximetry was observed. The model described here seems useful to understand some of the pathophysiological characteristics of acute IH.

The impairment of the cerebrovascular reactivity index infers on vasomotor component (myogenic control) of cerebral autoregulation. However, the neural and biochemical components may be preserved. The variation of CPP is one of the variables that most influence the cerebrovascular reactivity index without intervening with mean cerebral autoregulation. Optimal CPP is associated with the lowest PRx possible. From this point, increasing CPP does not improve the oxygen supply because it remains constant.[29] Maintaining an optimised cerebrovascular reactivity index is important in order to maintain an adequate oxygen supply without the need for extreme variations of cerebral perfusion.

In this case report there was a later impairment of PRx and cerebral autoregulation, with the need for a decompressive craniectomy in order to control intracranial hypertension. Therefore, this report supports regular autoregulation assessment in ICH.

CONCLUSION

Advances in multiparametric neuromonitoring allow a better understanding of cerebral

autoregulation in SICH and a better analysis of previously considered theoretical concepts. Changes in practice based on autoregulation impairment will become a reality when we include these autoregulation monitoring methodologies in bedside assessment.[31]

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AUTOMATED QUANTIFICATION OF STROKE DAMAGE ON BRAIN COMPUTED TOMOGRAPHY SCANS: e-ASPECTS

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ABSTRACT

Emergency radiological diagnosis of acute ischaemic stroke requires the accurate detection and appropriate interpretation of relevant imaging findings. Non-contrast computed tomography (CT) provides fast and low-cost assessment of the early signs of ischaemia and is the most widely used diagnostic modality for acute stroke. The Alberta Stroke Program Early CT Score (ASPECTS) is a quantitative and clinically validated method to measure the extent of ischaemic signs on brain CT scans. The CE-marked electronic-ASPECTS (e-ASPECTS) software automates the ASPECTS score. Anglia Ruskin Clinical Trials Unit (ARCTU) independently carried out a clinical investigation of the e-ASPECTS software, an automated scoring system which can be integrated into the diagnostic pathway of an acute ischaemic stroke patient, thereby assisting the physician with expert interpretation of the brain CT scan. Here we describe a literature review of the clinical importance of reliable assessment of early ischaemic signs on plain CT scans, and of technologies automating these processed scoring systems in ischaemic stroke on CT scans focusing on the e-ASPECTS software. To be suitable for critical appraisal in this evaluation, the published studies needed a sample size of a minimum of 10 cases. All randomised studies were screened and data deemed relevant to demonstration of performance of ASPECTS were appraised. The literature review focused on three domains: i) interpretation of brain CT scans of stroke patients, ii) the application of the ASPECTS score in ischaemic stroke, and iii) automation of brain CT analysis. Finally, the appraised references are discussed in the context of the clinical impact of e-ASPECTS and the expected performance, which will be independently evaluated by a non-inferiority study conducted by the ARCTU.

Keywords: Ischaemic stroke, Alberta Stroke Program Early CT Score (ASPECTS), e-ASPECTS, automated, computed tomography, patient selection.

INTRODUCTION

Stroke is a devastating disease with a paramount associated social and healthcare cost. In Europe stroke is the second leading cause of mortality, with nearly 1.3 million deaths each year, and the primary cause of disability resulting in long-term residential care. On average, 0.27% of gross domestic product is spent on stroke by national health systems internationally.[1] An ischaemic stroke occurs when

a blood vessel in the brain becomes blocked by a blood clot or an embolus. This prevents oxygen and nutrients from reaching nerve cells in the affected area of the brain. These nerve cells can die within minutes and the area of the body that they control may cease to function. This damage can be permanent, especially if the patient is not immediately treated.

Patients who have experienced a stroke will most likely be taken to a nearby hospital. Upon arriving at the hospital, medical staff will attempt to treat the patient, considering the clinical presentation together with information obtained from an emergency non-contrast computed tomography (CT) scan of the patient's brain.[2] The focus of immediate care for patients who have suffered a stroke is to re-establish blood flow (reperfusion) to the brain either by

- thrombolysis, administered within 4.5 hours from symptom onset with recombinant tissue plasminogen activator (rt-PA)
- endovascular treatment with stent-retrievers or aspiration within 8 hours, or
- a combination of both (bridging)

THE DIFFICULTY IN DETECTING EARLY ISCHAEMIC DAMAGE ON BRAIN NON-CONTRAST COMPUTED TOMOGRAPHY SCANS

Eligibility for stroke treatment depends not only upon time from stroke onset, but also on the extent of ischaemic damage on CT scans. Changes on the CT scan denote predominately irreversibly infarcted tissue that appears hypodense, representing the infarct core. In the first 6 hours following stroke onset, stroke detection is challenging[3] and requires significant expertise, as only subtle signs of cerebral ischaemia are present on CT. These include hyperdense artery sign, the insularribbon sign, obscuration of the lentiform nucleus, blurring of grey—white matter differentiation, and sulcal effacement.[4] Even amongst experts quantification of these signs remains highly reader dependent with significant inter and intra-reader variability.[5-7]

Kunst et al.[8] describe that detection of signs of early ischaemia on non-contrast CT is influenced by several factors. These include the severity of the infarct, as measured by clinical examination and National Institutes of Health Stroke Scale (NIHSS), and the time between symptom onset and imaging. The studies that the authors reviewed demonstrated that the detection rate for signs of early ischaemia within the 3-hour time window is 67% or less in most trials, and may be as low as 31%. At 6 hours the rate of detection increased to approximately 82%, but this is outside the therapeutic window for intravenous (IV) rt-PA.

Lack of Experts

A consultant neuroradiologist should ideally carry out proper assessment of the patients' CT scans. However, many hospitals in the UK and around the world do not have 24/7 access to an expert neuroradiologist. Therefore, they are unable to provide an optimal stroke service as they inevitably rely on non-expert interpretation of CT scans during the therapeutic time window.

Inter-Reader Variability

There is discussion on the inter-reader variability in quantifying the extent of infarction. Even experienced clinicians show only 39% agreement in identifying if ischaemic changes on non-contrast CT involve greater than one-third of the middle cerebral artery (MCA) territory.[5] Mullins et al.[9] conducted a systematic review of CT scan interpretation by visual inspection of the scan. It highlighted the general lack of definitions for early infarction signs. Investigators in a substantial proportion of the studies did not define the infarction signs they sought. Looking at the literature it becomes clear that a standardised evaluation method is needed in acute ischaemic stroke.[10-13]

THE DEVELOPMENT OF THE ASPECTS SCORE

The European Cooperative Acute Stroke Study (ECASS) pioneered the importance of assessing early ischaemic changes (EIC) to predict benefit from thrombolysis and introduced the 'one-third' rule.[8] A post-hoc analysis suggested that the extent of EIC is an important predictor of the response to IV thrombolysis.[3] Increased risk of symptomatic intracranial haemorrhage (sICH) was confirmed in secondary analysis of the ECASS-2 CT scans.[14] Given the difficulties with the reliability of the one-third MCA rule[15] the Calgary Stroke Program developed the Alberta Stroke Program Early CT Score (ASPECTS) as a systematic approach to assessing EIC on non-contrast CT.[16] ASPECTS enables a quantitative evaluation of early ischaemic changes in the MCA territory.

The overall inter-observer agreement of ASPECTS seems good compared with that of the one-third MCA rule and provides a systematic method to analyse head CT scans. Clinician agreement was shown to be superior to that of the one-third MCA rule.[10]

ASPECTS is a topographic scoring system that divides the brain hemisphere affected by stroke into ten regions of interest. Areas are weighted according to functional importance with equal weighting given to smaller structures and larger cortical areas. The score is calculated from evaluation of two standardised levels of the affected hemisphere: the basal ganglia level, which includes the caudate, insula, internal capsule, lentiform, and M1-M3, and the supraganglionic level, which includes M4-M6. For each of the defined regions, a single point is subtracted for an area of early ischaemic damage, such as loss of grey—white matter interface, focal swelling, and parenchymal hypoattenuation. Parenchymal hypoattenuation is defined as a region of abnormally decreased attenuation of brain structures relative to attenuation of other parts of the same structures or of the contralateral hemisphere. Focal brain swelling or mass effect is defined as any focal narrowing of the cerebrospinal fluid space due to compression by adjacent structures, such as ventricular compression or effacement of cortical sulci. An ASPECTS score of zero indicates diffuse ischaemic damage. A normal CT scan is assigned an ASPECTS score of ten.

Clinical Validation of the ASPECTS Score as a Selection Tool for Intravenous Thrombolysis

The ASPECTS score is recommended by the American Society of Neuroradiology[17] and was shown to be a reliable and strong predictor of functional outcome and sICH following thrombolytic treatment.[10,16,18,19] Clinical studies have demonstrated that patients with an ASPECTS score >7 were most likely to benefit from treatment,[18] while those scoring <5 were unlikely to see any improved outcome and were exposed to a significantly higher risk of sICH following thrombolysis.[20]

Clinical Validation of the ASPECTS Score as a Selection Tool for Endovascular Treatment

The most relevant study regarding ASPECTS as a selection tool for endovascular stroke treatment is the ESCAPE trial.[21] Patients were selected for treatment by a pre-specified ASPECTS range of 6-10, thereby identifying patients with a small infarct core. In the majority of other trials, ASPECTS has been applied post-hoc, which is of far less clinical significance. In the Interventional Management of Stroke (IMS-1) study, patients with an ASPECTS score >7 were more likely to benefit from the combined IV-intra-arterial (IA) approach than from IV rt-PA alone (based on matched patients from the National Institute of Neurological Disorders and Stroke rt-PA study ASPECTS analysis), with the number needed to treat at ten.[22] Patients with an ASPECTS score of <8 were less likely to benefit from combined IV-IA than from IV thrombolysis, and more likely to be harmed by interventional therapy. Overall, these data are evidence of both a qualitative and quantitative interaction effect with ASPECTS.

AUTOMATION OF BRAIN COMPUTED TOMOGRAPHY ANALYSIS

Recently a new software, e-ASPECTS (Brainomix Ltd., Oxford, UK), for automated detection of acute ischaemic stroke using the validated ASPECTS score was introduced.[23] An independent clinical validation study was conducted by Anglia Ruskin University comparing the performance of the software with expert neuroradiologists. The aim of this study was to demonstrate that e-ASPECTS is non-inferior to experienced neuroradiologists. The CE-marked e-ASPECTS software has been developed to automate the ASPECTS scoring system for ischaemic stroke patients. The algorithm processes brain CT scans in a similar way to a human expert, applying the ASPECTS score. It takes non-contrast brain CT scans as input; the patient's brain is registered to an atlas so that anatomical features of the brain can be recognised and the ASPECTS regions segmented from the 3D data set. A scoring module then looks at each region for signs of ischaemic damage, and the ASPECTS score is generated with a report detailing the overall ASPECTS score, as well as which regions were found to contain ischaemic damage (Figure 1). There is overall agreement in the literature that a standardised, independent, and automated CT assessment tool is needed and could positively impact patient care, although all other publications identified present technologies that have been developed in a research environment with no intention for clinical use.

The first approach to automate stroke detection on CT scans simply compared the whole left-hand side of a brain CT scan with the right-hand side.[24]

Figure 1: Automated scoring output of the electronic Alberta Stroke Program Early CT Score (e-ASPECTS) web interface.

There is fresh ischaemic damage in the left caudate and lentiform. The ASPECTS score is 8.

The proposed method consisted of image enhancement, detection of midline symmetry, and classification of abnormal slices. A windowing operation was performed on the intensity distribution to enhance the region of interest. A two-level classification scheme was used to detect abnormalities using features derived in the intensity and the wavelet domain. The proposed method was evaluated on a limited dataset of 15 patients, giving 90% accuracy and 100% recall in detecting abnormality at patient level. Average precision of 91% and recall of 90% at the slice level was described. The surprisingly high sensitivity and specificity on this small dataset possibly indicates over-fitting.

Tang et al.[25] proposed a novel 'circular adaptive region of interest' method to analyse CT images of the brain. Results indicated that for emergency physicians and radiology residents there was a significant improvement in sensitivity and specificity when using computer-aided detection ($p<0.005$). The authors used an image-feature approach for computer-aided detection of ischaemic stroke with well-described results. Compared with e-ASPECTS the approach was limited to detection of stroke versus no detection, i.e. there is no consideration of the extent of damage.

Boers et al.[26] used a semi-automated delineation of follow-up CT scans. The cerebral infarct volumes of 34 consecutive patients were segmented with an automated, intensity-based, region-growing algorithm, which included partial volume effect correction near the skull, midline determination, and ventricle and haemorrhage exclusion. Damage was assessed based on a seed point selected by a radiologist, thus not addressing the subtle, early ischaemic changes that e-ASPECTS looks for. The Pearson correlation for the automated method compared with the reference standard was similar to the manual correlation (R=0.98). The accuracy of the automated method had a mean difference of 0.5 ml with limits of agreement of -38.0-39.1 ml, which were more consistent than the inter-observer variability of the two observers (-40.9-44.1 ml). However, the Dice coefficients were higher for the manual delineation. The performance was very slow with the technique apparently taking 2 hours per scan.

Rajini et al.[27] looked for small infarcts (e.g. lacunes) only. The proposed method consists of pre-processing, segmentation, tracing the midline of the brain, extraction of texture features, and classification. The application improved efficiency and accuracy of clinical practice with an average overlap metric, average precision, and average recall between the results obtained to the ground truth of 0.98, 0.99, and 0.98, respectively. From the publication it was not clear if the authors had separate training and test sets. The algorithm only tested for the presence or absence of damage on a per-slice basis. The authors only tested a small dataset with the results probably indicating over-fitting.

Bentley et al.[28] evaluated a tool for prediction of sICH following thrombolysis. CT images acted as input into a support vector machine (SVM), along with non-image features (specifically NIHSS score). Predictive performance compared favourably with that of prognostic scores (original and adapted versions: 0.626-0.720; $p<0.01$). The SVM also identified 9 out of 16 sICHs as opposed to 1-5 using prognostic scores, assuming a 10% sICH frequency ($p<0.001$). The dataset appears to be of an adequately high number (n=106), but the algorithm was only tested via cross-validation, which can lead to over-fitting. The authors acknowledged that they could improve their image analysis by using image features rather than all the voxels, which is what e-ASPECTS does with a variety of image features.

Przelaskowski et al.[29] described a system for image enhancement to improve interpretation by the human eye. The system defines a 'stroke window' that adjusts the contrast of the image to better show hypodense areas. They did not automate the actual detection of damage, that is left to radiologists, but the publication does demonstrate that radiologists performed better when looking at their system.

Shieh et al.[30] developed an automatic ASPECTS scoring system using contralateral comparison. Receiver operating characteristic analysis based on evaluation of 103 patients with symptoms of acute stroke showed that the system's dichromatic classification of patients into thrombolysis-indicated or thrombolysis-contraindicated groups achieved a high accuracy, with area under curve equal to 90.2%. The average processing time for a single case was 170 seconds.

CONCLUSION

This literature review underlines the need for standardised image interpretation to identify appropriate treatment options in acute stroke management that translate into clinical benefits for patients. Imaging of the brain parenchyma is a composite surrogate for time elapsed from stroke onset and collateral status, as well as severity of ischaemia and extent of thrombus. However, it must be remembered that imaging is only one factor in a complex equation. Even expert physicians in current practice will often not agree on treatment decisions. As such, they will never use ASPECTS or e-ASPECTS in isolation, but will use it as complementary information.

In the hyperacute setting, ASPECTS has been validated as a predictor of functional outcome in acute ischaemic stroke patients receiving IV alteplase and endovascular treatment. Therefore, integration of the ASPECTS score into a clinical care pathway as a decision-support tool would be reasonable. However, the required expertise that the manual application of ASPECTS carries can limit its use in clinical care. In addition, intra and inter-observer variability is an issue not only in the clinical environment but also in clinical trial enrolment when using image selection criteria. The development of the e-ASPECTS software enables fast and standardised assessment of the brain CT scan using the validated ASPECTS score irrespective of the expertise of the interpreter, thus eliminating inter and intra-observer variability. It will be of great value to assess how standardised use of ASPECTS translates into long-term outcomes that are meaningful to patients in terms of overall health status, functional ability, cognition, and quality of life.

The conclusions about the performance and safety of ASPECTS outlined in this literature review are intended to represent the consensus of a global forum of stroke experts, and to provide a framework for the assessment of acute stroke care provision, using the CE-marked, standardised software e-ASPECTS, with regard to access to care and patient outcomes in both the hyperacute and acute hospital setting, as well as in clinical trial enrolment. The e-ASPECTS non-inferiority study will provide the necessary evidence to demonstrate the reliable performance of e-ASPECTS in a clinical setting.

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REPERFUSION STRATEGIES FOR ACUTE ISCHAEMIC STROKE FROM PAST TO PRESENT: AN OVERVIEW TOWARDS FUTURE PERSPECTIVES

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ABSTRACT

Timely reperfusion of brain ischaemic tissue is the main therapeutic target for acute stroke. In the last few decades many recanalisation strategies have been studied by randomised controlled trials (RCTs), including intravenous (IV), intra-arterial (IA), and combined approaches. Clinical research is addressed to identify the drug associated with the better reperfusion properties and the lower rate of side-effects. To date, according to current evidence-based guidelines, IV tissue plasminogen activator (tPA) is the only approved treatment for acute ischaemic stroke (AIS) within 4.5 hours from onset. Other IV thrombolytics, such as tenecteplase and desmoteplase, have shown promising results in preliminary RCTs and are currently being investigated to produce further evidence. Endovascular catheter-based treatments (including IA administration of thrombolytics or mechanical thrombectomy) have quite inferior feasibility, being performed only by stroke-trained interventional neuroradiologists. Until a few months ago, many trials had investigated the safety and efficacy of endovascular techniques compared with IV tPA without consistent results, limiting their application to patients with contraindications or poor response to IV tPA. More recently, the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN), Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times (ESCAPE), and Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-arterial (EXTEND-IA) trial results have demonstrated the superiority of endovascular procedures associated with standard care in AIS due to proximal arterial occlusion in the anterior cerebral circulation. These data are going to change the current decision-making process and the care pathway in AIS patients.

Keywords: Reperfusion, stroke, thrombolysis, intravenous, intra-arterial, endovascular.

INTRODUCTION

Stroke represents a heavy social burden in terms of mortality, morbidity, and costs.[1] Ischaemic stroke accounts for approximately 80% of all strokes[2] and its severity is directly linked to the size and location of the lesion.[3] The main therapeutic target in ischaemic stroke is a rapid vessel recanalisation and the subsequent restoration of blood perfusion into the ischaemic area. It has been highlighted that patients who underwent revascularisation strategies have lower mortality rates and better functional outcome at 3 months than untreated patients.[4] Since underperfusion damage is time-dependent, timeliness is one of the critical issues in disease management. According to the well-known aphorism 'time is brain', the earlier the reperfusion, the better the outcome for the patient. It has been estimated that each spared minute in establishing therapy increases the chances of functional improvement.[5]

To avoid delays, implementation of stroke care systems has been set up[6] to reach the goal of the fastest assessment and treatment for acute stroke patients. Hyperacute stroke management starts in the community: an increased public awareness about stroke symptoms and needs has enhanced the rapid emergency system alert and consequently allows faster transfers to appropriate emergency departments. To enhance access to care considering the available resources, the current goal would be a 'hub-and-spoke' model in which resources are centralised and patients tend to flow from peripheral facilities ('spokes') to larger clinical centres ('hubs'). The subsequent in-hospital phase includes a focussed clinical assessment and appropriate imaging in order to evaluate and put into practice the best therapeutic options according to the patients' needs. The therapeutic strategies for revascularisation include both intravenous (IV) and endovascular approaches, with different features in terms of feasibility, safety, and efficacy.[7-9] In this paper we will review the options that are currently available.

SYSTEMIC REPERFUSION THERAPIES

Systemic reperfusion therapies consist of IV administration of thrombolytic agents. The most well-known drug of this category is tissue plasminogen activator (tPA). To date, alteplase (recombinant tPA) is the only approved treatment for acute ischaemic stroke (AIS) within 4.5 hours from onset of symptoms. Dose of administration is based on the patient's weight (0.9 mg/kg, with a maximum dose of 90 mg; 10% in bolus, the remaining 90% in 1-hour IV infusion). The first study that reported a safe benefit from tPA treatment was conducted by the National Institute of Neurological Disorders and Stroke (NINDS),[10] which considered patients treated within 3 hours from symptom onset. The narrow therapeutic window, which limits the eligible patients to those who arrive in time at the emergency room, has always been considered to be the main disadvantage of IV tPA; the subsequent randomised controlled trial (RCT) research has addressed trying to widen this window. This timeframe has been extended after European Cooperative AcuteStroke Study III (ECASS 3) trial results: better outcome without higher mortality rate for patients treated within 4.5 hours, compared with placebo.[11,12]

Further extension of the therapeutic window has not been firmly supported by recent RCTs. The third International Stroke Trial (IST-3) considered patients treated within 6 hours from onset, and reported higher rates of intracranial bleeding and mortality rates without consistent benefit to outcome.[13] The main selection criteria that weigh on tPA treatment are represented by bleeding exclusion and determining time of symptom onset (however, some studies suggest that even wake-up strokes - without early ischaemic signs on imaging - could be safely treated with tPA thrombolysis).[14] Other important contraindications are: seizures at onset, unmanageable hypertension, international normalised ratio >1.7, and blood glucose <50 or >400 mg/dl. Complications of tPA treatment can result from the thrombolytic effect itself (intracerebral and/or systemic haemorrhage, reperfusion injury with cerebral oedema, and seizures), its ineffectiveness (reocclusion), or secondary embolisation due to redistribution of the lysed clot.[15]

A combined administration of tPA with antiplatelet or low-molecular-weight heparin has been proposed to avoid early vessel reocclusion. These therapeutic schemes[16,17] are burdened with a higher risk of symptomatic cerebral haemorrhage, which overrides the clinical benefit. The combination of a glycoprotein IIb/IIIa antagonist, eptifibatide, with IV tPA (0.6 mg/kg) has been investigated in the Study of the Combination Therapy of Rt-PA and Eptifibatide to Treat Acute Ischemic Stroke (CLEAR-ER), with promising results in terms of lower rate of symptomatic intracranial haemorrhage compared with standard IV tPA alone; a trend has also been observed towards a better functional outcome,[18] but further studies are needed to confirm efficacy. Other glycoprotein IIb/IIIa antagonists have been tested in AIS treatment, but with unconvincing results: in the Safety of Tirofiban in acute Ischemic Stroke (SaTIS) trial, IV tirofiban has been given to AIS patients within 22 hours from symptoms onset, with good safety and lower mortality but no significant clinical benefit in the treated group compared with placebo;[19] abciximab has been tested in only one RCT (Abciximab in Emergency Treatment of Stroke Trial [AbESTT-II]), which was prematurely stopped because of the high number of intracranial bleeds.[20] A direct thrombin inhibitor, argatroban, has been studied in the Argatroban in Ischemic Stroke (ARGIS-I) trial; patients treated with argatroban showed neither significant clinical benefit nor higher bleeding rate.[21] In the Argatroban tPA Stroke Study

(ARTTS) trial argatroban has been combined with IV tPA, reporting a good rate of complete recanalisation at 24 hours.[22]

The other thrombolytic agents (streptokinase, ancrod, tenecteplase [TNK], desmoteplase), which work by converting plasminogen into active plasmin and are currently used for thromboembolic disease such as acute myocardial infarction or pulmonary embolism, have not yet demonstrated sufficient evidence to deserve their promotion among treatments recommended for AIS. This is generally due to a higher risk of bleeding not counterbalanced by better outcome, or to complex methods of administration. Streptokinase administered intravenously within 6 hours from symptom onset showed a high mortality rate compared with 300 mg aspirin in two studies (the Multicenter Acute Stroke Trial [MAST-I] and [MAST-E]);[23,24] a safer and more effective profile was found from the Australian Streptokinase Trial, but only if treating patients within 3 hours from onset.[25]

Ancrod, a serine protease with fibrinogen-depleting properties extracted from Malayan pit viper venom, has been tested in the Stenting in Aneurysm Treatments (STAT) trial by administering a 72-hour infusion of ancrod versus placebo within 3 hours from stroke onset followed by a 1-hour infusion at 96 and 120 hours. Better clinical outcome and insignificantly higher rate of haemorrhage have been observed in the treated arm, thus the complexity of administration has to be considered.[26] TNK is a semi-synthetic tPA with longer half-life and higher fibrin affinity. It is administered as a bolus and is able to induce faster thrombolysis with fewer bleeds and reocclusions. Safe doses (0.1-0.25 mg/kg) have been identified in a Phase IIB trial, prematurely interrupted due to slow enrolment.[27] The following Tenecteplase versus Alteplase for Acute Ischemic Stroke (TAAIS) trial (TNK 0.1/0.25 mg/kg versus tPA in patients with perfusion >20% ischaemic core and computed tomography angiography occlusion) found that TNK 0.25 mg/kg had the better benefit-to-risk ratio for all efficacy outcomes[28] (probably thanks to the inclusion criteria that favoured patients most likely to benefit from the treatment[9]).

Desmoteplase is extracted from vampire bat saliva and has a longer half-life and higher fibrin affinity than tPA. The Desmoteplase In Acute Ischemic Stroke (DIAS) trial had the aim of finding the dose with better safety and efficacy in patients with perfusion—diffusion mismatch within 3-9 hours from onset: after reporting a high number of symptomatic bleeds the dose had been weight-adjusted, with subsequent clinical benefit for treated patients compared with placebo.[29] The following trials, Dose Escalation of Desmoteplase in Acute Ischemic Stroke (DEDAS) and DIAS-2, had inconclusive results due to the low number of patients recruited and the study design.[16] Desmoteplase is currently being investigated in two ongoing trials, DIAS-3 and DIAS-4, considering patients within 9 hours from onset.[30]

Sonothrombolysis could be defined as an enhanced version of systemic thrombolysis, where the mechanical pressure waves given by transcranial ultrasounds help the penetration of tPA inside the clot, improving its fibrinolytic effect.[31] The efficacy of the technique has been proven in the Combined Lysis of Thrombus in Brain Ischemia with Transcranial Ultrasound and Systemic TPA (CLOTBUST) trial, and a subsequent meta-analysis confirmed its safety and effectiveness compared with tPA treatment alone.[32] A further development of this mechanism has been obtained by combining systemic thrombolysis with ultrasound-guided gaseous microspheres, which seems able to improve tPA action.[33] Despite all of these efforts in research, the standard and recommended treatment for AIS is still IV thrombolysis with the tPA alteplase.[12]

Apart from guidelines, it has to be noted that the outcome of the treated patient is strongly influenced by multiple clinical and anatomical variables such as: age and comorbidities of the patient, with worse outcomes for older and vulnerable patients;[2] thrombus size and composition (small and fibrin-rich clots are more likely to be lysed);[2,34] site of occlusion,[35] with fewer chances of recanalisation for large calibre vessels (internal carotid artery, proximal middle cerebral artery); the presence of residual flow that enhances tPA action;[36] and the validity of collateral circulation[37] that promotes better clinical outcome.[2] Imaging diffusion—perfusion profile is another crucial item. Recent studies (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study [DEFUSE] and [DEFUSE-2]) have outlined how perfusion-mismatched patients are more likely to benefit from reperfusion. On the other hand, a 'malignant mismatch' has been identified, with diffusion-weighted imaging area >100 ml correlated to worse outcome and higher risk of haemorrhagic transformation.[38,39]

ENDOVASCULAR TREATMENT

The need for and development of endovascular catheter-based approaches derive from the limitations of systemic therapies, mainly concerning their narrow therapeutic window and poor efficacy against large vessel occlusion.[9] Proximal occlusion of the major intracranial arteries accounts for more than one-third of anterior circulation strokes[40] and only about one-third of these patients could obtain early recanalisation after IV thrombolysis.[41] Intra-arterial (IA) topical delivery of the thrombolytic agent has been the first attempt in the field: the Prolyse in Acute Cerebral Thromboembolism (PROACT) trial[42] reported a favourable 3-month outcome in patients treated with IA pro-urokinase up to 6 hours from stroke onset, although with a higher rate of symptomatic intracranial bleeding that prevented the FDA endorsement as an alternative treatment to IV tPA. A 'bridging' treatment (IV tPA followed by IA administration of tPA) has been compared with conventional systemic tPA, showing similar safety and outcome measures.[43,44]

Conceived to treat proximal large artery occlusion in particular, the most recent type of endovascular approach consists of clot retrieval or thrombectomy with mechanical devices, currently performed in centres equipped with stroke-trained interventional neuroradiologists.[9] The earliest systems were the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retriever,[45] designed to engage, proximally withdraw, and then aspirate the clot, and the PENUMBRA device,[46] able to aspirate the clot directly from the site of occlusion. The therapeutic window was initially wider than that of systemic thrombolysis, up to 8 hours. The delayed, although complete, recanalisation obtained by thrombectomy was associated with worse clinical outcome compared with IV tPA,[47] probably due to the difference in time windows favouring systemic tPA due to starting treatment earlier.[9] Subsequently, the stent-retriever devices SOLITAIRE FR and TREVO have been endorsed by the FDA[48] for acute stroke caused by large vessel occlusion for their safer and more effective profile than the MERCI system.[49] These devices also play a crucial role in the treatment of basilar artery occlusion, with proven safety and effectiveness.[50]

The results of subsequent prospective endovascular RCTs (Interventional Management of Stroke [IMS] III, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR RESCUE], and SYNTHESIS Expansion) have demonstrated that the IV and endovascular approaches have consistently similar safety profiles; thus, endovascular treatments are not superior to IV thrombolysis[51] and have to be applied only in selected conditions. The neutral results should be read considering that these studies were tarnished by some critical issues: a widespread use of old, first-generation devices and limited use of stent-retrievers, lack of pre-treatment angiographic imaging causing a number of futile interventions in patients without large vessel occlusion (nearly 47% of the study population in the IMS-III), non-consecutive inclusions, and long delays from clinical onset to achieve recanalisation. However, current American Heart Association/American Stroke Association guidelines recommend IA thrombolysis in AIS patients with contraindications to systemic approach within 6 hours from onset, and suggest that patients with large vessel occlusion and a poor response to IV tPA could benefit from a 'rescue' treatment with IA thrombolysis or thrombectomy.[48]

Recent studies have promoted the acceleration of the use of endovascular approaches, to result in timely and better reperfusion of ischaemic penumbra and achieve clinical improvement, especially for large artery obstruction for which recanalisation is required to avoid a poor prognosis.[52,53] The MR CLEAN trial has recently proved that IA treatment (thrombolysis and/or mechanical procedures) associated with 'usual care' (that could include systemic thrombolysis) within 6 hours from onset of symptoms in AIS patients with a proximal intracranial occlusion of the anterior circulation (radiologically confirmed) is effective and safe; compared with usual care alone, it is associated with a better 3-month functional outcome (an absolute difference of 13.5 percentage points in the modified Rankin score) and no significant differences in terms of mortality or bleedings.[54] MR CLEAN will change perspectives about endovascular treatment; thanks to these positive results, it could be considered in patients other than those with contraindications or poor response to IV thrombolysis. The beneficial effect of endovascular treatment has been confirmed even in subgroup analysis for age, stroke severity, and ASPECTS score.[54]

Further evidence comes from the ESCAPE trial, the results of which have recently been published. The trial reported improved functional outcome

and lower mortality rates compared with standard care alone for the rapid (within 12 hours from onset) endovascular treatment added to standard care in ischaemic stroke patients with small infarct core, proximal intracranial artery occlusion, and moderate-to-good collateral circulation.[55] The study design highlights the importance of a careful patient selection to identify the subgroup of individuals who would benefit from treatment. This method has been applied also in the EXTEND-IA trial, by setting precise perfusion-imaging inclusion criteria (large vessel occlusion and an ischaemic core <70 ml on CT perfusion). This study demonstrated that such patients, treated with IV alteplase and early (within 4.5 hours from onset) thrombectomy with the SOLITAIRE FR device compared with standard systemic thrombolysis, showed better reperfusion, earlier neurological recovery, and better 3-month functional outcome.[56] Both the ESCAPE and EXTEND-IA trials were stopped after the release of the MR CLEAN results on the advice of the data safety monitoring board, because the predetermined boundary for efficacy had been reached.[55,56] These latest RCTs highlight the need for adequate vessel imaging before selecting patients for an endovascular procedure. The limited use of such techniques has probably contributed to determining the inconsistent results of previous trials. From these considerations we could infer that endovascular approaches cannot alter the natural history of AIS in the absence of large arterial occlusion.

LACUNAR SYNDROMES

Lacunar stroke is an expression of small vessel disease, for which the implementation of thrombolytic treatment is currently under debate. First of all, lacunar syndromes are not usually associated with high clinical severity and generally show a good prognosis (while in the long term, a higher incidence of recurrent stroke and dementia is reported). A mechanism of thrombosis has never been proven for lacunar strokes, hence the questions about the need for the advocacy of reperfusion for its treatment. However, a recent review states that thrombolysis can be judged to be an effective treatment in acute lacunar stroke. On the other hand, the presence of small vessel disease increases the risk of intracranial haemorrhage during thrombolysis, even if it is not considered as an absolute exclusion criterion.[57] Evaluating the extent of small vessel disease should be done with MRI and could be difficult with neuroimaging techniques that are available in the emergency setting.

CONCLUSION

Even though IV alteplase is still the recommended therapy for AIS patients, the most recent data from endovascular RCTs would probably determine a revolution in the world of stroke care, promoting interventionists to become essential, at least for every 'hub' stroke centre, and perhaps also changing the fundamental requirements, in terms of neurovascular imaging, for primary stroke centres. In this fight against the time-dependency of recanalisation and clinical efficacy, neurologists and interventionists should be activated in parallel to decrease the time to the procedure.[58]

From the aforementioned, we can conclude that the patient-selection process plays a fundamental role in acute stroke treatment, possibly causing biases that deeply influence the results of RCTs and consequently guideline recommendations. The desirable direction to take in future studies is to further refine this process, investigating AIS patients with an extensive imaging (evaluation of large vessels by angio-imaging, evaluation of brain parenchyma by the use of MRI to rule out or quantify small vessel disease) and clinical workup, to achieve the most targeted treatment according to their needs.

Key Points

- IV tPA (0.9 mg/kg, maximum dose 90 mg) is the recommended therapy for AIS patients within 4.5 hours from onset
- Endovascular procedures must not be applied as an alternative to IV tPA in patients who are eligible to systemic thrombolysis
- IA treatments (IA thrombolysis, thrombectomy, or both) associated with usual care (that could include systemic thrombolysis) are likely to be beneficial if performed in patients with AIS due to proximal arterial occlusion in the anterior cerebral circulation (intracranial internal carotid artery, proximal middle cerebral artery, proximal anterior cerebral artery) within 6 hours from onset
- IA treatments associated with usual care can be performed in patients with AIS due to arterial occlusion of posterior large vessels

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UPDATE ON ALZHEIMER'S DISEASE

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ABSTRACT

With the disproportionate growth of the elderly population, Alzheimer's disease (AD), as the most common cause of dementia, has become a major public health and socio-economic problem of our time. Updated consensus criteria for clinical diagnosis and new biomarkers have increased the diagnostic accuracy to over 90%, with a sensitivity versus other dementias of around 85% and a specificity of up to 78%, although a definite diagnosis depends on neuropathological examination. However, due to overlap between dementing disorders and frequent concurrence of multiple pathologies in the aged brain, both clinical and post-mortem studies entail biases that affect their validity. Harmonised interdisciplinary approaches are required to increase the accuracy and reproducibility of AD diagnosis as a basis for neuroprotection and efficient treatment. Preventative measures can minimise risk factors and confounding diseases, whereas anti-dementive treatment with drugs and non-pharmacological interventions can currently only delay the progression of the clinical course without causal effects. Better early diagnosis, active immunotherapies, and disease-modifying measures are the most important challenges for modern neurosciences.

Keywords: Alzheimer's disease (AD), dementia, neuropathology, biomarkers, treatment.

INTRODUCTION

Alzheimer's disease (AD) is a form of neurocognitive disorder characterised by a progressive multi-domain cognitive impairment with a profound decrease in the ability to perform daily living activities.[1] AD is the most frequent form of dementia (around 60% of cases), followed by dementia with Lewy bodies (DLB) (15-30%), vascular dementia/cognitive impairment, and other dementia processes (10-15% each); most frequent are mixed forms or multi-aetiology dementias (50-70%).[2] AD affects more than 40 million people worldwide. The principal risk factor is age: its incidence doubles every 5 years after age 65, and the odds for a diagnosis of AD after age 85 exceed one in three. With the disproportionate growth of the elderly population, the prevalence of AD is predicted to approach around 115 million worldwide in 2050.[3] The total costs for AD in 2013 were approximately US$205 billion in the USA alone and about US$605 billion worldwide, not including the contributions of unpaid caregivers.[4,5] Thus, AD has become a major public health and socio-economic problem that threatens to become the scourge of the 21st century. The clinical and neuropathological diagnosis of AD, as well as the current and future treatment options, are the focus of the present mini-review.

CLINICAL DIAGNOSIS

Early diagnosis of AD and its distinction from other dementing disorders is crucial to the implementation of effective treatment strategies and management of patients. Diagnostic procedures play a major role in the detection of preclinical AD and mild cognitive impairment (MCI).[6] Diagnosis of MCI requires a cognitive complaint or evidence for longitudinal decline (at least 1.5 standard deviations) on cognitive test performance, generally intact global cognition, minimal or no functional impairment, and no dementia according to DSM-IV criteria. The different subtypes of MCI include amnestic and non-amnestic single and multi-domain forms. Progression to dementia has been reported in 10-15% of cases per year, while others may not progress to AD or

other dementias.[7] MCI, being common in elderly people (average prevalence: 20-30%), is associated with future cognitive decline and progression to dementia in 90% of cases within 9-10 years (10-15% of cases per year) as opposed to the 1-2% incidence in age-matched general populations.[8] For its diagnosis, several stages were proposed (Figure 1a),[9] by which 97% of cognitively normal persons were classified.[10] The pathology and mechanisms of MCI were summarised recently.[11]

Updated consensus criteria for the clinical diagnosis of AD include the revised National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) guidelines, the National Institute on Aging-Alzheimer's Association (NIA-AA), and European Federation of Neurological Societies – European Neurological Society (EFNS-ENS) guidelines,[12] consensus from the Canadian Conference on the Diagnosis of Dementia (CCCD), and the International Working Group-2 criteria for AD.[13] All these updated diagnostic criteria considering clinical phenotypes, preclinical states and mixed AD, adequate neurophysiological/cognitive assessment, neuropsychological testing, cerebrospinal fluid (CSF) biomarkers (decreased β-amyloid [Aβ], increased phospho-tau [p-tau], p-tau/Aβ42 ratio >0.52 – a robust marker for AD), and neuroimaging procedures (volumetric and functional magnetic resonance imaging [MRI] demonstrating early and progressive hippocampal and parietal atrophy in mixed AD and AD,[14-16] fluorodeoxyglucose positron emission tomography [PET], amyloid detection by ^{11}C-labelled Pittsburgh Compound-B PET) increase the clinical diagnostic accuracy to about 95%.

Combining the best CSF and MRI data using standardised operational measures allows for a more precise diagnostic prediction, and will be further increased by using multimodal techniques and novel biomarkers already in the early (preclinical) stages of development.[17-22] A large proportion of cognitively normal elderly people develop Aβ pathology 5-10 years before disease manifestation, but there are conflicting results with biomarker changes and disease progression. Therefore, longitudinal biomarker evidence is needed.[23] Meanwhile, the advances in tau imaging will enable better identification of AD.[24] The current definition of AD is given in Table 1.[25,26] The diagnostic criteria for AD have been revised recently as follows:[27]

- Definition of dementia concerns essential entities (AD, DLB, vascular dementia, frontotemporal dementia, prion disorders)
- Classical definition of MCI fills gap between cognitively normal state and dementia
- Contains central points of the NICDS-ADRDA criteria
- Biomarkers (CSF, serum protein, neuroimaging) as parts of expanded criteria are necessary
- Quantitative clinical and pathological criteria to be used together with disease categories

Meta-analysis of several sets of autopsy cases from the National Alzheimer's Coordinating Center Registry USA revealed a higher diagnostic accuracy for AD (sensitivity of 71-85% and specificity of 44-78%), with both values being slightly better for imaging procedures than for CSF markers. However, the data varied due to heterogeneity of the study designs.[28,29]

NEUROPATHOLOGICAL DIAGNOSIS

AD is a neurodegenerative disorder with a well-defined neuropathological background characterised by the accumulation of tau protein within neurons (neurofibrillary tangles [NFTs]) and the extracellular deposition of Aβ (plaques, amyloid angiopathy) in the brain parenchyma, which is associated with neuronal and synaptic loss.[30] The histopathological examination of the brain using modern molecular-biological methods under standardised conditions still represents the 'gold standard' for AD diagnosis, although the frequent overlap of various processes and multimorbidity of the ageing brain have to be considered.[31-33] The current algorithms for the neuropathological diagnosis of AD are based on the assessment of senile plaques and NFTs, providing inter-rater agreement when using standardised criteria.

Guidelines for the neuropathological diagnosis of AD include quantitative cut-off values for plaques and tangles, their semi-quantitative assessment and age-adjustment (Consortium to Establish a Registry for Alzheimer's Disease [CERAD] protocol), topographic staging of neuritic/tau pathology (Braak staging), and the progress and distribution of Aβ deposition, which differs from tau pathology. The recent NIA-AA guidelines consider AD pathology regardless of the clinical history of a given individual. They include: (i) the recognition that AD pathology may occur in the absence of cognitive impairment; (ii) an 'ABC'

score of AD pathology that incorporates assessment of amyloid plaques (A), staging of tangles based on the Braak staging system (B), and scoring of neuritic plaques based on semi-quantitative assessment in at least five neocortical regions (C), based on CERAD criteria (Figure 1b);[34-37] and (iii) more detailed approaches for assessing comorbid conditions, such as DLB or vascular pathology.

Preliminary testing of the revised NIA-AA guidelines distinguished AD from non-demented cases with a sensitivity of 71% and a specificity of 99%. However, there is growing appreciation, not yet incorporated into these guidelines, that the neuropathology of AD is heterogeneous and includes a number of subtypes, e.g. limbic-predominant, hippocampal-sparing, and typical forms,[38] and primary age-related tauopathy (PART), previously referred to as 'tangle-only dementia',[39] without evidence of Aβ accumulation.[40] Further diagnostic challenges include the fact that neuropathology of AD in very old patients differs considerably in both intensity and distribution from younger age groups.

A.

Stage	PIB-PET	HVa	FDG-PET	Cognitive disorder
0	-	-	-	-
1	+	-	-	-
2	+	- (+)	+ (-)	-
3	+	- (+)	+ (-)	+
SNAP	-	- (+)	+ (+)	- (+)
Unclassified	- (+)	-	-	+

B.

Level of AD neuropathologic change						
Thal phase for Aβ plaques	A	B			C	*CERAD*
		0 or 1	2	3		
0	0	Not	Not	Not	0	*neg*
1 or 2	1	Low	Low	Low	0 or 1	*neg or A*
1 or 2	1	Low	Intermediate	Intermediate	2 or 3	*B or C*
3	2	Low	Intermediate	Intermediate	Any C	*neg or A to C*
4 or 5	3	Low	Intermediate	Intermediate	0 or 1	*neg or A*
4 or 5	3	Low	Intermediate	High	2 or 3	*B or C*
		Braak 0-II	*Braak III-IV*	*Braak V-VI*		

Figure 1: The role of biomarkers in the diagnosis of preclinical Alzheimer's disease (AD)/mild cognitive impairment (MCI) and ABC criteria for the neuropathological diagnosis of AD.

A: Preclinical AD stages (MCI) in cognitively normal patients using biomarkers with 90% sensitivity for the diagnosis of AD and 10th percentile of normal cognitive score. *Modified from Jack CR Jr et al.*[9] B: ABC criteria for the diagnosis of AD-related pathology. The level of AD neuropathological change is determined by assessing A, B, and C scores. A ('A' for amyloid) scores are related to phases of β-amyloid (Aβ) deposition (first column; described by Thal DR et al.[34]). Score 1 includes phases 1+2, score 2 = phase 3, score 3 includes phases 4+5, score 0 indicates absence of Aβ deposits. B ('B' for Braak): neurofibrillary degeneration should be assessed based on the Staging system described by Braak and Braak[35] and on tau immunohistochemistry. Score 1 includes Stages I+II (transentorhinal), score 2 includes Stages III+IV (limbic), score 3 includes Stages V+VI (isocortical), and score 0 indicates absence of neurofibrillary tau pathology. C ('C' for CERAD): evaluation of neuritic plaques is based on the semi-quantitative scoring system described by Mirra et al.[36] Score 0 indicates absence, score 1 refers to sparse, score 2 to moderate, and score 3 to frequent neuritic plaques. *Modified from Montine TJ et al.*[37] FDG: fluorodeoxyglucose; HVa: hippocampal volume; PET: positron emission tomography; PIB: Pittsburgh compound B; SNAP: suspected non-Alzheimer pathophysiology; CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

Table 1: Definition of Alzheimer's disease (AD) dementia from the National Institute on Aging and Alzheimer's Association Workgroup.

A. Probable AD dementia is diagnosed when the patient:
1. Meets criteria for dementia, and has the following characteristics: 2. Insidious onset. Symptoms have a gradual onset over months to years; and 3. Clear-cut history of worsening of cognition by report or observation; and 4. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: a) *Amnestic disorder:* the most common syndromic presentation of AD dementia b) *Non-amnestic disorders:* – language disorder – visuospatial disorder – executive and behavioural disorder. 5. Exclusions: the diagnosis of probable AD dementia should not be applied when there is evidence of: a) Substantial concomitant cerebrovascular disease; or b) Core features of dementia with Lewy Bodies (DLB) other than dementia itself; or c) Prominent features of behavioural variant frontotemporal dementia; or d) Prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or e) Evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or medication use that could have a substantial impact on cognition.
B. Possible AD dementia is diagnosed when the patient meets one of the two following criteria:
1. *Atypical course:* meets the core clinical criteria (1) and (4) (above) for probable AD dementia, but either had a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline; or 2. *Aetiologically mixed presentation:* meets all core clinical criteria (1) through (4) for probable AD dementia but has evidence of: a) Concomitant cerebrovascular disease; or b) Features of DLB other than the dementia itself; or c) Evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial impact on cognition.
C. Research definition of probable AD dementia with biomarkers*
1. Meets clinical criteria (1) through (5) for probable AD dementia and has the following levels of probability of AD pathophysiology based on the profile of neuroimaging and cerebrospinal fluid (CSF) biomarkers: a) Highest probability: β-amyloid marker (CSF or imaging) 'positive' and neuronal injury marker (CSF tau, FDG-PET, or structural MRI) 'positive' b) Intermediate probability: β-amyloid marker 'positive' or neuronal injury marker 'positive' c) Uninformative: biomarkers unavailable, conflicting, or indeterminate.
D. Research definition of possible AD dementia with biomarkers*
1. Meets clinical criteria for possible AD dementia and has the following levels of probability of AD pathophysiology based on the profile of neuroimaging and CSF biomarkers: a) High, but does not rule out second aetiology: β-amyloid marker 'positive' and neuronal injury marker 'positive' b) Uninformative: any other configuration of biomarkers

*A biomarker is considered 'positive' if it has a value that is regarded as diagnostic of AD pathophysiology. As of 2011, there are no universally accepted standards for what is considered diagnostic of AD pathophysiology for any of the biomarkers listed in this table. Therefore, standards based on local experience would be used.

FDG: fluorodeoxyglucose; PET: positron emission tomography; MRI: magnetic resonance imaging.

Table modified from Knopman D,[25] data source taken from McKhann GM et al.[26]

There is considerable overlap between demented and non-demented seniors, dementia in the oldest (90+ years) being only modestly related to AD, while cerebrovascular pathologies may cause cognitive impairment in patients with low AD pathology scores.[41,42] However, dementia lacking a known pathological background is extremely rare.[43]

Table 2: Drug treatment of cognitive symptoms in Alzheimer's disease.

	Evidence classification	Efficacy	Clinical recommendation
1. Cholinesterase inhibitors			
Donezepil (Aricept®)	1a	++	A
Rivastigmine (Exelon®)	1a	++	A
Galantamine (Reminyl®)	1a	++	A
2. Other cognitive-enhancing drugs			
Memantine (Axura®, Ebixa®)	1a	++	A
Cerebrolysin® - intravenous	1b	+	B
Selegiline (Jumex®, Cognitive®, Selegiline Genericon®, Xilopar®)	2b	+	C
Tocopherol (vitamin E)	1b	+	D
Dihydroergotoxine (Codergocrin®, Dorehydrin®, Ergomed®, Hydergine®)	2b	+/-	D
Piracetam (Cerebryl®, Nootropil®, Novocephal®, Pirabene®)	2b	+/-	D
Idebenone (co-enzyme Q10 derivate)	3	+/-	D
Nimodipine (Nimotop®)	2b	+/-	D
Ginkgo biloba (Cerebokan®, Ceremin®, Gingel®, Tebofortan®, Tebonin ret.®)	1a	+	B
Nicergoline (Ergotop®, Nicergin®, Sermion®)	2a	+	B
Propentofylline	3	+/-	B
Pentoxifylline (Hemodyn®, Pentohexal®, Pentomer®, Pentoxi 'Genericon'®, Pentoximed®, Trental [Vasonit®])	3	+/-	D
Vincamine	3	+/-	D
Substitution of oestrogen	2b	+/-/-	D

++ significant; + good; +/- questionable.

Evidence classification

1a: by several randomised controlled studies and/or meta-analyses. 1b: by one randomised controlled study. 2a: by one methodologically correct but not randomised study. 2b: by one methodologically correct, e.g. experimental study. Intervention without control (e.g. application study). 3: by methodologically correct, not-experimental observation studies (e.g. case reports). 4: by experimental statements.

Clinical recommendation

A: recommended with definite clinical reliability. B: recommended with moderate clinical reliability. C: recommended on the basis of individual circumstances. D: cannot be recommended according to available data.

Modified from Schmidt et al.[51]

Another major diagnostic problem is the frequent presence of multiple pathologies in the aged brain that coexist with AD and affect its clinical course. About two-thirds of aged human brains show non-AD type pathology, which is often missed clinically and cannot be identified without neuropathological examination.[31-33] The burden of vascular, AD type, and other pathologies are consistent with an additive or synergistic effect of these types of lesions on cognitive impairment.[41-44]

CURRENT TREATMENT OPTIONS

Current treatment of AD patients includes: (i) drug treatment of cognitive and non-cognitive symptoms including neuropsychiatric complications;

(ii) non-pharmacological treatment options such as cognitive training and psychosocial activation; and (iii) preventive measures to reduce risk factors.

Drug Treatment

Current first-line drugs in the treatment of AD include cholinesterase inhibitors (CHI) – donepezil (oral or transdermal application), rivastigmine, galantamine, and the N-methyl-D-aspartate receptor channel blocker memantine, or their combination. CHIs are approved for mild-to-moderate AD, whereas memantine is approved for moderate-to-severe AD. The use of a combination of CHIs plus memantine rather than CHIs alone in patients with moderate-to-severe AD has been recommended, in particular for moderately severe AD cases with behavioural symptoms.[45,46] Meta-analysis of the efficacy of these drugs showed that they are able to stabilise or slow decline in cognition, function, behaviour, and global change, with better tolerability than memantine.[47] However, like other cognitive-enhancing drugs (cerebrolysin, ginkgo biloba), they have only mild-to-moderate effects on memory and capabilities for daily living, inducing delay of progression for about 6-12 months, with stable efficacy over years.

A recent long-term study of gingko biloba extract, however, did not find significant differences compared with placebo.[48] Changes between treatments in cases of intolerance and/or inefficacy are possible. Efficient and approved pharmacological treatment options for MCI as a prodromal syndrome of AD are still lacking.[49] For a critical review of cognitive enhancers (nootropics) please refer to Froestl et al.[50] Many other treatments (hydergine, nicergoline, piracetam, pyritinol, etc.) cannot be recommended in view of indefinite efficacy (Table 2).[51] The benefit–cost ratio of AD drugs was validated cautiously as being low between drug and non-pharmacological applications. Most drugs entering the AD drug-development pipeline have failed and there exists an urgent need to increase the support of the AD drug-development ecosystem.[52] Recent studies of intravenous immunoglobulin that sequesters Aβ and was suggested to interfere with AD progression failed.[53]

Drug therapy of non-cognitive symptoms, such as depression and other neuropsychiatric complications (behavioural and psychological symptoms of dementia [BPSD]), in addition to CHIs and related drugs, includes cautious use of new antipsychotic drugs (risperidone, olanzapine, quetiapine, clozapine) and anti-depressive drugs (in particular, selective serotonin reuptake inhibitors such as sertraline and citalopram; less efficient tricyclic antidepressive drugs, which have an anticholinergic potential that is a negative feature in AD; and potentially fluvoxamine and paroxetine), the cautious use of benzodiazepines in case of anxiety and aggression, and occasionally anticonvulsive drugs (carbamazepine, valproate). CHIs and atypical antipsychotics could improve BPSD in AD patients, but with adverse safety outcomes.[54]

Non-pharmacological options include combined programmes to increase cognitive functions, behaviour, mood, daily activities, independence, and thus quality of life. Close co-operation between caregivers, family, and therapists with the patient may ameliorate their motivation and remaining capacities by activation of the cognitive reserve, as well as influence their mood. Changes in lifestyle, physical and psychological activity, and reduction of common risk factors such as hypertension, hyperlipidaemia, obesity, diabetes, and smoking are of highest priority for the prevention of AD and related processes. A slowing of disease progression until 2050 could reduce the number of cases by about 12 million.[55] AD and other dementia disorders are currently incurable but can be prevented, at least in part.

Immunotherapies for AD

Recent advances in the understanding of AD pathogenesis have led to the development of numerous compounds that can modify the disease process. Both passive and active immunotherapies have been shown to reduce Aβ accumulation and prevent downstream pathology in animal models, indicating that intervention appears to be effective in the early stages of amyloid accumulation.[56] Several trials demonstrated by post-mortem examination and *in vivo* imaging that Aβ can be removed from the human AD brain, although this increases cerebral amyloid angiopathy.[57] The most developed method for targeting Aβ is the use of monoclonal antibodies, including bapineuzumab, solanezumab, and crenezumab, as suitable drug candidates in preventative clinical trials for AD.[58,59] However, the evidence for unequivocal cognitive benefits has been disappointing so far.[60,61]

As the aggregation and accumulation of the microtubule-associated protein tau is a

pathological hallmark of AD and other tauopathies, tau-based immunotherapy has been considered as a novel therapeutic target in AD, and a number of animal studies have shown the efficacy of both passive and active immunisation;[62,63] human trials will be performed in the future.[64] Another approach may be to combine second-generation anti-Aβ vaccines with a drug that inhibits β-site amyloid precursor protein-cleaving enzyme 1 (BACE1), which disrupts cleavage of amyloid precursor protein and Aβ formation. A combination trial in patients at risk of developing AD was announced in July 2014,[65] but BACE1 inhibitors have had a mixed track record to date.[66] Other BACE1 inhibitors are in Phase I testing.

The goal of ongoing studies is the assessment of clinical efficacy with adequate safety and tolerability, but a final judgement of the immunotherapeutic modalities and other disease-modifying procedures is impossible. Future treatment strategies using multimodal and multifunctional substances influencing causal disease processes, such as amyloid production and phosphorylation of tau protein, and their interrelation with neurodegeneration are necessary and should be applied in early/preclinical stages of the disease.

CONCLUSION AND FUTURE DEVELOPMENT

Recent insights into the molecular pathogenesis of AD and updated clinical and neuropathological consensus criteria have increased the diagnostic accuracy and early recognition of AD. Interdisciplinary projects for the standardised assessment of clinical phenotype, neuroimaging, and biomarkers are currently under way.[27,67] Use of the updated diagnostic criteria for AD considering clinical phenotype, CSF and other biomarkers, modern neuroimaging, and multimodal techniques have increased the clinical diagnostic accuracy of AD to approximately 90%, while modern molecular, genetic, and standard laboratory methods can achieve a final diagnosis or classification in up to 96% of cases. In the majority of cases, excepting those with known genetic or metabolic background, clinical and pathological examination may not be able to clarify the causes/aetiology of AD and other dementing disorders. Therefore, the reliability and clinical relevance of the current diagnostic criteria need better qualification and validation in order to enable an early diagnosis of preclinical AD and related disorders as a basis for further neuroprotective and effective disease-modifying treatment options.[68]

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TREATMENT OF STATUS EPILEPTICUS – A NARRATIVE REVIEW OF THE EVIDENCE SO FAR AND A PROPOSAL FOR THE DESIGN OF RETROSPECTIVE STUDIES

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ABSTRACT

Randomised controlled studies of the treatment of status epilepticus (SE) are difficult to perform due to ethical reasons. Therefore, the evidence for treatment guidelines is mainly based on observational studies, case series, case reports, and retrospective database analyses. The diversity of approaches used to determine the termination drug in a treatment episode of SE shows that the scientific community has not yet found a global means of defining when and if an antiepileptic drug is successful in terminating SE. More meta-analyses are needed in order to compare the treatment effects in the subtypes of non-convulsive SE because these are only small heterogeneous subdivisions in large database analyses. Furthermore, we propose that future case series, observational studies, or retrospective database analyses should follow certain standards to make them more comparable.

Keywords: Outcome criteria, subtypes of non-convulsive status epilepticus, status epilepticus (SE).

INTRODUCTION

Status epilepticus (SE) is a serious medical condition affecting at least 20 of every 100,000 Caucasian individuals per year.[1] The diagnosis of SE should be made when there are either continuous seizures lasting at least 5 minutes, or two or more discrete seizures between which incomplete recovery of consciousness occurs.[2] Randomised controlled trials (RCTs) of SE treatment are difficult to perform due to ethical reasons. Therefore, the evidence for treatment guidelines is mainly based on observational studies, case series, case reports, and retrospective database analyses. For example, in a study of levetiracetam (LEV) it was shown that retrospective studies report a higher efficacy rate than prospective studies, which indicates a possible publication bias.[3] It has been questioned whether there are truly sufficient reliable data to establish evidence-based guidelines for the treatment of SE.[4] In this narrative review we will present the evidence derived from prospective RCTs of SE treatment, with a focus on trials performed in adults. Furthermore, we will highlight some aspects of the evidence originating from reviews of safety studies, case series, case reports, observational studies, and retrospective database analyses. Included at the end of the review is a proposed procedure to improve the proficiency of the treatment of SE without prospective RCTs. It must be acknowledged that we focus on antiepileptic treatment with regard to the efficacy of the various antiepileptic drugs (AEDs).

THE EVIDENCE SO FAR

Prospective Randomised Controlled Trials

Prospective RCTs for the treatment of SE are rare: there have only been five prospective RCTs for the first-line treatment of SE. In the Veteran Affairs Status Epilepticus Study, 0.1 mg/kg lorazepam (LZP) was found to be superior to 18 mg/kg phenytoin (PHT) in terminating SE. Barring this superiority, no other statistically significant

differences were observed. This study also included treatment with 15 mg/kg phenobarbital (PB) and the combination of 0.15 mg/kg diazepam (DZP) with PHT.[5] In another study, 30 mg/kg valproate (VPA) was observed to be more effective than 18 mg/kg PHT in terminating generalised clonic status epilepticus (GCSE).[6] Two studies suggested a superiority of LZP (in doses of 2 mg and 4 mg) to DZP (in doses of 5 mg and 10 mg) as a first-line treatment for SE.[7,8] However, a statistical significance in the difference between the two drugs could not be shown. In addition, according to the World Health Organization's Collaboration Centre for Drug Statistics Methodology,[9] the authors compared 50% or 100% of a standard daily drug dose (DDD) of DZP with 80% or 160% of a DDD of LZP. The results may therefore be confounded by the low dose of DZP.

In another study it was proposed that LEV is as effective as LZP as a first-line treatment for terminating GCSE.[10] However, the sample size in this study was <80% of the calculated sample size for detecting a 20% difference, and so minor differences in efficacy may have been missed. The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) showed that intramuscular midazolam is at least as safe and effective as intravenous LZP for prehospital seizure cessation in patients with convulsive SE.[11] There is only one prospective RCT concerning the second-line treatment of SE. In this study, VPA as a second-line treatment was found to be as effective as PHT.[12] For the treatment of refractory SE there is also only one randomised trial,[13] which is under-sampled. Nevertheless, this trial shows significantly longer mechanical ventilation time with the use of barbiturates compared with propofol.

Reviews of Case Series, Case Reports, and Retrospective Database Analyses

All other evidence concerning the treatment of SE is derived from non-randomised safety studies, case series, case reports, and retrospective database analyses. For example, efficacy rates for termination of SE calculated in narrative reviews were 55.9% for LEV,[14] 58% for lacosamide (LCM),[15] 47% for pregabalin,[16] and 37% for topiramate (TPM).[17] These reviews predominantly address the treatment of refractory SE. There may be a considerable publication bias in favour of these substances because in a large database analysis the success rate in terminating SE was between 30-55% regardless of the substances used.[18] When general anaesthesia cannot terminate SE the condition is termed super-refractory SE. The treatment of this issue is *terra incognita* from the point of view of evidence-based medicine.[19]

PROBLEMS FOR REVIEWS OR META-ANALYSES OF OBSERVATIONAL STUDIES, CASE SERIES, CASE REPORTS, AND RETROSPECTIVE DATABASE ANALYSES

Outcome Criteria

A review of TPM in SE describes eight different criteria for possible or certain treatment effect of an AED,[17] which were different from the criteria commonly used in prospective RCTs in SE.[5] In another review on LEV as second-line treatment of SE,[2] seven different criteria for a treatment effect of an AED were described. Some of these criteria are very similar to others mentioned in the review or to those mentioned in the review on TPM;[17] for an overview of these criteria see Table 1.[20-30] The time frame for the attribution of a treatment effect to the administration of a new AED ranges from 3 minutes to 72 hours. In a meta-analysis[31] of published studies concerning the relative effectiveness of LCM, LEV, PB, PHT, and VPA in the treatment of benzodiazepine-resistant convulsive SE, only about half of the articles cited a specified time frame in which they considered the seizure termination to be successful. The most commonly stated specification was the termination of seizures within 30 minutes of infusion (six articles, 22.2%). However, the time frames of other studies ranged from 3 minutes to 48 hours. One study even linked the time of the cessation of SE with the end of the infusion. These different approaches show that the scientific community has not yet found a global means of defining when and if an AED is successful in terminating SE. In this meta-analysis, the authors tried to control the effect of different criteria with statistical methods. Unfortunately, this cannot be done without knowing the extent of the effect.

In a case series concerning the treatment effect of perampanel (PER) in non-convulsive SE and simple partial SE,[32] four different outcome criteria were compared with each other. These criteria were: 1) The last AED administered before SE termination is defined as effective, regardless of the latency between its first administration and SE cessation; 2) The AED that was the last drug introduced into

the antiepileptic therapy <72 hours before the cessation of SE and without changes in the co-medication; 3) The AED that was the last drug introduced into the antiepileptic therapy or increased in dose <24 hours before the cessation of SE and without changes in the co-medication; 4) The AED that was the last drug introduced into the antiepileptic therapy <72 hours before the cessation of SE, even allowing changes in the co-medication. In this study, PER was the terminating drug in two cases according to Criterion 1, in three cases according to Criterion 2, in four cases according to Criterion 3, and in six cases according to Criterion 4 (i.e. range of efficacy rates from 20-60%). A statistical definition of these differences in outcome seems to be difficult.

Different Entities of SE

Apart from generalised convulsive SE and simple partial SE, there is a large group of different types of non-convulsive SE with different responses to treatment. Shorvon[33] proposed 22 different types of non-convulsive SE, which, as shown in an extensive review, are partly associated with their own specific electroencephalographical patterns.[34] Unfortunately, in a retrospective database analysis these data could not be fully reproduced.[35] In the same database analysis[36] it was shown that the frequency of refractory courses differed between the types of SE. This was mainly due to the fact that all episodes of limbic SE were refractory, which stands in contrast to the episodes of generalised convulsive SE, non-limbic complex SE, and subtle SE.

Table 1: Criteria for a possible or certain treatment effect of an AED in the treatment of status epilepticus.

Reference	Criterion
20	• Successful: Clinical improvement and electroencephalographic resolution of refractory SE within 24 hours after starting with the new AED with no requirement for further AEDs. • Probably successful: Improvement occurring within 72 hours after starting treatment with the new AED, which may however also be due to other therapeutic measures or self-termination after longer treatment with no requirement for further AEDs.
21	• Successful: Increased alertness and responsiveness and electrographical improvement occurring within 96 hours following introduction of the new AED without modification of concomitant AEDs. • Possibly successful: Termination of SE associated with introduction or increase of the AED concomitantly with other AEDs.
22	• Full responder: Seizure activity terminated within 24 hours of initiation of the new AED. • Partial responder: Marked reduction or no seizure activity in response to increased doses of the new AED within 72 hours after first administration.
23	EEG status resolves within 24 hours after the start of the new AED and no further antiepileptic agents are added to the treatment protocol during this time period.
24	• In patients in burst suppression due to pharmacological coma, seizure response to the new AED was defined as the absence of electrographical seizure activity for 24 hours following the emergence from burst suppression. • Resolution of electrographical seizure activity within 4 hours of administration of the new AED.
25	Cessation of seizure activity within 3 days of initiation or dose increase of the new AED without addition or adjustment of other AEDs in the same time frame.
26	The last AED introduced before improvement in the EEG.
27	Clinical or electroencephalographical cessation of seizures within 24 hours after start of the new AED without need for other AEDs.
28	No need to introduce a further compound to control SE.
29	The absence of seizures within 24 hours after infusion of the new AED with no other AEDs administered during this time and no recurrence of SE during the hospital stay.
30	Cessation of the clinical manifestation of convulsive SE and electroencephalographically in non-convulsive and subtle SE within approximately 3 minutes.
10	Clinical seizure cessation within 30 minutes.

AED: antiepileptic drug; SE: status epilepticus; EEG: electroencephalogram.

Non-convulsive SE in the postictal phase of tonic—clonic seizures and cases of coma due to acute brain injury with epileptiform electroencephalogram changes were more often refractory than generalised convulsive SE. Since generalised convulsive SE has a more overt semiology than non-convulsive SE, treatment is initiated earlier than in other subtypes of SE.

The efficacy rates of some AEDs were also different in the various subtypes of SE. Anaesthesia and clonazepam both terminated generalised convulsive SE more effectively than non-convulsive SE and simple partial SE. LEV was the only AED that seemed to be more effective in terminating non-convulsive SE or simple partial SE than generalised convulsive SE. However, the discrepancy was not as significant due to the small number of patients treated with LEV. Because there were only small subgroups, no statistical comparison between the individual subtypes of non-convulsive SE was performed. It must be assumed that when the quota of refractory courses differs between the subtypes of non-convulsive SE then this will influence the efficacy rates of the AEDs used for treatment.

A PROPOSAL FOR THE DESIGN OF RETROSPECTIVE STUDIES

The implementation of RCTs is difficult due to ethical reasons. To broaden the evidence, especially for the treatment of non-convulsive SE, further database analyses are needed and outcome criteria should be standardised in order to better compare the studies of different research groups. We need more meta-analyses so that we can compare the treatment effects in the different subtypes of non-convulsive SE, which make up only small subgroups even in large database analyses. Therefore, we propose that future case series, observational studies, or retrospective database analyses should report their efficacy rates with reference to the subtypes of non-convulsive SE, even if there were no statistically significant differences in the reported sample of treatment episodes.

To make the studies more comparable, several outcome criteria should be used simultaneously. For first-line treatment, a treatment effect within 10 minutes seems to be favourable, and for second-line treatment a treatment effect within 30 minutes is probably reasonable because these time frames are used in guidelines for treatment of generalised convulsive SE. When second-line treatment in generalised convulsive SE does not work according to all guidelines, anaesthesia should be used. The situation in refractory non-convulsive SE is more complicated. We suggest that authors of future studies on this topic should at least use Criterion 3 of the study on PER as one of their outcome criteria (see above).[32] This criterion is very similar to the 24-hour criterion used in many studies cited in Table 1. This must be qualified by saying that for AEDs with a terminal half-life of <8 hours, the 24-hour criterion is appropriate only when a loading dose is used, otherwise the steady state of trough plasma levels will be reached later. It must be acknowledged that the time to treatment effect may not be the only relevant outcome criterion.

In one study, the return to baseline in the general condition after SE was taken as an outcome criterion.[37] Perhaps, in the future, outcome criteria like this should be taken into consideration as well. Another problem is that one AED may start to have an effect after another one has been introduced. Therefore, the last-introduced AED may be erroneously considered the effective one. This may particularly be the case with PER. After oral administration, peak plasma concentrations of PER have been observed within 15 minutes to 2 hours after application.[38] PER distributes into the body tissue, and the remaining plasma fraction has a terminal half-life of about 105 hours. Peak plasma concentrations, as well as trough plasma levels, increase for about 14 days if the initial daily dose is maintained. Because of these effects, if 6 mg PER is administered for the first time in a patient with 'normal' weight, there will probably only be a time frame of a few hours in which the plasma concentration is at a therapeutic level, but with repeated administrations the plasma concentration will increase considerably. Therefore, the effectiveness of PER to terminate SE should increase from day to day and it may have a considerable role in the termination of refractory SE even >72 hours after first administration.

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STATUS EPILEPTICUS IN CRITICALLY ILL PATIENTS

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ABSTRACT

Status epilepticus (SE) is a common diagnosis in critically ill patients that may bear significant morbidity and mortality. Nowadays it is defined as continuous seizure activity lasting for more than 5 mins and requiring a specific treatment. A generalised convulsive state is a medical emergency burdened by high mortality, especially in the elderly, because repeated seizures swiftly induce significant metabolic and cardiocirculatory derangement. Two different kinds of SE are commonly recognised, depending on the presence of convulsion: convulsive SE and non-convulsive SE, which have different electroencephalographic patterns and require different therapies. In this review we provide an overview of this intriguing issue, focussing on critically ill patients.

Keywords: Status epilepticus (SE), intensive care, seizure.

INTRODUCTION

Status epilepticus (SE) is a common diagnosis in critically ill patients that may bear significant morbidity and mortality. For this reason it is extremely important that it is properly diagnosed and treated. According to the traditional criteria, SE is defined as continuous seizure activity lasting 30 mins or as two or more discrete seizures between which consciousness is not fully regained.[1] Numerous studies have recently revised this definition assuming that seizures lasting more than 5 mins require the same treatment as that used for traditional SE.[2,3] This is because the mechanisms responsible for the seizure's self-termination fail, thus impairing homeostasis of the body and thereby causing the condition to become life-threatening due to the deterioration of various organs and systems as well as from direct damage to the brain cells related to neurotransmitter release.[3] Neuronal injury results from several cellular alterations involving extracellular and intracellular ionic balances, as well as the activation of inflammatory processes and the cell death mechanism.

The opening of the blood—brain barrier during SE has a short-term pro-epileptic effect, causing equilibration of serum electrolytes with cerebrospinal fluid. This results in an increased interstitial space, a lowered extracellular Ca^{2+} concentration, and the facilitation of neuronal excitability.[4] The release of cytokines and neuropeptides with a variety of cytological and chemical reactions affects the brain vascular permeability and determines pro-inflammatory and immune reactions.[5] The most well-known cytokines include interleukin (IL)-6, IL-1β, tumour necrosis factor α, and the activation of the IL-1 Type 1 receptor/Toll-like receptor signal pathway. Seizures trigger neuronal death by an active form of necrosis requiring a mitochondrial death programme and/or the activation of a caspase cascade.[6]

Convulsive Status Epilepticus

Convulsive status epilepticus (CSE) is a condition characterised by epileptic seizures associated with rhythmic contractions of the extremities, tonic–clonic movement of the limbs, altered mental state (coma, lethargy, confusion), and possible focal neurological deficits in the postictal period.

Non-Convulsive Status Epilepticus

Non-convulsive status epilepticus (NCSE) is defined as altered consciousness or behaviour

for 30 mins or more, the absence of overt clinical signs of convulsive activity during that period, and the electroencephalographic (EEG) confirmation of seizures or activity that responds to treatment along with improved consciousness.[7] NCSE is increasingly recognised as a common occurrence in the intensive care unit (ICU) but in coma patients continuous lateralised epileptiform discharges (coma–LED) need to be distinguished from generalised epileptiform discharges (coma-GED), and it is often difficult to understand if the coma is caused by SE or by an underlying brain disorder and thus correlate this with suitable prognosis and therapy.[8]

Refractory Status Epilepticus

SE is defined as refractory when it does not respond to standard therapeutic regimens. Brophy et al.[2] suggest considering patients to be in refractory status epilepticus (RSE) whenever they continue manifesting clinical or EEG signs after an adequate dose of benzodiazepine (BZD) followed by a second anti-epileptic drug (AED) which is deemed effective. The number of AEDs to which patients have not responded that is required for a diagnosis of RSE, and whether or not to consider the duration of the SE from the initiation of treatment for the purpose of classification, remain controversial.

EPIDEMIOLOGY

SE, and in particular NCSE, has been identified in many studies as a very common nosological entity in ICUs, with a higher incidence in neurological ICUs partly due to medical and metabolic conditions, and partly due to the drugs used that predispose patients to the condition.[9] The incidence of SE in Europe varies from 9.9/100,000 in Switzerland and 10.7/100,000 in Italy[10] to 17.1/100,000 in Germany,[11] with a bimodal distribution involving a high incidence in infants <1 year of age and in the elderly (>60 years of age). In the event of subarachnoid haemorrhage, epileptic seizures are known to be a very common sequela, and some recent scientific evidence shows an underestimated frequency of the non-convulsive type in these patients, especially in those subject to sedation.[12] Even intraparenchymal haemorrhage has proven to be complicated by SE in a high percentage of cases (i.e. 18-21%), due to SE being a factor in midline shift, increased haemorrhaging, and a worsening of the outcome. Ischaemic and haemorrhagic stroke have been shown to be correlated with CSE and NCSE in such a significant percentage of cases as to suggest the early use of EEG monitoring to reveal the presence of periodic lateralised epileptiform discharges, which were followed in a study by Mecarelli et al.,[13] by SE in 70% of cases. To study the incidence of NCSE within the spectrum of SE, some authors have proposed associating prolonged video-EEG recording with standard EEG, reaching a diagnosis of NCSE in 59% of cases studied on the basis of a specific clinical suspicion and in 41% of cases in patients with no clinical evidence. This finding yet again shows the utility of EEG monitoring.[14]

DIAGNOSIS AND ELECTROENCEPHALOGRAPHIC PATTERNS

The initial diagnosis of SE is still based on the clinical assessment of altered motor performance and mental status, but it must inevitably rely on prolonged EEG monitoring in some cases where findings from the first two assessments are not temporally correlated with the EEG findings, both during or after the SE, or in particular forms of SE, such as NCSE. Table 1 shows the characteristic findings for each of the three assessments associated with the different forms of SE. Remarkably, EEG criteria for convulsive SE have been clearly delineated, but a combination of clinical and EEG criteria have to be met for NCSE diagnosis.

Clinical manifestations of SE in the variant of NCSE in patients admitted to intensive care can be blurred due to the underlying condition and drugs administered, such as anaesthetics, muscle relaxants, and anticonvulsants. Furthermore, there are no pathognomonic encephalographic characteristics that precisely identify SE to differentiate it from electrical epiphenomena caused by cerebral dysfunction. In fact, although the significant generalised activity of spike discharges is indicative of severe encephalopathy, this can more often be associated with anoxic phenomena or to NCSE.[8] Furthermore, advanced stages of coma are frequently accompanied by continuous or periodic epileptiform phenomena, considered by some to be the very cause of the severe encephalopathy and the coma. Holtkamp and Meierkord et al.[15] suggested formulating a diagnosis of NCSE only if, in addition to EEG abnormalities, there is clinical evidence of epilepsy

derived from the patient's clinical history or if episodes of epileptic seizures or SE have occurred. In 2010, two further definitions were introduced to attempt to better clarify this complex clinical situation — coma-GED and coma-LED — definable on the basis of the EEG and that can effectively distinguish NCSE from comatose NCSE, as described previously.[8]

Lastly, subtle SE is a form of NCSE that arises from insufficiently treated SE. It may be an unrecognised cause of coma.[16] The distinctive features include a comatose state and the absence of prominent motor features. Nevertheless, there can also be discrete muscle twitching, and EEG tracings mostly show generalised periodic discharges, although lateralised and regional discharges can also occur. The most recent guidelines put forth by the Neurocritical Care Society[2] and by the European Society of Intensive Care Medicine[17] recommend continuous EEG monitoring for comatose patients, patients with intracranial haemorrhage, and patients with recent clinically overt epileptic seizures without normalisation. In particular, continuous EEG monitoring is recommended for at least 48 h for coma patients to assess the presence of NCSE.

NON-EPILEPTIC CONDITIONS THAT MIMIC THE MANIFESTATIONS OF NCSE

A number of conditions can mimic NCSE without there being periodic or rhythmic EEG abnormalities. These include migraine aura, transient global amnesia, transient ischaemic attack, stupor, and dissociative disorders. Pseudostatus epilepticus can present in various forms, such as with bizarre motor features or a simulation of loss or impairment of consciousness without motor features. None of these conditions is accompanied by EEG alterations. In the impossibility of EEG monitoring, 2 mg of intravenous (IV) lorazepam (LZP) can be administered to clarify the diagnosis of NCSE.[15]

There are, however, situations treated in the ICU that can give rise to confusion, both clinically and electroencephalographically with NCSE.

Table 1: Clinical features and electroencephalography (EEG) pattern of convulsive and non-convulsive status epilepticus.

			CLINICAL FEATURES	EEG PATTERN
CONVULSIVE	GENERALISED	*Tonic–clonic seizures*	**Tonic phase:** Sustained powerful muscle contraction, which arrests ventilation **Chronic phase:** Alternating contraction and relaxation (rhythmic jerk), causing a reciprocating movement which could be bilaterally symmetrical or 'running' movements; possible urinary or faecal incontinence, possible morsus	**Tonic phase:** Progressively higher amplitude and lower frequency discharge pattern observed simultaneously in both cortical hemispheres, reaching a maximum of 10 Hz **Chronic phase:** Slow spikes develop progressively into repetitive complexes of high-amplitude spike-and-slow-wave activity
		Myoclonic status	Normal or moderately impaired consciousness and generalised myoclonia (predominantly affects the upper extremities and shows some asymmetry) Anoxic coma	Slowing of background rhythm and high-voltage generalised spike and wave discharges Normal background activity with high amplitude, 5 to 15-Hz rapid bursts of generalised polyspikes synchronous with the myoclonia
	FOCAL	*Epilepsia partialis continua*	Consciousness usually preserved Focal motor clonic seizures without Jacksonian march; lasting for at least 60 mins and often for hours, days, weeks, or even longer; often treatment resistant	Few or no paroxysmal abnormality Irregular 0.5-3 Hz slowing in the frontocentral region with reduction of beta-activity

Table 1 continued.

			CLINICAL FEATURES	EEG PATTERN
NON-CONVULSIVE	GENERALISED	*Typical absence status*	Impaired consciousness; behavioural changes: disorientation, decreased spontaneity, slow speech, hallucinations; rhythmic blinking; slight myoclonic jerking; abrupt onset	2-3 Hz spike-wave discharges Interictal background activity normal
		Late-onset absence status	Impaired consciousness; behavioural changes: disorientation, decreased spontaneity, slow speech, hallucinations; rhythmic blinking; slight myoclonic jerking	Rarely 2-3 spike-wave discharges More frequently 0.5-4 Hz spike-wave discharges
	FOCAL	*Complex partial status epilepticus*	Impaired consciousness; 'epileptic twilight state' with confusion and strange behaviour; oral or manual automatism; gradual development of symptoms	Variable with focal and bilateral spike and spike-waves; surface EEG with good sensitivity
		Subtle status epilepticus	Loss of consciousness; no or subtle movements such as rhythmic twitching of the arms, legs, trunk or facial muscles, tonic eye deviation, or nystagmoid eye jerking	Generalised or lateralised spike or spike-wave discharges Flat periods
	COMATOSE	*Coma with generalised epileptiform discharges (coma-GED)*	Anoxic coma: possible myoclonias and other motor abnormalities disappearing with anaesthesia Impaired consciousness after intoxication, vascular infarcts, cardiopulmonary arrest, infections, space-occupying lesions, and metabolic disorders may present as various degrees of coma	Continuous or periodic generalised spikes and waves with flat periods in between Burst suppression pattern Bilateral triphasic waves with and without spikes EEG pattern tends to mirror the depth of coma
		Coma with lateralised epileptiform discharges (coma-LED)	Focal or lateralising neurologic signs resulting from focal brain lesions (in most cases acutely acquired) or diffuse abnormalities (rarely)	Continuous focal spiking PLEDs (periodic lateralised epileptiform discharges) Bi-PLEDs (bilateral PLEDs) Unilateral burst suppression Unilateral triphasic waves

Post-anoxic encephalopathy often leads to EEG alterations characterised by sharp generalised periodic, single, or grouped discharges, which appear within a flat or slow-activity background; myoclonus can arise from the first day, and is usually sensitive to stimuli. The point of administering an AED in these cases seems purely 'cosmetic' and has no evident benefit for the patient;[15] even so, diminishing myoclonus can simplify treatment for nurses and family. A recent article suggests that in some rare cases, low frequency and non-progressive epileptiform discharges can correspond to NCSE rather than to post-anoxic encephalopathy. In these events, propofol can 'unmask' the underlying state of epilepsy, revealing the absence of biological activity and, therefore, can be used as a 'diagnostic' drug second to BZD.[18]

Table 2: Management of status epilepticus.

Immediate measures (0-5 mins)	Non-invasive or invasive airway protection and oxygenation Vital signs monitoring (O_2 saturation, HR, BP) Fingerstick blood glucose Establish intravenous access Laboratory tests: complete blood count, electrolytes, liver enzymes, arterial blood gases, toxicology screen, serial troponins, AED blood levels Emergent initial AED therapy (if no IV access available, give midazolam IM, PO, or intranasally, or diazepam PR) Fluid resuscitation If serum glucose <60 mg/dl, administer 100 mg thiamine first and then 50% dextrose Call for EEG
Immediate measures (5-15 mins)	Neurological examination Urgent AED therapy for SE control Vasopressor support if needed Continuous EEG monitoring
Urgent measures (15-60 mins)	Urinary catheter Depending on clinical presentation: intracranial pressure monitoring and neurological diagnostic testing (MRI, CT, LP)
RSE measures (20-60 mins after 2nd AED)	RSE therapy if needed EEG continually running for titrating therapy and monitoring AED response

EEG: electroencephalographic; HR: heart rate; BP: blood pressure; AED: anti-epileptic drug; IV: intravenous; IM: intramuscular; PO: oral administration; PR: rectal administration; SE: status epilepticus; MRI: magnetic resonance imaging; CT: computed tomography; LP: lumbar puncture; RSE: refractory status epilepticus.

SE may occur in the setting of several internal or neurological diseases. In some forms of encephalopathy, of varying aetiology (i.e. metabolic, toxic, or immunologic), the clinical and EEG findings can be similar to those of NCSE, but treatment with BZD does not impact upon the patient's condition, which actually improves with treatment of the base disease. Some authors highlight, for example, the importance of considering anti-neutrophil cytoplasmic antibody (ANCA) dosage in patients with SE of unclear origin, and propose to promptly start adequate immunotherapy in patients with inflammatory changes at brain magnetic resonance imaging (MRI), with or without other systemic signs of ANCA-associated vasculitis.[19] Monoclonal antibody-based B cell depletion may represent a therapeutic alternative for antibody-mediated encephalopathy achieving a good outcome. Other authors have reported, therefore, a case of NCSE induced by acute hypothyroidism in a critically ill patient, and recommended studying the thyroid function in those patients presenting with unexplained SE accompanied with acute anasarca.[20]

NEURONAL AND CLINICAL CONSEQUENCES

A generalised convulsive state is a medical emergency burdened by high mortality, especially in the elderly, because repeated seizures swiftly induce metabolic and cardiocirculatory failure, hyperthermia, cerebral oedema, and potentially irreversible neuron damage. Excessive and prolonged muscular twitching leads to increased creatine kinase and, in the most severe cases, rhabdomyolysis, hyperkalaemia, hypocalcaemia, myoglobinuria, and potential renal failure; metabolic acidosis, caused by depletion of glycogen stores and anaerobic glycolysis, is also frequent. Many patients can develop respiratory acidosis by pulmonary aspiration, diminished respiratory drive, and efficacy of the skeletal-muscle pump. Lastly, a massive amount of circulating catecholamines can cause cardiac arrhythmias, cardiomyopathy (especially Takotsubo), and hyperglycaemia.

Many animal studies have shown how prolonged epileptic seizures, even non-convulsive, can lead to neuron damage. The increase in extracellular glutamate at excitotoxic levels,[21] associated with

an increased lactate/pyruvate ratio, can bring on cellular swelling, increased intracranial pressure, and cellular death, in addition to producing free radicals, inflammation, gliosis, atrophy, and synaptic reorganisation. A recent study also demonstrated that brief seizures result in structural and functional brain alterations, but confirmed that those caused by prolonged seizures are considerably more severe.[22] A number of anecdotal studies using MRI found cerebral acute oedema and chronic atrophy, as well as evidence of neuronal loss on magnetic resonance spectroscopy following NCSE.

Basic research and animal studies are essential to understanding the cellular and molecular mechanism of SE-induced brain pathology and to develop target-specific AEDs for these patients. Duration and frequency of epileptic activity correlates with the extent of neuron damage, so that optimal targeted therapy should provide fast and effective control of the SE and treatment of the accompanying symptoms during the first 6-20 mins.

The duration of SE prior to the initiation of treatment influences its effect, regardless of the type of drug used. The randomised clinical trial on prehospital treatment of SE revealed that the placebo group suffered from unfavourable consequences of prolonged seizure such as acquired neurological deficits or death, confirming that the emergency team have a high chance of administering BZD during the early SE time when the probability of seizure termination with drugs is the highest and neuronal damage is not yet established.[23]

According to many authors,[24] we suggest a time-dependent scale:

- 5-20/30 mins: Early SE (0-5 min interval within which most seizures spontaneously stop; 5-15 min optimum interval for initiation of emergent treatment)
- 20/30-60 mins: Established SE (urgent treatment)
- >60 mins: Refractory SE (refractory treatment)

It is important to underscore that an accumulation of complications is usually encountered in coma patients with SE and it is truly difficult to individuate complications due to persistent seizure activity from those originating from the causative medical disorder or from pharmacological treatments. The cause of SE remains the most important prognostic factor, with alcohol and AED withdrawal having the best outcomes; structural brain injuries such as anoxia-ischaemia, vascular lesions, and brain tumours have the worst prognosis. A prognostic score, the SE severity score (STESS), has been developed to predict survival before initiation of SE treatment (range: 0-6).[25] This score relies on the assessment of age, previous history of seizures, seizure type (simple partial, complex partial, absence of, or myoclonic seizure, generalised tonic–clonic seizure, or NCSE in a coma), and the extent of consciousness impairment.

TREATMENT

The main goal is to stop epileptic activity from both a clinical and an EEG standpoint. The initial treatment strategy involves the management of airways, ventilation and haemodynamics, initial pharmacological treatment of the seizure, analyses to investigate the trigger of the SE, and treatment of the identified cause (Table 2). The guidelines published in 2012 by the Neurocritical Care Society divide the therapeutic strategy into three phases: emergent initial AED therapy, urgent control AED therapy (in association with anti-epileptic maintenance therapy, even if the SE is immediately controlled), and potentially refractory therapy (reserved for SE failing to respond to the first two AEDs administered). The most recent guidelines from the USA and Europe on initial therapy (Emergent Initial Therapy) advocate the use of BZD, preferably IV, although intramuscular and rectal administration is possible. LZP is preferred for IV therapy, whereas midazolam is indicated for intramuscular administration (although it can also be administered intravenously, nasally, or orally) and diazepam for rectal administration (also available in IV form). Clonazepam is not frequently used. Controlled studies defining the exact dosages of SE treatment are not available. Although all reported dosages are derived from observational studies, they are widely used, as the dosage is based on numerous well-controlled clinical studies (Table 3).

The second step is to initiate control therapy of the SE (urgent control therapy), unless the trigger is resolved and if the seizure appears to have ended. For patients whose SE has been resolved, the aim is to reach therapeutic levels of an AED and to continue the maintenance therapy; for ongoing SE, the aim is to stop the seizures. The agents generally used are phenytoin/IV fosphenytoin,

valproic acid, phenobarbital, levetiracetam, or continuous infusion of midazolam; IV fosphenytoin is generally the drug of choice, except in patients with pre-existing epilepsy in whom use of sodium valproate is favoured. Serum levels of phenytoin and fosphenytoin should be carefully monitored due to their nonlinear and saturable kinetics, resulting in highly variable concentrations.

Table 3: Status epilepticus (SE) and refractory status epilepticus (RSE) pharmacological treatment.

DRUG	MECHANISMS OF ACTION	INITIAL DOSE & ALTERNATIVE DOSING	DOSAGES	RSE INITIAL DOSE	RSE CI TITRATED WITH EEG
DIAZEPAM Emergency treatment	Enhancement of GABA-ergic transmission (bond with $GABA_A$ receptor and increase of Cl^- conductance due to increase of channel opening frequency)	0.15 mg/kg IV up to 10 mg may repeat in 5' (*NCS-EFNS*) 0.1 mg/kg IV, may repeat in 10' (*LICE*)	Up to 5 mg/min		
FOSPHENYTOIN Emergency treatment Urgent treatment Refractory treatment	Extension of voltage-dependent Na+ channel refractory period	20 mg PE/kg IV, may give additional 5 mg/kg (*NCS*)	Up to 150 mg PE/min; may give an additional dose 10 mins after loading infusion (*NCS*)		
ISOFLURANE Refractory treatment	Inhibition of NMDA receptor Enhancement of GABA-ergic transmission (bond with $GABA_A$ receptor and increase of Cl^- conductance)			0.8-2 vol % (*LICE*)	Titrate with EEG
LIDOCAINE Refractory treatment	Inhibition of voltage-dependent Na+ channel			1.5-2 mg/kg bolus, may repeat only once (*LICE* - alternative treatment)	Up to 50 mg/min
LORAZEPAM Emergency treatment	Enhancement of GABA-ergic transission (bond with $GABA_A$ receptor and increase of Cl^- conductance due to increase of channel opening frequency)	0.1 mg/kg IV up to 4 mg may repeat in 5-10' (*NCS-EFNS*) 0.05-0.1 mg/kg IV, may repeat in 10' (*LICE*)	Up to 2 mg/min (IVP)		
MIDAZOLAM Emergency treatment Urgent treatment Refractory treatment	Enhancement of GABA-ergic transmission (bond with $GABA_A$ receptor and increase of Cl^- conductance due to increase of channel opening frequency)	0.2 mg/kg IM up to 10 mg (*NCS*) 5-10 mg IM or 5-10 mg rectal may repeat only once; 0.1-0.3 mg/kg IV bolus, up to 4 mg/min; 10 mg PO (the only formulation officially recommended in Italy for epilepsy treatment) (*LICE*)		RSE: 0.2 mg/kg at 2 mg/min (*NCS*) RSE/subtle SE: 0.2 mg/kg bolus (*EFNS*)	RSE: 0.05-2 mg/kg/h CI Breakthrough SE: 0.2 mg/kg bolus, increase CI rate by 0.05-0.1 mg/kg/h every 3-4 h (*NCS*) RSE/subtle SE: 0.05-0.4 mg/kg/h CI (*EFNS*) RSE: 0.05-0.4 mg/kg/h (*LICE*)

Table 3 continued.

DRUG	MECHANISMS OF ACTION	INITIAL DOSE & ALTERNATIVE DOSING	DOSAGES	RSE INITIAL DOSE	RSE CI TITRATED WITH EEG
PENTOBARBITAL Refractory treatment	Enhancement of GABA-ergic transmission (bond with GABAA receptor and increase of Cl^- conductance due to increase of channel opening time)			RSE: 5-15 mg/kg IV, may give additional 5-10 mg/kg; infusion rate ≤50 mg/min (*NCS*)	RSE: 0.5-5 mg/kg/h CI Breakthrough SE: 5 mg/kg bolus, increase CI rate by 0.5-1 mg/kg/h every 12 h (*NCS*)
PHENOBARBITAL Emergency treatment Urgent treatment Refractory treatment	Enhancement of GABA-ergic transmission (bond with GABAA receptor and increase of Cl^- conductance due to increase of channel opening time)	20 mg/kg IV, may give an additonal 5-10 mg/kg (*NCS*) 10-20 mg/kg (*LICE* - alternative treatment)	50-100 mg/min IV, may give additonal dose 10 mins after loading infusion (*NCS*) 50-75 mg/min IV (*LICE* - alternative treatment)	RCPSE: 20 mg/kg IV (*EFNS*)	RCPSE: 50 mg/min IV (*EFNS*)
PHENYTOIN Emergency treatment Urgent treatment Refractory treatment	Extension of voltage-dependent Na+ channel refractory period	20 mg/kg IV, may give an additonal 5-10 mg/kg (*NCS*) 18 mg/kg IV (*EFNS*) In patients already treated with benzodiazepines 15-18 mg/kg IV, may give an additonal 5 mg/kg (*LICE*)	Up to 50 mg/min IV; may give additonal dose 10 mins after loading infusion (*NCS*)		
PROPOFOL Refractory treatment	Enhancement of GABA-ergic transmission (bond with GABAA receptor and increase of Cl^- conductance due to increase of channel opening time) Block of voltage-dependent Na+ channel			RSE: start at 20 µg/kg/min, with 1-2 mg/kg loading dose (*NCS*) RSE/subtle SE: start with 2-3 mg/kg bolus, then 1-2 mg/kg boluses until seizure control (*EFNS*) RSE: 2-5 mg/kg bolus (*LICE*)	RSE: 30-200 µg/kg/min Breakthrough SE: Increase CI rate by 5-10 µg/kg/min every 5 mins or 1 mg/kg bolus plus CI titration (*NCS*) RSE/subtle SE: 4-10 mg/kg/h CI (*EFNS*) RSE: 5 mg/kg/h CI for at least an hour (*LICE*)
THIOPENTAL Refractory treatment	Enhancement of GABA-ergic transmission (bond with GABAA receptor and increase of Cl^- conductance)			RSE: 2-7 mg/kg, ≤50 mg/min (*NCS*) RSE/subtle SE: 3-5 mg/kg bolus, 1-2 mg/kg every 2-3 mins until control (*EFNS*) RSE: 5-7 mg/kg/20' then 50 mg every 2-3 mins for "suppression burst" (*LICE*)	0.5-5 mg/kg/h CI Breakthrough SE: 1-2 mg/kg bolus, increase CI rate by 0.5-1 mg/kg/h every 12 h (*NCS*) 3.7 mg/kg/h CI (*EFNS*) 3-5 mg/kg/h CI (*LICE*)

Table 3 continued.

DRUG	MECHANISMS OF ACTION	INITIAL DOSE & ALTERNATIVE DOSING	DOSAGES	RSE INITIAL DOSE	RSE CI TITRATED WITH EEG
TOPIRAMATE Refractory treatment	Enhancement of GABA-ergic transmission Inhibition of excitatory transmission (action on kainate and AMPA receptor) Inhibition of carbonic anhydrase			200-400 mg NG/PO (*NCS*)	300-1,600 mg/day orally (divided 2-4 times daily) (*NCS*)
SODIUM VALPROATE Emergency treatment Urgent treatment Refractory treatment	Increase of PIP3 levels in the brain Inhibition of voltage-dependent Na+ channel Inhibition of voltage-dependent Ca^{2+} channel Alteration of GABA turnover resulting in inhibition of GABA catabolism	20-40 mg/kg IV, may give an additional 20 mg/kg (*NCS*) 15-30 mg/kg IV (*LICE* - alternative treatment)	3-6 mg/kg/min, may give additional dose 10 mins after loading infusion (*NCS*) 1-2 mg/kg/h CI (*LICE* - alternative treatment)	RCPSE: 25-45 mg/kg IV (*EFNS*)	RCPSE: Up to 6 mg/kg/min (*EFNS*)

Emergency treatment: initial therapy; urgent treatment: SE control therapy (if SE has been controlled with the emergency treatment, the aim is to achieve therapeutic levels of anticonvulsants and establish a maintenance therapy — if SE has not been controlled, the aim is to stop the crisis); refractory treatment: drug treatment indicated for SE unresponsive within 60 mins of emergency and urgent treatment.
$GABA_A$ receptor: γ-aminobutyric acid receptor; NCS: Neurocritical Care Society; EFNS: European Federation of Neurological Societies; LICE: Lega Italiana contro l'Epilessia (Italian League Against Epilepsy); PE: phenytoin equivalent; IV: intravenous; IM: intramuscular; PO: oral administration; CI: continuous infusion; subtle SE: subtle status epilepticus; NMDA receptor: N-methyl-D-aspartate receptor; RSE: refractory status epilepticus; RCPSE: refractory continuous partial status epilepticus; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NG: nasogastric administration; PIP3: phosphatidylinositol 3,4,5-trisphosphate; CI: chloride; Ca^{2+}channel: calcium channel; IVP: intravenous pyelogram.

Refractory Status Epilepticus

Control of the SE should be achieved within 60 mins using the two treatments mentioned above. If unsuccessful the SE is considered RSE. In this case, it is possible to repeat a bolus of the drug used in the second step, or to start an additional agent,[2] since no data suggest that watchful waiting is safer than initiating more aggressive therapy immediately. If the intermittent bolus therapy fails, it is advisable to use continuous infusion; however, it is recommended to first consider boluses of a drug not previously used (fosphenytoin/phenytoin, levetiracetam, sodium valproate). Bolus doses of the agent used for the continuous infusion should also be started and repeated, in addition to the infusion. If the drug chosen is ineffective it is advisable to use another one from the list (Table 3).

The intensity of the treatment is dictated by the EEG findings, with the aim of obtaining burst suppression. Conversely, definite indications are lacking on what duration of treatment is needed to maintain. As a rule, after 24-48 h the continuous infusion drug dose is gradually weaned; if at this point the patient again shows signs of relapse, the prior or a higher dosage is reinstated for a greater period of time, with or without an additional agent. No data are available indicating how much time should pass before a treatment

is considered useless; some patients need to be treated for weeks or months before recovering. Furthermore, studies defining a standard guideline on discontinuing the continuous infusion and starting the intermittent maintenance treatment with an AED have yet to be conducted.

Alternative Therapy for Refractory Status Epilepticus

The onset of RSE is mediated in part by γ-aminobutyric acid ($GABA_A$) receptor internalisation in a condition of sustained neuroexcitation with consequent loss of response to GABA-ergic drugs.[26] There is also evidence of increased α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-D-aspartate (NMDA) receptor expression on the synaptic membrane, which determines increased sensitivity to excitatory neurotransmitters. Thus, research is aiming to develop drugs acting as excitatory antagonists/inhibitory agonists that may block $GABA_A$ receptor internalisation or increased excitatory receptor expression. Ketamine, by way of its NMDA channel blocking action, has been used on occasion with less than stellar results and with significant side-effects such as psychosis and severe neuron damage.[27]

Recently, in a systematic review of inhaled anaesthetics used to treat RSE, Zeiler et al.[28] individuated isoflurane as an agent that can be used with fair efficacy (Oxford level 4, Grade D) after the failure of other therapies. Hypothermia is now routinely used in several centres around the world for patients with RSE despite an extremely small evidence base, as well as magnesium sulphate infusion.[29] IV pyridoxine is an effective treatment in both rare patients with an inborn error of metabolism of pyridoxine and SE patients with no clear deficit in pyridoxine metabolism.[29] Finally, immunotherapy with steroids, IV immunoglobulins, plasma exchange, or immunosuppressive drugs could constitute an interesting treatment choice in cases of SE associated with immunological disorders, as mentioned above.[29]

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SIALORRHOEA: HOW TO MANAGE A FREQUENT COMPLICATION OF MOTOR NEURON DISEASE

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ABSTRACT

Sialorrhoea, the unintentional loss of saliva through the mouth, is the frequent complication of neurological disorders affecting strength or coordination of oropharyngeal muscles, such as motor neuron disease/amyotrophic lateral sclerosis (MND/ALS) or Parkinson's disease. Sialorrhoea might affect up to 42% of ALS patients, with almost half of them having poorly managed symptoms. Sialorrhoea can impair patients' social life, while dermatological complications, such as skin rashes, may arise due to constant exposure to moisture. Moreover, the excess mouth-retained saliva in ALS patients may lead to serious complications, such as choking, which causes anxiety, and aspiration with the consequent pneumonia. The inclusion of a sialorrhoea-related item in the ALS functional rating scale testifies both the incidence and importance of sialorrhoea during the ALS clinical course. Because of the progressive nature of ALS, presence and severity of sialorrhoea should be assessed at every visit and, when present, active treatment pursued. Available treatments include behavioural therapy, i.e. techniques to enhance periodic swallowing of saliva, systemic or local anticholinergic medications, botulinum toxin injection, electron beam irradiation, and surgical techniques. This review paper briefly describes the available options with related side-effects and current guideline recommendations for managing sialorrhoea in ALS patients.

Keywords: Amyotrophic lateral sclerosis, motor neuron disease, sialorrhoea, drooling.

BACKGROUND

The term 'motor neuron diseases' (MNDs) describes a group of neurodegenerative disorders affecting motor neurons, among which amyotrophic lateral sclerosis (ALS) is the most frequent and best-characterised subset. ALS invariably leads to death due to respiratory insufficiency within, on average, 3-5 years from onset.[1] The disorder affects both upper and lower motor neurons: lower motor neuron degeneration causes muscle weakness, fasciculation, and progressive muscle atrophy; while the loss of upper motor neurons may cause spasticity and weakness. Sialorrhoea, or drooling, defined as the unintentional loss of saliva through the mouth, can often present in these patients, presumably due to lack of strength and coordination of oropharyngeal muscles. Sialorrhoea is a frequent and early feature of bulbar ALS presentations, but complicates later stages in spinal onset patients as well. Saliva is the mixed product of three pairs of major salivary glands: the parotid, submandibular, and sublingual. They account for 95% of saliva production; the remaining saliva is secreted by minor glands. Adult individuals produce approximately 1.5 litres of saliva daily, the secretion of which is modulated by the autonomic nervous system.[2]

Sialorrhoea should not be confused with hypersalivation, which is the increase of the amount of secreted saliva. Hypersalivation may sometimes cause sialorrhoea; however, an individual with preserved saliva clearance (i.e., the ability to swallow) can easily eliminate the excess. The main cause of sialorrhoea in ALS is the impairment

of saliva clearance due to degeneration of both upper and/or lower motor neurons controlling oropharyngeal muscles. Spasticity or weakness of such muscles causes dysphagia so that secretions build up in the mouth. Finally, weakness of buccal muscles impairs the ability to retain saliva, causing it to spill. Hypersalivation does not appear to be a prominent feature of ALS, while it may characterise other motor system disorders like Parkinson's disease (PD). For this reason, results of sialorrhoea trials in PD may not be applicable to ALS. These patients, rather than complaining of watery serous secretions, more often complain of the accumulation of thick mucous secretions. Indeed, salivary glands produce both. Serous secretions are controlled by parasympathetic, cholinergic, and sympathetic alpha receptors, while thick secretions are produced upon the activation of sympathetic beta-receptors.[2]

Sialorrhoea impairs quality of life by several means. It can impair mastication and speech, and it can embarrass patients engaged in social activities, prompting their isolation; often this latter issue is reported as the most disturbing complaint by patients. Constant exposure of the skin to moisture can cause skin lesions. Furthermore, pooled saliva can contribute to the sensation of choking and anxiety, while its aspiration may cause a life-threatening pneumonia. Such respiratory complications, however, are not the result of sialorrhoea; the loss of saliva through the mouth is, in fact, an alternative pathway of saliva clearance, which prevents aspiration. Instead, sialorrhoea and aspiration pneumonia share a common cause: dysphagia. For this reason, treatments aimed at reducing salivation could prevent both sialorrhoea and respiratory complications. Finally, tolerance of non-invasive ventilation, a key component of ALS care, also depends on successful control of sialorrhoea.[3]

Assessment of Sialorrhoea

In a multicentre study[4] enrolling 143 ALS patients, 41% had saliva-related problems, and only 25% of those treated for sialorrhoea deemed their treatment effective. Therefore, any physician involved in ALS care should readily address sialorrhoea. Patients will often complain about the symptom because of its disturbing nature. As already stressed, sialorrhoea depends on the symptomatic involvement of bulbar-innervated muscles; this could be the result of the disease extending to bulbar segments or of an aggravation of the already present impairment. Dysphagia is frequently associated with this. Usually, overt sialorrhoea is preceded by loss of saliva during sleep; however, despite the potential benefit of early intervention (i.e., the prevention of aspiration pneumonia), such a strategy has never been investigated. Therefore, at this stage, assessment followed by treatment should be reserved for patients complaining about sialorrhoea or excess saliva.

The first step of sialorrhoea assessment should be the review of drug therapy for medications known to cause hypersalivation, such as cholinergic drugs (e.g., neostigmine, clozapine). Second, a quantification of sialorrhoea may help the physician to estimate symptom severity. Even if several objective measures of sialorrhoea are available (e.g., number of handkerchiefs used, weight gain of cotton rolls placed in the mouth for a set amount of time), clinical choices should be oriented by patient-reported distress. The salivary item of the ALS functionality rating scale is an already-known and easy-to-apply five-point scale for sialorrhoea quantification and could be sufficient for symptom staging.

Other ALS-dedicated tools measuring sialorrhoea severity[5] and patient-perceived impact[4] are the Oral Secretion Scale, the Sialorrhoea Scoring Scale, and the Clinical Saliva Scale for MND (CSS-MND). In particular, CSS-MND is a patient-reported measure for sialorrhoea impact, strongly correlating with a Likert scale measure of sialorrhoea severity. This scale may be a useful tool for research purposes because the impact of sialorrhoea over a patient's life appears to be a better outcome than its severity, as the two do not correlate.[6] Previous studies report the use of a 6-item tool for assessing the quality of daily living,[7] or of a 10-item dedicated tool, the drooling impact score.[8] General quality of life dedicated scales, such as the SF-36[9] have never been applied selectively to the assessment of sialorrhoea impact in ALS.

MANAGEMENT OF SIALORRHOEA

Non-invasive intervention modalities are often designated as the first-line therapy for sialorrhoea. In fact, treatments aimed at saliva flow reduction (i.e., drug therapy) may improve sialorrhoea without intervening over its cause. Rehabilitative and prosthetic treatments, on the other hand, may reduce sialorrhoea by re-establishing the physiological mechanism of saliva retention and clearance. Because of this, when postural deficits

(i.e., falling head/chin) are the putative cause of sialorrhoea, their correction should precede other treatments. In such cases, for example, a chin support could reduce the symptom. Analogously, sialorrhoea was successfully controlled by the application of a lip-sealing intraoral prosthesis in a single ALS patient.[10] Obviously, the use of a customised device limits the reproducibility of such a technique to the general patient population. Other rehabilitative interventions include oral motor therapy, behavioural modification via biofeedback, and orofacial regulation therapy;[11] these techniques, however, were developed for paediatric patients with neurological deficits and their applicability to ALS remains open to discussion. Finally, patients affected by sialorrhoea may benefit from aspiration devices, which can be operated by the caregiver or by the patient themselves. When no postural deficit causes sialorrhoea or when its correction is not sufficient to control the symptom, drug therapy should be the next step.

PHARMACOLOGICAL TREATMENTS

First-Line Drug Therapy

Saliva production can be decreased by the blockade of parasympathetic stimulation to salivary glands. This is achieved by anticholinergic medications, whose efficacy in clinical practice is well documented. However, to date, no study has compared the efficacy of different anticholinergic medications for the treatment of sialorrhoea in ALS. Reportedly, the most commonly used drugs in this category are amitriptyline tablets/oral solution, and scopolamine patches.[12] Sometimes even a few milligrams of amitriptyline (e.g., 4-6 mg three times daily [t.i.d.]) or scopolamine (e.g., 1.5 mg patch every 3 days) might be sufficient to control sialorrhoea, albeit the doses can be slowly increased, carefully monitoring for side-effects. Butylscopolamine, i.e., scopolamine butylbromide, is another effective option and is also available for subcutaneous administration. Glycopyrrolate is a muscarinic antagonist that is widely used in anaesthesia and palliative care and has been identified as a potentially efficacious treatment for sialorrhoea.[13] This drug seems to produce fewer side-effects than alternative anticholinergic agents, due in part to poorer penetration across the blood—brain barrier[14] and a possible higher selectivity for muscarinic receptors in gastrointestinal rather than cardiac tissue.[15] A randomised double-blind crossover trial demonstrated that oral glycopyrrolate is an effective treatment for severe sialorrhoea in PD.[16] Although, as stated above, the results of PD trials cannot be generalised at the moment, a case of treatment-resistant bulbar ALS is described where subcutaneous glycopyrrolate was effective without significant side-effects.[17] In our anecdotal experience, an oral dose of 0.5 mg twice daily (b.i.d.) or t.i.d. is usually sufficient. This suggestion, however, has still to be tested in randomised controlled trials before concluding on its validity.

Unsurprisingly, the unselective blockade of muscarinic receptors frequently causes side-effects alongside therapeutic ones, albeit the use of locally administered drugs tends to confine them to the area of administration. For instance, atropine drops can be administered sublingually: a pilot study in patients with PD demonstrated a statistically significant decline in saliva production.[18] For ALS patients 0.25–0.75 mg t.i.d. is empirically recommended.[19] When a systemic drug is chosen, those that cannot pass the blood—brain barrier should be preferred in order to minimise the most distressing symptom. Finally, saliva is an important factor for the mineralisation and protection of teeth.[2] For this reason, a reduction in its production may have deleterious effects on dental health. Therefore, patients should be instructed to increase oral hygiene. Table 1 reports the initial doses of the most effective pharmacological options for managing sialorrhoea in ALS patients.

Patients under anticholinergic blockade may sometimes complain of increased thickness of secretion, often localised in the back of the mouth, so that patients may not clear it by coughing. This may be caused by the unopposed stimulation of sympathetic beta-receptors. This principle is supported by the study of Newall et al.,[20] in which patients reported subjective benefit over saliva thickness through the use of beta-blocker therapy. Other medications for this purpose include: guaifenesin, nebulised saline, or acetylcysteine.[21] When these secretions are not localised in the back of the mouth, aspiration devices may prove useful. Breath-stacking techniques and cough-assist machines,[22] which alternate positive and negative pressures to improve cough airflow[23] may also be useful.

Notably, at the highest tolerated doses, drugs not infrequently fail to control sialorrhoea in these patients, and both the American Academy of

Neurology (AAN) (2009) and the European Federation for Neurological Societies (EFNS) (2012) clinical practice parameters for ALS management[24,25] suggest the options of botulinum toxin (BTx) injection or parotid gland irradiation. The most frequently reported side-effect is drowsiness, followed by constipation (see Table 1); in our experience they occur in ALS patients with the same modalities observed in patients treated with anticholinergic medications for other conditions, such as amitriptyline for headache. Other side-effects might arise in susceptible patients (e.g., arrhythmia in patients affected by concomitant heart disease).

BOTULINUM TOXIN INJECTION

Much interest has grown around BTx injection, as it appears to be an easy-to-replicate, highly effective, reversible, safe, and cost-effective technique. This toxin is produced by *Clostridium botulinum* and other bacteria of the *Clostridium* species. *Clostridia* are Gram-positive, rod-shaped, spore-forming, obligate anaerobic bacteria. Seven distinct types of BTx serotypes have been identified, named A-G. However, only Type A and B are commercially available, marketed as Botox®, Dysport® and Xeomin® (BTxA), and Neurobloc/Myobloc® (BTxB). Both of these toxins act by cleaving the soluble N-ethylmaleimide sensitive factor attachment protein receptor (SNARE) proteins, responsible for acetylcholine release. An exhaustive insight into BTx molecular mechanism of action is available in a review by Kammerer and Benoit.[26]

BTx injection has been the main subject of several clinical trials, among which are two randomised double-blind trials.[27,28] BTxA was the most frequently used toxin in non-randomised trials; however, BTxB efficacy has a higher level of recommendation in clinical practice parameters because evidence comes from an AAN Class I study.[27] Also, a more recent trial[28] compared the efficacy of the two neurotoxins and found BTxB to have shorter latency and equal duration of effects in comparison with BTxA without an increase in adverse effects. The study, however, is biased by the inclusion of PD and MND patients together. Moreover, BTxB comes at lower pricing. Transcutaneous injection of BTx is preferred to the transductal approach because of the unacceptable side-effects of the latter.[29] Notably, regarding the BTx injection targets, the submandibular glands contribute 70% of the unstimulated saliva secretion (i.e., the secretion not depending on the saliva reflex),[2] while the stimulated secretion depends mainly on the parotid glands. Therefore, for control of saliva production under both stimulated and unstimulated conditions, both pairs of salivary glands should be targeted.

Table 1: Drugs for sialorrhoea treatment.

Drug	Route	Suggested initial dose	Notable side-effects
Amitriptyline	Tablets, oral solution	4 mg t.i.d.	Anticholinergic effects*, REM sleep abnormalities, seizures, orthostatic hypotension, nausea, vomiting, increased appetite, mental status changes. Withdrawal symptoms are possible, careful de-escalation is advised.
Scopolamine Butylscopolamine	Patches Subcutaneous	1.5 mg patch every 3 days	Anticholinergic effects*, rash, dryness of the skin, erythema and dermatitis (at the application site). Unilateral eye dilatation/anisocoria may result from eye contamination (hand wash is suggested after drug application). Rebound cholinesterase activity may develop after drug discontinuation.
Glycopyrrolate	Tablets Subcutaneous	0.5 mg b.i.d.	Anticholinergic effects*, headache, mental status changes.
Atropine	Sublingual drops	0.25 mg t.i.d.	Anticholinergic effects*, hypotension, hallucinosis, seizures, delirium.

*Anticholinergic effects are particularly disturbing when drugs are received systemically and include: drowsiness, mydriasis and cycloplegia (resulting in blurred vision), tachycardia, arrhythmias, flushing, constipation, and urine retention.
b.i.d.: twice daily; t.i.d.: three times daily; REM: rapid eye movement.

The main injection patterns found throughout studies were four-gland injection (i.e., bilateral parotid and submandibular glands) and bilateral parotid injection alone. There are no studies, however, comparing injection patterns. Glands can be identified either by palpation or by ultrasound imaging. BTx injection under continuous guidance with a 7.5 MHz superficial probe has been shown to reduce the amount of injected toxin; this could reduce side-effects caused by the diffusion of the toxin to oropharyngeal muscles.[30] The most consistently used dose of BTxB is 2,500 U diluted in 1 ml of saline,[7,28,31] of which 1,000 U (in 0.4 ml of saline) are injected in each parotid gland at two different sites, and 250 U (in 0.1 ml of saline) in each submandibular gland in one site. Alternatively, the injection of 500 U in each parotid and 750 U in each submandibular gland, with two injection sites each, is reported.[27] BTxA equivalent dose depends on the brand; Guidubaldi et al.[28] described an equivalent dose of Dysport® being 250 U diluted in 1 ml of saline with 100 U injected in two sites in each parotid gland, and 25 U in one site in each submandibular gland. A review of the most commonly used doses is available in literature.[32]

A suggested approach is to begin treatment at low doses, which can be cautiously increased if the patient does not show side-effects.[33] Benefits arise as early as the first week after injection, peak for 1 or 2 months, and last up to 3 months.[28] At 4 weeks, 90% of patients treated with BTxB report an improvement of symptoms against the 40% of those treated with placebo.[27] In our experience, the rate of response may be variable. The main side-effects of the procedure are local, such as pain at needle injection sites and swelling. Some patients will complain about dry mouth, which can be a distressing symptom especially during sleep; in this case the interruption of other anticholinergic medications can partially release parasympathetic blockade and improve the symptom. Alternative short-term treatments are hydration during day time or environmental humidifier for night time mouth dryness. Otherwise, a BTx dose reduction in the following treatments is advised.

Increased saliva thickness is possible, and has already been addressed above. More disturbing side-effects include a worsening of dysphagia and problems in chewing. An author reported acute deterioration of bulbar function after BTxA treatment.[33] This is probably caused by the diffusion of BTx outside salivary gland boundaries, and the effects upon oral and pharyngeal muscles; evidence also shows that the injection of more diluted solution may facilitate toxin diffusion.[34] The exact advantage of repeating doses of BTx has never been consistently investigated as well as the most advantageous time interval among different doses. Anticholinergic drug treatment could be discontinued upon reduction of sialorrhoea, albeit a pragmatic approach based on a gradual dose reduction should probably be recommended at this stage, aiming at defining the minimum optimal dose controlling each patient's symptoms.

NON-PHARMACOLOGICAL TREATMENTS

Photocoagulation and Radiation Therapy

Gland and salivary duct photocoagulation is an innovative, minimally invasive technique that has been used to reduce sialorrhoea in children affected by cerebral palsy.[35] It consists of gland and related duct coagulation though the use of laser light, via a catheter introduced through the parotid duct. Reported complications were haematoma, infection, and cystic formation. Facial swelling is possible but transient. This technique may be preferred to surgical procedures; however, it has not yet been tested in ALS.

Salivary gland irradiation is a non-invasive alternative to BTx injection for medical refractory sialorrhoea, endorsed by both AAN and EFNS clinical practice guidelines. It presents the theoretical advantage of reduced side-effects. Furthermore, it may be used as a third-line approach for patients not tolerating BTx injection or not achieving an adequate control of secretion. Response duration lasts for 4-9 months[36] so that patients tolerating the first treatment may need a re-irradiation. Another drawback is the reproducibility of the technique, being limited to centres with adequate infrastructure. Borg and Hirst[37] report that a reduction of sialorrhoea can be obtained with five 4 Gy fractions (20 Gy total dose) of electron beam irradiation both to the parotid and submandibular glands. Care has to be taken to spare the upper part of the parotid from the radiation field, in order to avoid the increase of secretion thickness. The low-dose radiation should also prevent temporomandibular joint fibrosis. This radiation dose has also been tested in ALS patients by Guy and colleagues.[38] In this retrospective case report, no patient treated with electron beam irradiation reported side-effects; on the contrary, those irradiated with photons

reported immediate and delayed side-effects (mucositis, oral pain, oedema, dry mouth). Therefore, we suggest using electron rather than photon beam irradiation. Other reported schemes include single parotid gland radiation[39] or use of 7.5-8 Gy single fraction.[40,41] A trial directly comparing BTx injection and radiation therapy has never been performed.

SURGERY

Invasive interventions for the management of sialorrhoea are neurectomy and salivary gland/duct procedures. Use of surgery in the care of ALS is discouraged by the EFNS clinical practice guidelines, while no recommendation is given by the AAN. They present the theoretical advantage of withstanding results. Furthermore, they may control sialorrhoea that is inadequately controlled by previous treatments or in patients not tolerating BTx. At present, the application of surgical techniques for sialorrhoea has not been investigated in ALS. Neurectomy consists of the destruction of the chorda tympani or the tympanic plexus. The destruction of nerve bundles carrying the parasympathetic innervation reduces saliva secretion by the submandibular and sublingual glands.

Bilateral neurectomy is believed to carry disadvantages (e.g., hearing loss) that outweigh the benefits, and appears to control sialorrhoea poorly when used alone. The chorda tympani also carries taste information for the anterior two-thirds of the tongue; an ethical dilemma arises regarding the reduction of a sense in patients who already have a reduced quality of life.[42] Surgery of the salivary glands and duct has reliably been applied to sialorrhoea, mainly in the field of paediatric surgery, due to their long-lasting effects and low side-effects. Bilateral ligation of the parotid gland duct with the combined removal of the submandibular glands appears to be a simple and effective procedure. Other techniques have also been applied.[11] Explorative studies regarding this topic are advised before clinical implementation.

CONCLUSION

Sialorrhoea assessment and treatment represent common issues of palliative care in ALS patients. Besides improvement in quality of life, sialorrhoea management might reduce the risk of aspiration-related complications, potentially resulting in extremely relevant benefits for these patients. Although anticholinergic drugs are most commonly used, they are often insufficient to control these symptoms, unless at the cost of severe side-effects. Therefore, physicians should be aware that different techniques are at hand for overcoming these limitations. These can be easily introduced in clinical practice; if required, patients should be referred to the closest specialised centre. Other studies are certainly required to provide more satisfactory options for managing this still troublesome problem. Currently, ongoing randomised clinical trials are predominantly focussed on exploring BTx options (ClinicalTrials.gov Identifier: NCT01565395, NCT01551940, NCT01994109), but other drugs might be considered as well, for example, those coming from similar fields, such as mirtazapine or guanfacine for clozapine-induced sialorrhoea.

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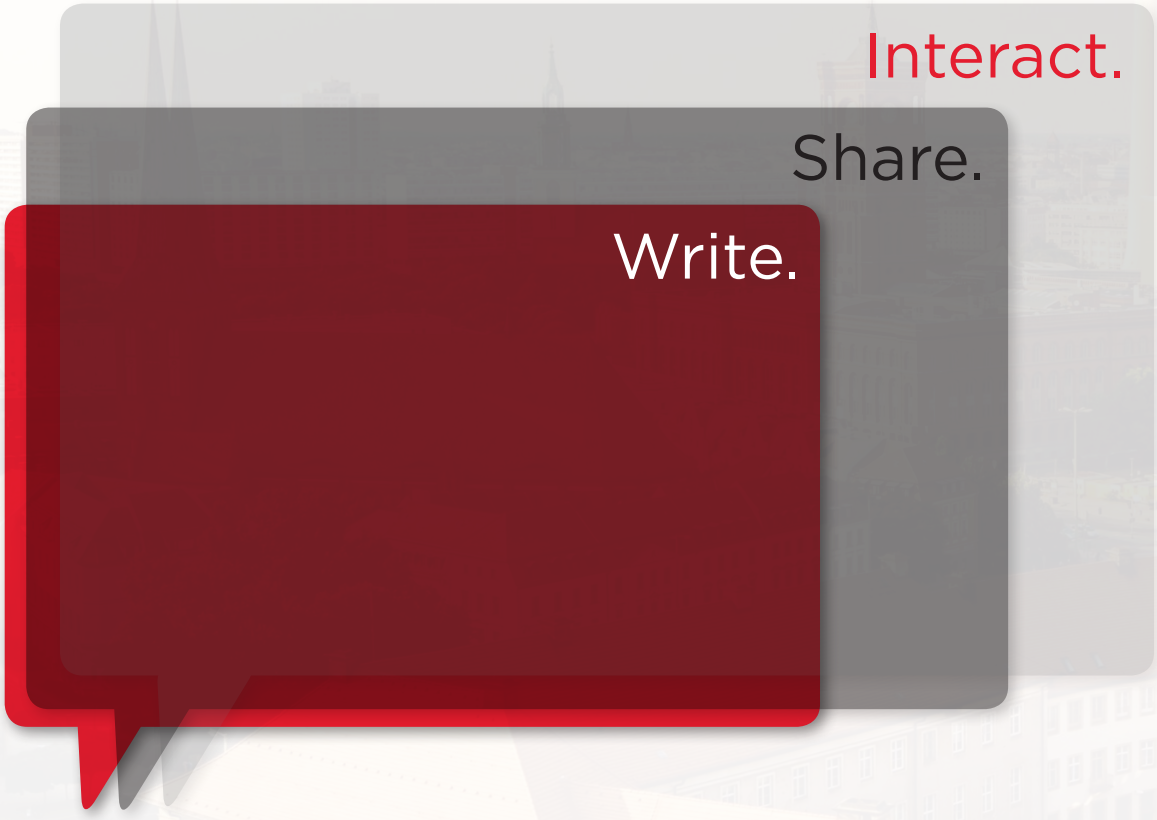

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