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INSIDE

Reviews of the

World Congress of Neurology 2013

Vienna, Austria

European Stroke Conference 2013

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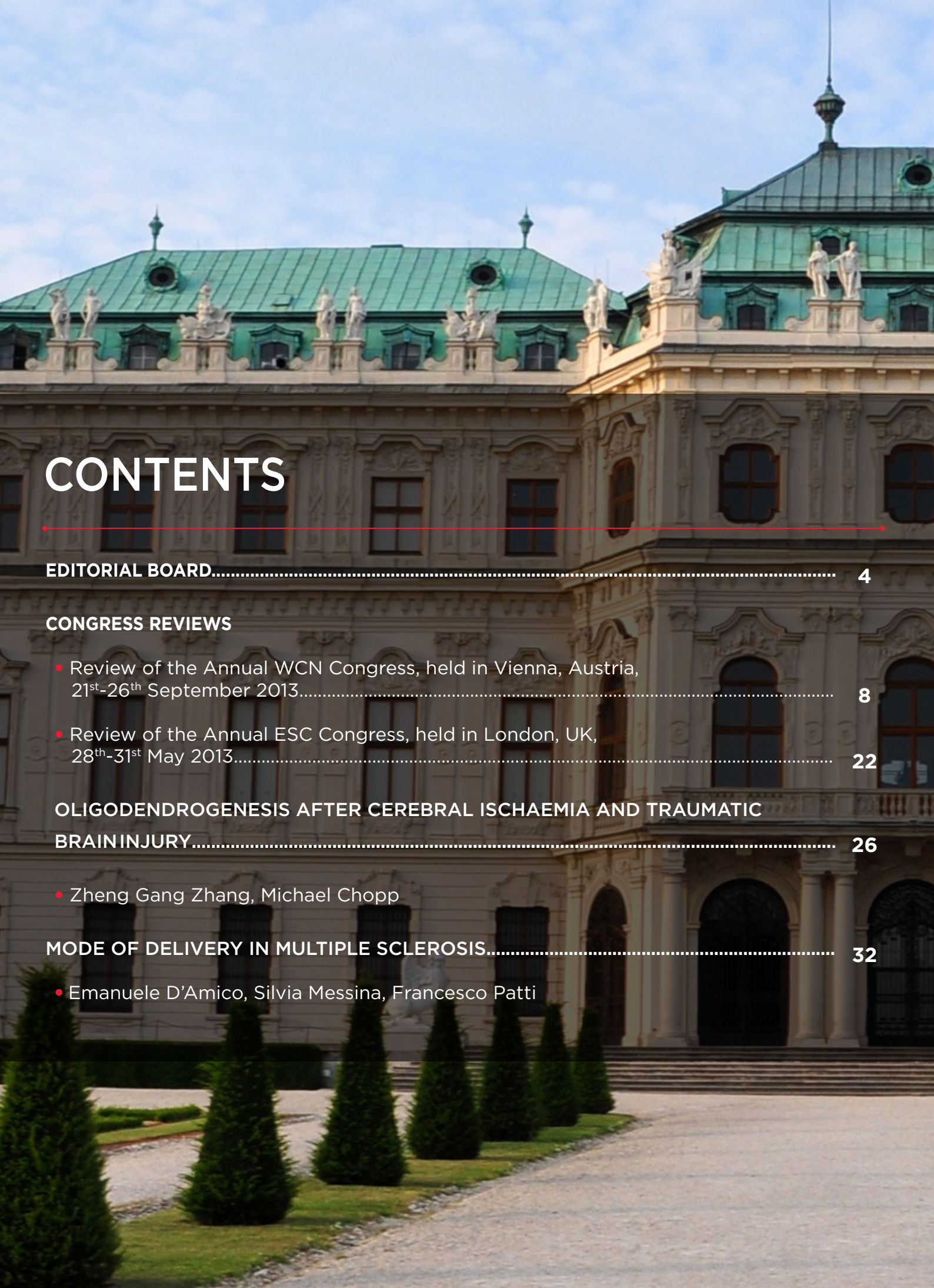

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Welcome

Welcome to the first edition of *European Medical Journal – Neurology*. This issue will provide you with the highlights of the XXI World Congress of Neurology (WCN), which was partnered with the European Federation of Neurological Societies, and the Österreichische Gesellschaft für Neurologie, displaying a real sense of collaboration within the neurological world. There were over 2,500 abstracts submitted and the congress featured world-class speakers with a rich scientific programme.

Dementia was one the main topics discussed at the WCN, held in Vienna, Austria this year. Although there is still no cure for dementia, neurologists continue to make progress in this area. In our 'Congress Review' section we report on the use of biomarkers for the early detection of dementia, which is a highly important discovery as it could decelerate the degenerative process; and in our 'What's New' section we report how ACE inhibitors could reduce the rate of deterioration caused by certain types of dementia. Further studies and behavioural links with neurological diseases were announced at WCN 2013, including that certain types of stress, such as grief, financial worries, and/or violent experiences, are related to the clinical onset of Alzheimer's disease, while Parkinson's patients have been shown to be less trusting and more likely to take risks.

Another hot topic discussed during the WCN was stroke. One of our featured papers, 'Neurorehabiliation After Stroke' written by Prof Rüdiger Seitz, describes how this topic has now become a clinical subspecialty, and argues that healthcare-givers treating these patients should identify areas of the brain that can be accessed during recovery and which will, in turn, support the restitution of function. During WCN the idea of stroke primarily relating to age was also discussed. It was suggested that those who have experienced a stroke under the age of 55 have a better chance of recovery without disability compared to their older counter-parts. Furthermore, a biomarker has been discovered that can predict how effective therapy will be in improving a patient's functional outcome after an ischaemic stroke. As part of our 'Congress Review' we also feature news from the European Stroke Conference, which was held in London from the 28th-31st May 2013 and had more than 4,200 attendees meeting to discuss the experimental research, post-stroke care, and clinical trials.

A revolutionary development, the growth of miniature brain cells, is featured alongside many other topics of interest in our 'What's New' section. This method, developed by researchers from the Institute of Molecular Biotechnology (IMBA) at the Austrian Academy of Sciences (OeAW), could help to treat conditions such as schizophrenia and autism. We also report on the benefits of an active lifestyle as it can have a positive impact on the brain in improving its functions, a subject which was also included during the WCN. Moreover, we discuss the role of palliative medicine and highlight that it may have uses other than pain relief; it may also be able to combat neurological symptoms and provide a greater quality of life for patients.

I hope that this edition of *EMJ – Neurology* will provide an interesting and vital source of the most up-to-date information from the field of Neurology, particularly for those that could not attend WCN or ESC 2013, the most important Neurological meetings of the year.

Kelly-Ann Lazarus

Editor, European Medical Journal

WCN CONGRESS 2013

MESSE WIEN EXHIBITION & CONGRESS CENTER
VIENNA, AUSTRIA
21st-26TH SEPTEMBER 2013

Welcome to the *European Medical Journal* review of the World Congress of Neurology 2013

EMJ EUROPEAN MEDICAL JOURNAL

WCN CONGRESS 2013

MESSE WIEN EXHIBITION & CONGRESS CENTER VIENNA, AUSTRIA

21st-26TH SEPTEMBER 2013

Welcome to the *European Medical Journal* review of the World Congress of Neurology 2013

VIENNA, Austria, is praised for its long tradition of excellent scientific and medical research. It has established itself as a conference city, making it an ideal choice for the 21st World Congress of Neurology (WCN).

This year's conference, which attracted over 8,000 delegates, displayed a real sense of collaboration within the neurological world. The event, held from the 21st-26th September 2013, was co-organised by the European Federation of Neurological Societies (EFNS), Osterreichische Gesellschaft für Neurologie (OeGN), and the World Federation of Neurology (WFN).

The theme of the Congress, chosen by the Austrian Society of Neurology (ASN), was "neurology in the age of globalisation". In the view of the EFNS, science, medicine, and neurology are becoming a worldwide practice, with brain diseases threatening to rise and overwhelm our healthcare systems. The World Brain Alliance emphasises the importance of prevention, and the need for a greater collaboration across disciplines in order to combat the growth in neurological disease.

Featured speaker, Prof Eric Kandel, a Vienna-born Nobel Prize winner, addressed the issue of the global burden of neurological disease. He emphasised that this universal interaction is beneficial to all neurologists as ideas, education, technical know-how, and vast amounts of data and studies will be shared.

"We have come a long way, but we have much further to go."

Prof Vladimir Hackinski,
President, World Federation of Neurology

This in turn will lead to improved quality, understanding, and communication.

Continuing the Congress theme, President of the WFN, Prof Vladimir Hachinski, focused his talk on global neurology and brain health, specifically on stroke and dementia, two diseases affecting a huge number of the population. He addressed the importance of development within an increasingly globalised and digital world, highlighting that: "In a knowledge-based society, we must develop a higher degree of intellectual competence in order to make the most of life lived in the digital age."

With an ever-growing population, Prof Hackinski has suggested that there needs to be more studies based on treatment, prevention, mechanisms, and pathophysiology. A greater degree of collaboration was also suggested, alongside the idea of stroke and dementia potentially being studied and treated together, rather than as separate topics. In the view of Prof Hackinski: "we have come a long way, but we have much further to go."

The WCN will help to shape the future of neurology; in their view, "brain health is key to health." Major breakthroughs within the field, in clinical practice, research, and technology were presented, promoting the idea of neurologists being the guardians of the brain, increasingly becoming "leaders in the fight for brain health."

Exercise: For a healthy body and mind

> "It was already known that physical movement provides a means of delaying cognitive decline. But it was unclear until now just which cognitive areas are influenced by physical activity."
>
> *Prof Franz Fazekas, Medical University Graz, Austria*

CARDIOVASCULAR benefits of exercise are understood, but in regards to brain function the benefits are not so well-known. A European research group, Leukoaraiosis and Disability (LADIS), presented a direct correlation between an active lifestyle and improved brain function at the WCN 2013.

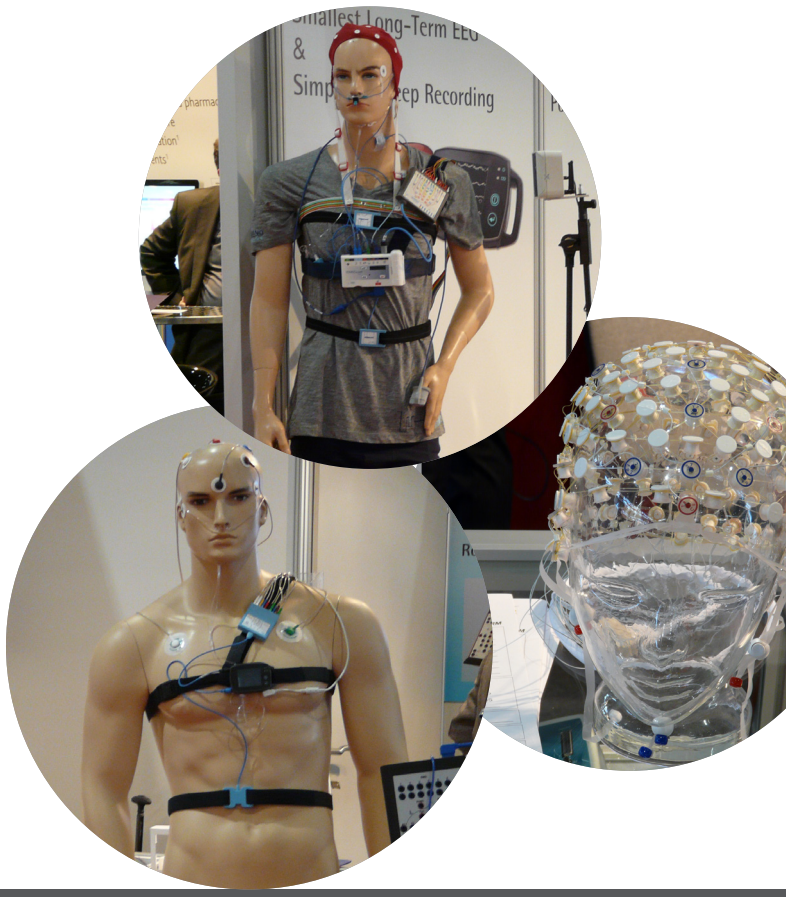
Prof Franz Fazekas, from the Medical University Graz, Austria, co-author of the LADIS study explained: "It was already known that physical movement provides a means of delaying cognitive decline. But it was unclear until now just which cognitive areas are influenced by physical activity."

The 282-person study assessed 164 women and 118 men, who were all free of dementia symptoms. The study period lasted 3 years, and each year the participants underwent magnetic resonance imaging examinations and tests on their degree of physical activeness and cognitive status.

The results revealed that the more physically active individuals showed better values in the executive function of the brain, both at the start of the investigation, as well as 3 years afterwards.

These findings suggest that being more physically active helps to accelerate thought faculty, and also the time in which it takes for the brain to process information. Being physically active also improves mental functions, such as the ability to plan, make decisions, and set goals, all of which are essential for a person's ability to control their behaviour.

However, these results showed no improvements concerning memory function. "Nevertheless, the available results offer one further reason to incorporate regular exercise into our daily lives and thereby to do good not only for the body, but for the mind as well," Prof Fazekas said.



Parkinson's causes mistrust and risk-taking

> "Various neuropsychiatric problems of the affected people may be related to exaggerated distrust due to the disease."
>
> *Dr Andrija Javor, General Hospital Linz, Austria*

A NEW development has been identified in the study of Parkinson's disease, which indicates those with the illness are less trusting and more likely to take risks than unaffected individuals.

Dr Andrija Javor of the General Hospital Linz, Austria indicated: "Particularly those brain areas that regulate trust behaviour are affected by the disease: the basal ganglia of the cerebrum, the frontal cortex and the limbic system. Moreover, dopamine and serotonin, neurotransmitters positively related to trust, are reduced when suffering from Parkinson's disease. It can therefore be assumed that various neuropsychiatric problems of the affected people may be related to exaggerated distrust due to the disease."

Computerised game tests and a dice game were used in this study to investigate the hypothesis. To measure the level of mistrust, 10 male and 10 female patients being treated for Parkinson's with dopamine were required to use a computer game. Those who participated in the study were experiencing a slightly advanced state of the disease, and were compared to the results of 20 healthy individual's behavioural patterns. The game involved giving participants a hypothetical €10 and then required each 'player' to decide how much to trust a neutral 'trustee' with. The results indicated that the healthy individuals were more generous and trusting giving an average of €5.50 to the virtual trustee, whereas the Parkinson's patients were restrained and trusted an average of €3.40.

However, the results overlooked "reduced risk-appetite," Dr Javor indicated. When participants engaged in playing the dice game, Parkinson's patients were more courageous and on average took around 10 risky decisions, whilst the average for healthy individuals was seven.

This is not fully conclusive as further research is required in order to fully comprehend the complications associated with Parkinson's disease.

Biomarkers furthering advances in dementia

DEMENTIA was one of the main topics of focus for the WCN this year. According to the WHO, 35.6 million people worldwide suffered from a form of dementia in 2010, and this number is expected to triple by 2030.

The use of highly discriminatory biomarkers has ensured that there have been many advances in the early detection of Alzheimer's and other forms of dementia, improving the ability to diagnose the disease.

According to Prof Werner Poewe, co-chair of the Scientific Programme Committee for the WCN 2013, some worldwide studies "are leading us in the direction of new therapies, for instance, a possible immunisation against beta-amyloid".

Technology, such as magnetic resonance tomography (MRT), renders visible deposits of beta-amyloid, while positron emission tomography (PET) ensures that changes in the metabolism in the cerebral cortex can be monitored. Moreover, measuring Tau proteins and beta-amyloid in cerebrospinal fluid is further improving the diagnosis.

While there is no cure for dementia, studies such as these are highly valued. Throughout the Congress there were a number of studies presented, focusing on diagnosing the disease in the symptom-free or early stages, through the study of plasma biomarkers.

Don't stress, it could lead to Alzheimer's

> "Research is solidifying the evidence that stress can trigger a degenerative process in the brain and precipitate dysfunction in the neuroendocrine and immune system."
>
> *Dr Edgardo Reich, Neurology Hospital Julio Mendez, Argentina*

STRESS, from consuming grief, financial worries, and violent experiences, can be related to the clinical onset of Alzheimer's disease, an Argentine research team suggested.

Dr Edgardo Reich, who presented the study at the Congress, found that nearly three out of four Alzheimer's patients (72%) had to cope with severe emotional stress. These patients were compared to a control group of 81 healthy individuals. In the control group, only 26% had experienced stress, grief, and sorrow during the preceding 2.1 years before the onset of symptoms.

Dr Reich found that of the 118 patients who were diagnosed with the disease, 24 cases

dealt with the death of a spouse or partner, while 15 cases experienced the death of a child. Violent experiences, such as physical assaults, robbery, or car accidents, accounted for 32 cases in total. Financial worries, concerning pensions or migration-related adaptive changes, were also prevalent among the patients.

Stress, however, is not the single cause for dementia, according to Dr Reich: "Research is solidifying the evidence that stress can trigger a degenerative process in the brain and precipitate dysfunction in the neuroendocrine and immune system." More studies are being conducted to assess the effect of stress and other causalities.

Psychosocial difficulties caused by epilepsy

EPILEPSY is one of the most common neurological disorders; those who have the condition do not only face drug side-effects, but also numerous psychosocial difficulties, including a lack of public understanding concerning the disease.

Using the Psychosocial Factors Relevant to Brain Disorders in Europe (PARADISE) protocol, the study group interviewed 40 men and 40 woman, each taking an average of two different anti-epilepsy drugs. The average age of the study participants was 41 years, with 69% of the patients classified as having a moderate-to-severe case of the disease.

Study author Dr Rui Quintas from the Istituto Neurologico Carlo Besta, Milan, Italy said: "To be able to develop the best possible care programme for people with epilepsy we need a comprehensive understanding of the specific psychosocial problems these patients face."

The researchers found that the most common problems were: restlessness, accounting for 80% of patients, alongside 74% mentioning emotional shock related to their health condition. Anxiety was noted among 69% of patients, depression, 66%, problems driving a vehicle, 60%, memory difficulties, 58%, and problems at work, 55%.

"To be able to develop the best possible care programme for people with epilepsy we need a comprehensive understanding of the specific psychosocial problems these patients face."

Dr Rui Quintas, Istituto Neurologico Carlo Besta, Italy

Although some of the patients said that their condition did improve over time, 27% reported that their problems remained unchanged. Dr Quintas said: "The external factors that most bothered this group were side-effects from drugs (59%) and a lack of sensitivity by others in dealing with epileptics (52%).

"This is not only a task for science, but also for the society to improve the situation by raising awareness."

Ischaemic stroke therapy outcomes are now predictable

> "Our findings continue to support the possible significance of biomarkers as predictors, for which there is more and more evidence."
>
> *Dr Thomas Seifert-Held, Medical University Graz, Austria*

A BIOMARKER, neutrophil gelatinase-associated lipocalin (NGAL), is able to predict how effective or ineffective therapy will be in improving a patient's functional outcome after an ischaemic stroke.

Dr Thomas Seifert-Held, from the University of Medicine, Graz, Austria, explained: "A range of circulating inflammatory reactants have been identified as biomarker candidates in ischaemic stroke. However, no study has yet demonstrated the additional value circulating inflammation related proteins have as predictors of the functional outcome for the patients. Our team has now managed to do so."

A week after one of the 46 patients suffered an ischaemic stroke, the team measured the plasma levels of NGAL, with another reading of their protein levels checked 90 days later alongside a reading of the patient's modified Rankin Scale (mRS), which shows the degree of disability after a stroke and also shows how much functional impairment a person has suffered.

The higher levels of circulating proteins, noted after a stroke, indicated that there would be a higher mRS score 90 days later, further indicating a reduced chance of living a similar standard of life which the patient enjoyed prior to the stroke.

The team will be continuing their studies with the greatest sensitivity and specificity to identify the biomarker. Dr Seifert-Held said: "Our findings continue to support the possible significance of biomarkers as predictors, for which there is more and more evidence."

Better outcomes for younger stroke patients

FUNCTIONAL outcomes following a stroke are primarily a question of age - according to an Austrian study group, who found that many patients under 55 years of age have better chances of survival without disability.

The aim of the study was to investigate the relationship between the age of the patient and the prospect of recovery without adverse effects. The study group found that younger victims had been underrepresented in previous analysis of ischaemic strokes.

Dr Michael Knoflach, from the Medical University of Innsbruck, Tyrol, Austria, highlighted that with increasing age,

independent of all other factors, the functional result gets progressively worse.

There are 43,163 patients on the Austrian Stroke Unit register, 14.1% of these were aged 55 years or under at the time of stroke occurrence. Of the register, 14,256 were free of disability before the stroke, 2,223 of whom aged 55 years or younger. 88.2% of the patients aged 55 years and below had a good functional outcome after ischaemic stroke.

The statistics also showed that patients who were aged between 18 and 35 years showed the best recovery results, whereas, after the age of 75, permanent disability becomes especially acute, with the results deteriorating in 10-year increments.

According to Dr Knoflach: "Age is therefore a significant prognostic factor for possible disabilities following stroke, independent of its severity, therapy, gender or additional complication."

New uses of palliative medicine

THE IDEA that palliative medicine is just used for pain management in the final stages of diseases is often judged to be overly simplistic, with supporters citing its ability to combat neurological symptoms and help to provide a greater quality of life for patients suffering from a long-term illness.

For the first time, the role of palliative medicine was discussed at the WCN 2013. Prof Wolfgang Grisold, from the Kaiser-Franz-Josef Hospital, Vienna, Austria, emphasised that the definition of palliative medicine as pain management purely for the final stages of illness is too narrow in its scope.

In his view, medicine such as this is necessary: "In an ageing society, an increasing number of people are in need of the long-term help offered by palliative care that focuses on neurological conditions. For example, cases of degenerative dementia can bring with them a whole range of neuropathic symptoms, from dizziness or muscle cramps, to epilepsy."

Concerning patients who have brain tumours, the use of palliative medicine can alleviate symptoms for up to a year, whereas in patients who have suffered from a severe intracranial haemorrhage, their symptoms may only be alleviated for a few weeks.

"The quality of life of patients with terminal illnesses can be significantly improved if they receive competent support for neurological symptoms such as dizziness, nausea, cognitive impairment, or epileptic seizures related to brain tumours," Prof Grisold said.

"The quality of life of patients with terminal illnesses can be significantly improved if they receive competent support for neurological symptoms such as dizziness, nausea, cognitive impairment, or epileptic seizures related to brain tumours."

Prof Wolfgang Grisold, Kaiser-Franz-Josef Hospital, Austria

Individualised treatment for multiple sclerosis

INNOVATIVE drugs are being developed to individualise treatments for the estimated 2.5 million people worldwide who suffer from multiple sclerosis (MS), in avoidance of serious side-effects.

The WCN President, Prof Eduard Auff from the Medical University of Vienna and Vienna General Hospital, said: "Many new treatment options are emerging at the moment, and there is justified optimism that we will soon be able to help people with MS more quickly and more effectively."

These new treatments which are currently available, or are being tested in large-scale clinical trials, are able to target the neuroimmunological processes; they are able to prevent autoreactive lymphocytes (aggressive immune cells) from penetrating the brain.

"In the treatment of multiple sclerosis (MS), we are seeing the development of drugs that are easier for patients to take and are better tolerated, and above all a trend towards therapies tailored to the individual patient," said Prof Auff.

Although there are developments within the field, there are a number of adverse effects from these treatments, including hair loss, bradycardia, and progressive multifocal leukoencephalopathy (PML), which is a dangerous viral infection.

It is for this reason, explains Prof Auff, that personalised treatment is needed: "Clinical courses and the degree of severity can differ widely from person to person, and the results achieved in different patients who are given exactly the same treatment can vary enormously. This means that efforts to increase personalisation of treatment are especially important."

Developing and/or testing treatment which can either be injected or taken orally is a big step in the neurological world towards more personalised treatment. According to Prof Auff: "A lot of work is being done to identify biomarkers that can reliably predict the efficacy of treatment and the side-effects that can be expected, so that the risks and benefits can be weighted up for each case."

Early detection of Parkinson's explored

PARKINSON'S disease remains incurable, however there have been many advances made in the early detection of the disease. It has now become one of the most effectively treatable neurodegenerative diseases, with respect to symptom control.

There are many international studies and groups which are devoted to exploring new leading indicators. Prof Warner Poewe, Co-Chair of the Scientific Programme Committee for the WCN 2013, from the Medical University Innsbruck, Tyrol, Austria, said: "It is important here to conduct biomarker research to pave the way for the earliest possible identification of individuals at especially high risk of contracting Parkinson's disease. The hope here is to validate risk markers that can be widely used and allow high-risk patients to be identified before the outbreak of the disease."

The early signs of the disease include rapid eye movement (REM) sleep disorders as REM is a sign of worsening motor symptoms after the disease breaks out. An impaired sense of smell has been closely associated with the risk of the disease, particularly in a Croatian observation study which has shown that 75% of Parkinson's patients examined had an impaired sense of smell.

As a result of this, simple smelling tests are being used as an effective screening tool, alongside ultrasonic examinations of the brain. Moreover, an injection of I-123 ioflupane in connection with single-photon emission computed tomography (SPECT) imaging, which uses a gamma camera to depict the nerve cells releasing dopamine, is a safe and precise way of detecting the early stages of Parkinson's disease.

Prof Poewe added: "The development of new therapeutic methods to slow down or halt the progression of the disease remains the big goal in Parkinson's research. It is still unstoppable today."

WCN CONGRESS 2013

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Revolutionary therapy expands possibilities of stroke prevention

INNOVATIVE therapies have been identified to prevent atrial fibrillation-generated strokes, although improved drugs are still required.

The current best practice includes thrombolytic therapy for dissolving blood clots through minimally invasive procedures. More people will have access to thrombolysis according to this new study, as the therapy will also be available for use in developing countries. Prof Werner Hacke, of the University of Heidelberg and Vice President of the WFN, indicated: "There is important evidence that expansion of coverage toward previously untreated patient groups could be possible."

However, various contradicting information has been released, which indicates no general advantage of the new procedure. Prof Hacke added: "Our task now is to clarify through further studies the specific subgroups of those affected who can benefit from the interventional therapy: for example, patients with very severe stroke, with stroke at the base of the skull or stroke at a very early point in the therapeutic window."

Stroke prophylaxis could prove effective in the inhibition of atrial fibrillation-related strokes. More strokes could be prevented through the new, 'convenient anticoagulants' as currently 25-30% of strokes are caused by emboli travelling from the heart to the brain, which, in turn, is caused by atrial fibrillation. Vitamin K antagonists are already available as preventatives, with 70-80% of strokes being prevented through this method if taken according to guidelines. There are detrimental effects of this treatment however, with haemorrhage risk and a large nutrition-dependent fluctuation range in absorbing the drug. Less than a quarter of patients will actually benefit from this method of prevention as it involves issues with dosage intake.

Prophylaxis, adjusted for risk, has become simpler and safer whilst remaining as effective. The thrombin-inhibitor dabigatran and the clotting factor Xa inhibitors rivaroxaban, and apixaban are new drugs which guarantee a crucial change in prescribing practice. According to Prof Hacke, these drugs are easier to take, and are effective in preventing strokes while lowing brain haemorrhage risks. He added: "The availability of these therapies will sustainably change the therapeutic practice, more patients will enjoy the benefit of more effective prevention, and a significantly greater number of strokes can be inhibited in the future."


DER ERINNERUNG AN DIE
ERRICHTUNG DER REPUBLIK
AM 12. NOVEMBER 1918
JAKOB REUMANN
VICTOR ADLER
FERDINAND HANUSCH


DR. KARL RENNER

ESC ANNUAL CONGRESS 2013

LONDON EXCEL CENTRE, ENGLAND, UK
28TH–31ST MAY 2013

Welcome to the *European Medical Journal* review of the Annual European Stroke Conference 2013

DESCRIBED as the most important stroke meeting in Europe, the 22nd European Stroke Conference (ESC 2013) is held in an era in which, according to WHO, 15 million people suffer from stroke on an annual basis.

Almost 4,000 delegates flocked to London's ExCel Centre, to take part in stimulating discussions on a variety of topics ranging from experimental and translational stroke research, to post-stroke care, and clinical trials.

"The ESC has become the premier educational and scientific event in the field, and attracts delegates from all over the world," Dr Martin M. Brown, of the ESC Programme Committee, said, reiterating the outstanding educational programme, based around speakers and topics suggested by the conference delegates themselves.

As seen by the stories below, great debate accompanied remarkable developments in the field of stroke treatment, paving the future towards the subsequent conference to be held in Nice, France, from 6th-9th May 2014.

Stroke ambulance treats casualties within invaluable 'golden hour'

STROKES strike the population every hour in Berlin alone, and a specially-equipped ambulance-style vehicle presents the opportunity to treat a patient within the first, so-called 'golden' hour of stroke onset.

Boasting the probability of reaching its destination 75% of the time within 16 minutes, the rescue vehicle called 'Stroke-Emergency-Mobile' or the STEMO van for short (pictured), contains an on-board CT scanner, as well as a stroke physician at all times to monitor the results.

> "The use of mobile stroke units can be integrated into the emergency medical system, they are safe, and they are superior to regular care for reducing time to tPA patients."
>
> *Dr Heinrich Audebert, Stroke Specialist, Charite Hospital*

Started in Berlin, Germany back in 2010, the project is driven by the Charité-University Medicine Berlin, the Berlin Fire Department, BRAHM GmbH and MEYTEC GmbH, and involves fitting one of the smallest computer tomography (CT) scanners in the world.

Presenting the Pre-Hospital Acute Neurological Treatment and Optimization of Medical care in Stroke (PHANTOM-S) trial, Dr Heinrich Audebert said: "We have shown that the use of mobile stroke units can be integrated into the emergency medical system, they are safe, and they are superior to regular care for reducing time to tPA patients."

Once the patient is on board, they undergo a CT scan. All medical data generated inside STEMO is then encrypted and transferred to a neuroradiologist, transmitted via 3G mobile technology. If deemed necessary, the patient is then administered tissue plasminogen activator (tPA) treatment inside the ambulance.

Co-author, Dr Martin Ebinger added: "This is a radical new approach. It is well proven that reducing time to tPA treatment can increase the chances of a good outcome. And we have shown that use of this mobile stroke unit can reduce time to treatment by about 25 minutes."

Though the rate of successful diagnosis was at 50% during initial trials – which the creators have argued to be a decent percentage considering how many other afflictions present similar symptoms to apoplexy – the procedure looks to become further refined and more cost-effective, in order to become more viable for other urban areas, and perhaps even rural areas.

Possible neurorestorative effects in traditional Chinese medicine

> "In China, there are more than 100 traditional Chinese medicines used for ischaemic stroke."
>
> *Dr Christopher Chen, National University of Singapore*

A NEW minor trend has been found in favour of the traditional Chinese medicine NeuroAid over a placebo in improving function following ischaemic stroke. A large randomised trial did not provide significant statistical differences between the medicine and placebo, but researchers suggest the results should be supported by further investigation.

Dr Christopher Chen, from the National University of Singapore, said: "In China, there are more than 100 traditional Chinese medicines used for ischaemic stroke, and there is widespread belief that they have some benefit. It is therefore difficult to conduct placebo-controlled studies there."

This Chinese Medicine Neuroaid Efficacy on Stroke Recovery (CHIMES) study was published in *Stroke* in June, where authors acknowledge that some traditional medicines present antioxidant, anti-inflammatory, vasodilatory, antiplatelet, antiglutamate, and protective effects against ischaemia and reperfusion injury, in pharmacologic studies.

The medicine, NeuroAid is a capsule comprised of extracts from nine herbal and five animal ingredients, and according to Dr Chen has been established to restore cellular and neurologic function in animal models of ischaemic stroke. Long-term (2 weeks to 6 months) treatment of stroke patients using the drug in clinical trials indicated improved recovery, however, these trials were not placebo-controlled.

The study was conducted in Southeast Asia and involved 1,100 patients with acute, moderately severe stroke, with a National Institute of Health Stroke Scale (NIHSS) score of 6 to 14. These participants were randomly given NeuroAid or the placebo. The treatment was taken 72 hours subsequent to the onset of the stroke and then sustained for 3 months.

The results from the subgroups indicated no heterogeneity in the statistics for the primary outcome; however, a trend was found towards the benefit in receiving treatment beyond 48 hours after the stroke. This trend supports the potential neurorestorative effects of NeuroAid. Negative side-effects were similar in both groups.

A new extension study, CHIMES-E, lasting 2 years, is now underway.

Debate: Are over 60s worth surgery costs?

A DEBATE on whether early decompressive surgery for older stroke patients with malignant infarctions of the middle cerebral artery was worth the economic costs rocked the ESC 2013.

Several members of the audience questioned results from the Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY II) trial, arguing although mortality rates were greatly reduced from early surgery, patients suffered a greater risk of being left in a severely disabled state.

The DESTINY II trial, originally presented at the 8th World Stroke Congress 2012, showed the primary endpoint – a modified Rankin scale (mRS) score of 0 to 4 after 6 months – occurred in 39% of the surgery group, compared to 17% of those conservatively treated, with the mortality rate at 6 months almost halved.

"This trial showed the benefits of a significant reduction in mortality and a few extra patients in mRS score 3 with surgery. But this is offset somewhat by the large number of very disabled patients left at a score 5," Prof David Mendelow, a Neurosurgeon of the University of Newcastle, UK, said while speaking to *Medscape Medical News*. "These patients cost up to £200,000 per QUALY [quality-adjusted life-year]. We have to ask ourselves if we can afford that."

Prof Mendelow added: "Yes, there was a small increase in those with a score of 3, signifying a worthwhile recovery, but this comes at an enormous cost of more people surviving in an extremely disabled state.

"I look after these patients, and they have terrible complications. We can't even resource our A&E [accident and emergency] departments properly in the UK, so we have to consider the health economic arguments here."

The presenter of the trial, Dr Werner Hacke, of the University of Heidelberg, Germany, disagreed wholeheartedly, countering: "If we just looked at economics, we would say the best outcome for stroke is death."

He concluded: "We have achieved a positive result in the primary endpoint, and have shown that decompressive surgery is associated with a significant increase in patients surviving with a modified Rankin score better than 5."

> "If we just looked at economics, we would say the best outcome for stroke is death."
>
> *Dr Werner Hacke, University of Heidelberg, Germany*

OLIGODENDROGENESIS AFTER CEREBRAL ISCHAEMIA AND TRAUMATIC BRAIN INJURY

Zheng Gang Zhang,[1] Michael Chopp[1,2]

1. Department of Neurology, Henry Ford Hospital, Detroit, Michigan, USA
2. Department of Physics, Oakland University, Rochester, Michigan, USA

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ABSTRACT

Stroke and traumatic brain injury (TBI) damage white and grey matter. Loss of oligodendrocytes and their myelin, impairs axonal function. Remyelination involves oligodendrogenesis during which new myelinating oligodendrocytes are generated by differentiated oligodendrocyte progenitor cells (OPCs). This article briefly reviews the processes of oligodendrogenesis in adult rodent brains, and promising experimental therapies targeting the neurovascular unit that reduce oligodendrocyte damage and amplify endogenous oligodendrogenesis after stroke and TBI.

Keywords: Cerebral ischaemia, traumatic brain injury, myelination, oligodendrocytes, oligodendrocyte progenitor cells.

INTRODUCTION

Stroke and traumatic brain injury (TBI) lead to white and grey matter damage and are leading causes of mortality and morbidity.[1-5] White matter mainly contains axons and oligodendrocytes, myelin forming cells, in the central nervous system (CNS).[1,3,5] Acute axonal injury is one of the most common pathological features of closed head injury.[3] Oligodendrocytes are vulnerable to ischaemic stroke.[1,6] Loss of oligodendrocytes and their myelin, impairs axonal function.[7] However, compared to investigations conducted in the area of neuroprotection, studies to reduce oligodendrocyte damage and to regenerate myelinating oligodendrocytes are few after stroke and TBI, which has impeded development of effective therapy for stroke and TBI.[1,8]

Emerging data indicate that in the adult rodent brain, new oligodendrocytes are generated to myelinate the previously unmyelinated axons in the cortical grey matter and subcortical white matter.[8-11] In addition to ensheathment of axons, which facilitates electrical conduction, oligodendrocytes in the adult brain contribute to neural plasticity and circuitry function.[8-11] New oligodendrocytes derived from non-myelinating oligodendrocyte progenitor cells (OPCs) are required to form myelin sheaths for sprouting axons during brain repair processes after brain injury, because mature oligodendrocytes do not proliferate in the adult brain and injured oligodendrocytes no longer form new myelin sheets.[7,12-16] Brain injury induces OPC proliferation, leading to a substantial increase in the number of OPCs. However, in the injured brain, OPCs do not effectively differentiate into myelinating oligodendrocytes.[8] Thus, it is imperative to elucidate the pathophysiology of white matter damage after stroke and TBI in order to develop therapies designed specifically to reduce oligodendrocyte damage and to enhance remyelination.

In light of the failures of neuroprotective therapies in clinical trials, promising new concepts suggest that therapies for brain injury should target the neurovascular unit.[17]

The neurovascular unit comprises of cerebral endothelial cells, astrocytes, neurons, and oligodendrocytes.[17,18] In this article, we will briefly review the processes of oligodendrogenesis in the adult rodent brain under normal and injured conditions, and experimental therapies targeting the neurovascular unit that reduce oligodendrocyte damage and amplify endogenous oligodendrogenesis after stroke and TBI.

AFTER STROKE AND TBI

Acute Oligodendrocyte Damage

OPCs comprise 3–9% of the total cell number in the adult CNS and are the majority of proliferating cells.[9,15,19] OPCs are locally present in the *corpus callosum*, the striatum, and the cortex, and are derived from neural progenitor cells in the subventricular zone (SVZ) of the lateral ventricle.[13,20-25] In the adult brain, OPCs continuously differentiate into mature oligodendrocytes to myelinate the previously unmyelinated axons throughout the grey and white matter.[7,9-11,15] Recent studies show that in addition to facilitating salutatory conduction, myelination in the adult brain contributes to maintaining axonal integrity, neural plasticity, and circuitry function.[8-11] For example, myelinating oligodendrocytes offset metabolic stress on neurons by providing trophic support to axons.[8,26]

Mature oligodendrocytes are acutely vulnerable to stroke, and damage of mature oligodendrocytes leads to the loss of myelin and axons.[1,6] However, there is a paucity of studies which characterise acute oligodendrocyte damage after TBI, although traumatic axonal injury has been intensively investigated.[3,27,28] Loss of myelinating oligodendrocytes exacerbates traumatic axonal injury, because myelinated axons are less vulnerable to damage compared to non-myelinated axons, following fluid percussion injury in the rat.[29] Injured oligodendrocytes no longer form new myelin sheets, and remyelination requires generation of new oligodendrocytes.[7,12-16] Thus, in addition to the neuroprotection, therapeutic approaches designed to reduce acute white matter damage may also require minimising mature oligodendrocyte injury. Mechanisms of oligodendrocyte injury include oxidative stress, excitotoxicity, proinflammatory cytokines, among others.[1,15] Clinical trials show that none of the neuroprotective drugs achieve clinical benefit for treatment of acute stroke and TBI, although neuroprotection has been demonstrated in experimental stroke and TBI.[3,4,30-32]

Stroke and TBI injure all brain cells, and a new integrative approach for treatment of stroke and TBI is emerging to restore the normal function of the neurovascular unit.[33,34] Treatment of acute stroke requires rapid restitution of cerebral blood flow (CBF) in the ischaemic cerebral microvascular bed, to preserve blood brain barrier (BBB) integrity, and to minimise ischaemic cell death.[32,35,36] Preclinical data support the concept of new therapies to target the neurovascular unit. For example, tissue plasminogen activator (tPA) is the only Food and Drug Administration (FDA) approved treatment for acute stroke (within 4.5 hours).[32,37] In addition to clot lysis, tPA induces brain haemorrhage and neurotoxicity, which limit its usage to a small minority of patients with acute stroke.[18,32] Experimental studies indicate that combination of tPA with neuroprotective agents or matrix metalloproteinase (MMP) inhibitors, substantially reduce the deleterious effects of tPA on disruption of the BBB and ischaemic cell damage.[18,38] Neuroprotective agents, or other agents that are to be used for the adjuvant treatment with thrombolysis, need to be safe without exacerbating brain injury, especially, brain haemorrhage.

Clinical data are emerging to examine the safety and efficacy of neuroprotective agents in conjunction with thrombolysis. Cerebrolysin®, a mixture of neurotrophic peptides, had a favourable outcome trend in patients with severe stroke when it was administered within 12 hours of the onset of stroke.[39] A recently published pilot clinical trial of combined treatment with tPA and Cerebrolysin® in acute ischaemic stroke including 119 patients with acute hemispheric stroke, has shown that this combination therapy is safe when tPA was administered within 3 hours of the onset of stroke, and Cerebrolysin® was given 1 hour after tPA treatment and subsequently daily for 10 consecutive days[40] [Combined Treatment With Alteplase (Rt-PA) and Cerebrolysin® in Acute Ischaemic Hemispheric Stroke (CERE-LYSE-1), www.clinicaltrials.gov, NCT00840671]. In addition, a clinical Phase III trial, Efficacy Study of Combined Treatment With Uric Acid and rtPA in Acute Ischaemic Stroke (Urico-Ictus, www.clinicaltrials.gov, NCT00860366), is currently underway to determine whether a combination therapy of uric acid and tPA is superior to a monotherapy of tPA

in patients with acute ischaemic stroke within 4.5 hours of symptom onset.[41,42] Uric acid is an endogenous product derived from the metabolism of purines and exerts neuroprotection by its antioxidant capacity.[41]

Another drug, a postsynaptic density-95 (PSD-95) protein inhibitor (NA-1), has marked potential for the combination therapy for patients with acute ischaemic stroke.[42] NA-1 substantially reduces ischaemic neuronal damage in rodent and primate models of stroke.[43,44] A published Phase II, randomised, double-blind, placebo-controlled trial showed that treatment of patients who underwent endovascular brain aneurysm repair, with NA-1 at the completion of aneurysm repair procedures, sustained fewer ischaemic infarcts than patients in the placebo group, as measured by diffusion-weighted MRI and fluid-attenuated inversion recovery MRI of the ischaemic lesion (Evaluating Neuroprotection in Aneurysm Coiling Therapy [ENACT] trial, www.clinicaltrials.gov, NCT00728182).[42,45] Although the effect of these combination therapies on oligodendrocyte injury has not been reported, one may expect that the integrative approach for treatment of acute brain injury may reduce oligodendrocyte damage.

Oligodendrogenesis During Brain Repair

Stroke and TBI are associated with chronically progressive cognitive impairment.[3,46-49] Myelination is essential for maintenance of the axon.[50,52] Failure of remyelination of axons after stroke and TBI could lead to axonal degeneration, and consequently, to cognitive impairment.[3,10,52,53] Remyelination involves oligodendrogenesis, during which new myelinating oligodendrocytes are generated by differentiated OPCs localised to the *corpus callosum* or derived from SVZ neural stem cells.[7,8,12-16] Loss of mature oligodendrocytes provokes remyelination.[50,54] Studies in the rodent indicated that stroke and TBI trigger a substantial increase in OPCs generated by actively proliferating OPCs not only in young but also in aged animals.[55-57] These OPCs are recruited to the injured tissue region and later some OPCs differentiate into myelinating oligodendrocytes, where sprouting axons are present.[12,55,56,58] However, endogenous oligodendrogenesis in response to stroke and TBI is limited.

The presence of inhibitory molecules predominantly blocks OPC differentiation into mature myelinating oligodendrocytes, which limits remyelination processes.[8,52] Treatment of stroke or TBI with mesenchymal stromal cells (MSCs) suppressed the expression of Nogo, an endogenous inhibitor of myelination, and was associated with substantial increases in mature oligodendrocytes in the peri-infarct striatum and *corpus callosum,* and with improvement of neurological outcome in the rodent 4 months after stroke.[34,59-65] These data suggest that the blockage of inhibitory molecules may enhance remyelination in the injured brain. Currently, there is a clinical Phase I safety trial to block a potent oligodendrocyte differentiation inhibitor, the LRR and Ig domain–containing Nogo receptor–interacting protein (LINGO-1), in multiple sclerosis (Safety Study of BIIB033 in Subjects With Multiple Sclerosis, www.clinicaltrials.gov, NCT01244139).[66,67] However, the relevance of LINGO-1 antagonist to enhance remyelination in the setting of stroke and TBI remains to be determined.

In addition to targeting oligodendrocyte differentiation inhibitors, preclinical studies show that therapies targeting the neurovascular unit increase endogenous oligodendrogenesis and axonal outgrowth after stroke and TBI.[34,55,62,66-68] Oligodendrogenesis couples with angiogenesis in the injured brain during the brain repair process.[34,69] *In vitro* studies show that cerebral endothelial cells may promote the proliferation of OPCs through the release of trophic factors, such as brain derived neurotrophic factor (BDNF) and basic fibroblast growth factor (bFGF).[69] Compounds that induce angiogenesis enhance the generation of oligodendrocytes. For example, EPO, in addition to regulating angiogenesis, promotes OPC differentiation into mature oligodendrocytes through interaction with its receptor EPOR.[70-74] Treatment of stroke with recombinant human EPO (rhEPO) induced sustained OPC proliferation and substantially amplified myelinating oligodendrocytes and increased myelinated axons in peri-infarct white matter, which was associated with improvement of neurological outcome.[66,75] Aging reduces oligodendrocytes in rodent and human brains.[54,76-78] Sildenafil, a potent phosphodiesterase type 5 (PDE5) inhibitor, induced cerebral angiogenesis after ischaemic stroke.[79,80] Moreover, the treatment of aged ischaemic mice with sildenafil markedly augmented new oligodendrocytes in peri-infarct *corpus callosum* and striatum.[55] These data suggest that even in aged animals, oligodendrogenic

potential is present in response to stroke and the treatment.

The Sonic hedgehog (Shh) signalling pathway regulates oligodendrogenesis and mediates OPC differentiation in the adult rodent brain.[81-85] Blocking of the Shh signalling pathway leads to a decrease of OPC proliferation and differentiation in a model of focal demyelination induced by lysolecithin in the *corpus callosum* of adult mice.[81] Stroke upregulates the Shh signal that is associated with the generation of new oligodendrocytes.[73,86] Compounds that amplify the Shh signals enhance oligodendrogenesis.[81,87] For example, treatment of stroke with Cerebrolysin® amplified the generation of OPCs and mature oligodendrocytes in white matter of the peri-infarct region.[87,88] Inhibition of the Shh signalling pathway abolished the therapeutic effect of Cerebrolysin® on brain remodelling, including oligodendrogenesis.[87] *In vitro* studies show that Cerebrolysin® induced upregulation of Shh expression in cerebral endothelial cells.[87] In addition to its action on oligodendrogenesis, the Shh pathway plays an important role in maintenance of BBB integrity.[89] Inactivation of the Shh pathway led to exacerbation of BBB leakage and demyelination in experimental autoimmune encephalomyelitis, a model of multiple sclerosis.[89] Collectively, these data suggest that amplification of the Shh signalling pathway has therapeutic potential for the enhancement of myelination after stroke and TBI.

CONCLUSION

Stroke and TBI induce demyelination which comprises of the functional unit of axon and oligodendrocyte. Remyelination involves oligodendrogenesis. Promising data, mainly derived from animal models of stroke and TBI, call for an integrative approach for minimising oligodendrocyte damage and amplifying oligodendrogenesis. Although the relevance of this approach in patients remains to be established, pilot clinical trials suggest that an integrative approach is achievable.

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MODE OF DELIVERY IN MULTIPLE SCLEROSIS

Emanuele D'Amico, Silvia Messina, Francesco Patti

Department G.F. Ingrassia, Section of Neurosciences, Università degli Studi di Catania, Catania, Italy

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ABSTRACT

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system, affecting women of childbearing age. Little is known about the possible association between mode of delivery and the risk of MS in offspring. Delivery represents a unique event in a woman's lifetime, with complex mechanisms controlling human parturition. Concurrent with the trend of increasing numbers of caesarean deliveries (CD), there has been an increasing frequency of autoimmune diseases such as MS. Several theories have emerged suggesting that environmental influences are contributing to this phenomenon. The data available in literature seem reassuring for women with MS, suggesting that the disease is not associated with adverse pregnancy or birth outcomes. On the other hand, there is little information in the literature regarding the role of mode of delivery in predicting the post-partum disease activity, pregnancy, and birth outcomes in women with MS. The aim of our review is to provide a brief summary of the available data on the role of mode of delivery in MS, and the eventual correlation with disease outcome.

Keywords: Multiple sclerosis, pregnancy outcome, delivery.

INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system and, together with epilepsy, the most common neurologic disorder affecting women of childbearing age.[1] Several prenatal and perinatal factors have been investigated in MS, founding modest associations with subsequent risk of MS for late initiation of prenatal care, lack of parental cohabitation at birth, elevated maternal pre-pregnancy body mass index, and maternal diabetes. In the past, there has been speculation about the possible role of pregnancy, together with other stressful life events, in the risk of developing a relapse, and the course of the disease.[2] Pregnancy involves a relative state of immunosuppression as the foetus carries paternally-derived antigens. It is likely that hormonal and cytokine changes during pregnancy are linked to a Th2-type immune response. In fact, a pathophysiological hypothesis, to explain the spontaneous remission of MS during pregnancy, is that pregnancy is associated with a decrease in cellular immunity and an increase in humoural immunity, and with a shift away from Th1 to Th2 responses; on the contrary, delivery is associated with an inversion of this balance and a shift from Th2 to Th1 response. Based on these assumptions, pregnancy is beneficial in patients with autoimmune inflammatory conditions such as MS.[3] With regards to the influence of pregnancy in modifying the disease-activity (i.e. the relapse rate and the progression of the disease), the large Pregnancy In Multiple Sclerosis (PRIMS) study reported that pregnancy status does not affect long-term prognosis in women with MS.[4] Little attention has been given to the possible association between mode of delivery and the risk of MS in offspring and in disease progression. It is well known that delivery represents a unique event in a woman's lifetime, with complex mechanisms controlling human parturition involving mother, foetus, and placenta. To this regard, we sought to review the current understanding of the putative role of the parturition in the risk of developing MS and in the modulation of the disease course. We believe

that gaining further knowledge on this topic might provide insight into additional treatment strategies for patients with MS.

PARTURITION AND MULTIPLE SCLEROSIS

The influence of pregnancy in median and long-term effects of MS is out of the scope of this review. Nonetheless, we have to underline that counselling women with MS about pregnancy has long been a matter of controversy. Until the late 1950s and 1960s, women were discouraged from considering pregnancy, which was believed to worsen the course of the disease, based on isolated case reports and small retrospective studies subject to many biases, such as recall bias for cases with a tragic outcome naturally.[5] Later, the PRIMS study[4] reported that the rate of relapses decreases during the pregnancy, increases during the first trimester of postpartum, then returns to the pre-pregnancy rate after delivery, leading to a major change in the counselling of women with MS. Only three factors seem independently predictive of an increase of relapses in the 3 month post-partum period: the number of relapses in the year before pregnancy, the number of relapses during pregnancy, and the duration of MS.[4] The possible role of breastfeeding is still under discussion.[6] Previously, it was described that maternal MS is more frequently associated with operative deliveries (caesarean section, use of forceps or vacuum extractor), but these data were not confirmed in a retrospective cohort study (analysing data from the British Columbia MS Clinics' database), which made comparisons between births to 432 women with MS and to a frequency-matched sample of 2,975 women without MS, and it found that maternal MS is generally not associated with adverse neonatal and delivery outcomes.[7] In the United States, the rate of vaginal delivery (VD) has reduced since 1996, reaching a level of 68.2% in 2007.[8] This trend is reflected in many parts of the world. Although a significant number of caesarean deliveries (CD) are performed for obstetric indications, some are simply because of maternal request. Concurrent with the trend of increasing CD numbers, the frequency of autoimmune diseases has increased, such as MS.[9] The occurrence of these diseases seems to be higher in more affluent, Western, industrialised countries, even if data from non-industrialised country are limited.

MODE OF DELIVERY

Disease Development

Several theories have emerged suggesting that environmental factors may contribute to the development of the disease. Among them, the hygiene hypothesis suggests that an exposition to clean environment, especially in early childhood, may contribute to the development of an abnormal immune system.[10] The interplay between the emerging microbial ecology of the gastrointestinal tract and the developing mucosal immune system serves as a backdrop for a relationship between CD and the emergence of autoimmune diseases. With the highly immunoreactive intestine serving as the largest surface area of the body that is exposed to a number of infective agents, especially a vast array of luminal microbes and antigens, it is intriguing to speculate that the intestinal environmental interaction during early development of the immune system may relate to these diseases. One intriguing component of this speculation relates to the early development of the intestinal microbiota, the developing immune system, and the early influence of CD versus VD on these phenomena. It has been suggested that different initial exposures depend on mode of delivery (VD versus CD). The microbes that develop in the intestine during either CD or VD may lead to changes in long-term colonisation and subsequent altering of immune development. Most current literature suggests that the gastrointestinal tract of a normal foetus is sterile. During birth, and rapidly thereafter, bacteria from the mother and the surrounding environment colonise the infant's gut. The long-term sequelae or impact of this difference in exposure on the child has yet to be determined. Although there is an increasing body of evidence that the intestinal microbiota play an essential role in the postnatal development of the immune system, the mechanisms remain poorly understood.[10] A case-control study (based on 449 MS cases recruited from the Isfahan MS Society database and 900 of their healthy siblings) reported a 2.3 to 2.7-fold increased risk of MS among the persons delivered by caesarean section, as compared to their VD siblings.[11] Information about mode of delivery and other perinatal characteristics were collected; however, they were based on self-reports.[11] Later, in a nationwide register-based cohort study

that included all individuals born in Denmark from 1973 to 2005, the association between being delivered by caesarean section and the risk of developing MS later was assessed.[12] The cohort of individuals, born from 1973 to 2005, consisted of 1,727,747 persons of whom 86.2% were born vaginally and 12.4% by CD. During follow-up, 645 women and 285 men were diagnosed with MS. Overall, the effect of CD on the subsequent risk of MS (RR = 1.17; 95% CI: 0.92–1.46) was not observed, when adjusted for age, calendar period, birth order, birth weight and gestational age.[12]

The role of mode of delivery in modulating various endocrinological axes in mother and offspring was scarcely studied. Concentrations of epinephrine (EP), norepinephrine (NOR), adrenocorticotropic hormone (ACTH), cortisol (CORT), prolactin (PRL), corticotropin-releasing factor, and beta-endorphin (BE) were investigated. It seems that CD is associated with significantly lower maternal concentrations of EP, NOR, ACTH, CORT, PRL, and BE, and lower newborn levels of EP, NOR, and CORT compared with all other modes of delivery. In a prospective observational study, concentrations of EP, ACTH and BE differed significantly in newborns delivered by normal VD, VD with epidural anaesthesia, and ventouse extraction. Since the role of hormones in the pathogenesis of MS has been widely studied, we may postulate that mode of delivery can influence hormone levels, increasing the risk of developing MS.[13] Data regarding a possible enhanced risk of MS in the offspring born from CD has to be confirmed in different epidemiological settings (e.g. population-based studies) and, the hypothesis that the intestinal microbiota and stress hormone levels could play an essential role in the postnatal development of the immune system and, as such, in the risk of MS, needs further attention.

Disease Progression

Regarding the influence of mode of delivery in predicting the postpartum disease activity, the data provided so far seem to show a lack of association between CD and worsening of the disease.[14] A recent Italian prospective study, collecting data on 423 pregnancies in 415 women with MS, found that 44.4% of patients underwent CD and 18.5% epidural analgesia (EA).[15] In the multivariate analysis, CD was not associated with a higher risk of postpartum relapses or disability progression (assessed by Expanded Disability Status Scale).[15] Regarding the EA, no controlled studies exist to assess any negative or positive associations with MS. It was described that the relapse incidence in women who received EA for VD did not significantly differ from that in women who received local infiltration analgesia,[16] and in the PRIMS,[4] women with or without EA did not differ in their risk of postpartum relapses. Also, no effect on disability progression has been found.[4] In the Italian cohort study, EA was performed in 18.5% of the patients, and it did not significantly affect postpartum relapses or disability progression.[15]

Several studies have investigated the role of mode of delivery on disease activity and pregnancy outcomes. Amato et al.[17] showed, in a large cohort of MS women, that CD together with IFNβ exposure were the only predictors of preterm delivery. Mode of delivery can also be influenced by disability. In a retrospective multicentre study, the authors found no factors can predict the risk of relapse during or after pregnancy, although they reported CD is associated with higher Expanded Disability Status Scale (EDSS) at conception and that SPMS patients are more likely to need a CD.[18] A recent study investigated the role of EA and CD in postpartum relapse. They found no correlation between EA, CD and postpartum relapse and disability.[19] An old study pointed to an increased risk of relapses after the administration of bupivacaine greater than 2.5 mg/ml.[20] However, this finding was not confirmed in more recent investigations.[21] With regards to the role of breastfeeding in the disease's progression, only conflicting data are provided to date. One hormone that is elevated during breastfeeding, but falls rapidly in the absence of breastfeeding is prolactin, suggesting a possible beneficial effect of prolactin postpartum, although several studies have correlated hyperprolactinemia with relapses of MS.[22]

In Table 1 we summarise the percentages about mode of delivery in the most relevant studies investigating pregnancy outcome in MS patients.[17-19,23-28]

CONCLUSION

In planning a pregnancy, women with MS usually want to know both the impact of a potential pregnancy on the disease, as well as the impact

Table 1. A summary of delivery mode data presented in studies investigating pregnancy outcomes in MS patients.

Author (date)	Study design	Therapy	Number of pregnancies	Caesarean delivery (%)	Vaginal delivery (%)	Relapse before pregnancy	Relapse during pregnancy	Relapse post pregnancy
De Las Heras et al. (2007)[18]	Retrospective, cohort	DMD	62*	10 (17.9%)	46 (82.1%)	N/A	N/A	N/A
Patti et al. (2008)[23]	Restrospective, cohort	IFN beta	36	28 (77%)	8 (22%)	N/A	N/A	N/A
Fernandez Liguori et al. (2009)[24]	Restrospective, cohort	IFN beta, GA	103	41 (39.8%)	62 (60.2%)	0.22° (0.12-0.32)	I 0.31° (0.10-0.52) II 0.19° (0.03-0.36) III 0.04° (0.00-0.12)	I 0.82° (0.42-1.22) II 0.50° (0.22-0.79) III 0.19° (0.03-0.36)
Amato et al. (2010)[17]	Prospective, cohort	IFN beta	75	34 (45.3%)	41 (54.7%)	N/A	N/A	N/A
Fragoso et al. (2010)[25]	Case series	GA	11	6 (54.5%)	5 (45.5%)	1.6±0.8**	0.4±0.9**	0.6±0.7**
Salminen et al. (2011)[26]	Case series	GA	14 (2 miscarriages)	2 (16.6%)	10 (83.3%)	N/A	N/A	N/A
Hellwig et al. (2011)[27]	Prospective, cohort	Natalizumab	35 (6 miscarriages)	14 (48.3%)	15 (51.7%)	0°°	I 1°° II 5°° III 2°°	6°°
Lu et al. (2012)[28]	Restrospective, cohort	IFN beta, GA	18	2 (11.1%)	16(88.9%)	N/A	N/A	N/A
Pastò et al. (2012)[19]	Prospective, cohort	DMD	349	155 (44.4%)	194 (55.6%)	0.4±0.7**	0.12±0.4**	0.45±0.7**

*See page 36 for abbreviations

I: first trimester; II: second trimester; III: third trimester;
*6 data about delivery method not available;
** mean ± standard deviation;
° annualised relapse rate (95% CI);
°° number of relapse.

of the disease on pregnancy and birth outcomes. Furthermore, the impact of therapy on pregnancy should be always discussed with patients. Women seeking to achieve pregnancy should generally discontinue therapy prior to attempting conception as current evidence has not reached a general consensus.[29] The data available in the literature seem to be reassuring for women with MS, suggesting that the disease is not associated with adverse pregnancy or birth outcomes. However, in detail, there is little information regarding the role of the mode of delivery in predicting the postpartum disease activity, pregnancy and birth outcomes in women with MS. Recent data about the putative role of mode of delivery and risk of developing MS in the offspring are conflicting. Two large studies investigated the association between mode of delivery and the risk of developing MS later;[11,12] due to the different design, a case-control and a nationwide cohort study, a comparison is difficult. Moreover, limitations due to chance, bias or methodological approach have to be considered in interpreting the results. Pregnancy is a stressor event and the modifications on the neuro-endocrine axis occurring during this event are well known.[13] Gaining more insight about the different profiles of risk regarding disease progression and risk of developing MS for the offspring, is a great opportunity to provide transparent, evidence-based information to both inquiring patients and to physicians who may be providing concurrent care.

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NEUROREHABILITATION AFTER STROKE

Rüdiger J. Seitz,[1] Leeanne M. Carey[2]

1. Centre of Neurology and Neuropsychiatry, LVR-Klinikum Düsseldorf, and Department of Neurology, University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany
2. Neurorehabilitation and Recovery, Stroke Division, Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre - Austin Campus, Heidelberg Victoria, Australia; Department of Occupational Therapy, LaTrobe University, Bundoora, Australia

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ABSTRACT

Recovery from ischaemic stroke is determined in the acute phase by the lesion impact of ischaemia and subsequently, by functional and structural network changes in the spared brain tissue. Neurorehabilitation supports the restitution of function using repetitive, learning-based and, more recently, technology-based training strategies.

Keywords: Stroke, ischaemia, recovery potential, brain lesion, fibre tracts, structural connectivity, functional connectivity, rehabilitation, learning strategies, robot training, virtual reality.

PROGNOSIS OF ISCHAEMIC STROKE

Ischaemic stroke is an acute disease and one of the leading causes of persistent disability in Western countries.[1] It results from an interruption of cerebral blood supply, with subsequent ischaemic brain damage bearing a dubious prognosis. Recovery of the deficits of motion, sensation, cognition, or emotion resulting from stroke, depends on cerebrovascular factors and mechanisms of tissue-remodelling, ranging from hours to many months.[2,3] Thrombolysis has opened new avenues to substantially reverse the neurological deficits in the acute phase after stroke.[4-6] However, even large brain infarcts may lead to only minor and transient deficits that resolve completely within a couple of hours when they spare brain areas critical for motion, somatosensation and vision. This is illustrated in a patient who presented with transient ischaemic attack consisting of a two-hour period of abnormal sensation of her left hand and arm, and in whom magnetic resonance imaging (MRI) showed a large territorial infarct of cardioembolic origin (Figure 1). Thus, minor clinical symptoms may be caused by substantial brain lesions. However, this example also shows that the recovery from stroke commences early after the ischaemic event. The most important mechanism for early recovery is related to rapid arterial recanalisation and reperfusion of brain tissue. In the acute phase of stroke it is difficult to predict the degree of ultimate recovery, since even small infarcts may be caused by severe and life threatening diseases of the heart.[7] Moreover, a low socioeconomic status impairs the rate of functional recovery.[8] Finally, while longitudinal observations have shown that the neurological state by day 4 predicts the long-term neurological outcome,[9,10] there is good evidence that minor neurological deficits remain that become apparent only upon proper testing.[11,12]

Recent developments in neurorehabilitation have aimed at tailoring rehabilitation methods depending on the deficit pattern of the patients. Neurorehabilitation approaches vary and may include very early mobilisation,[13] anti-gravity support for walking,[14] basic arm training, arm ability training,[15] constraint movement therapy,[16] somatosensory discrimination training,[17] and language therapy.[18] Learning-based approaches

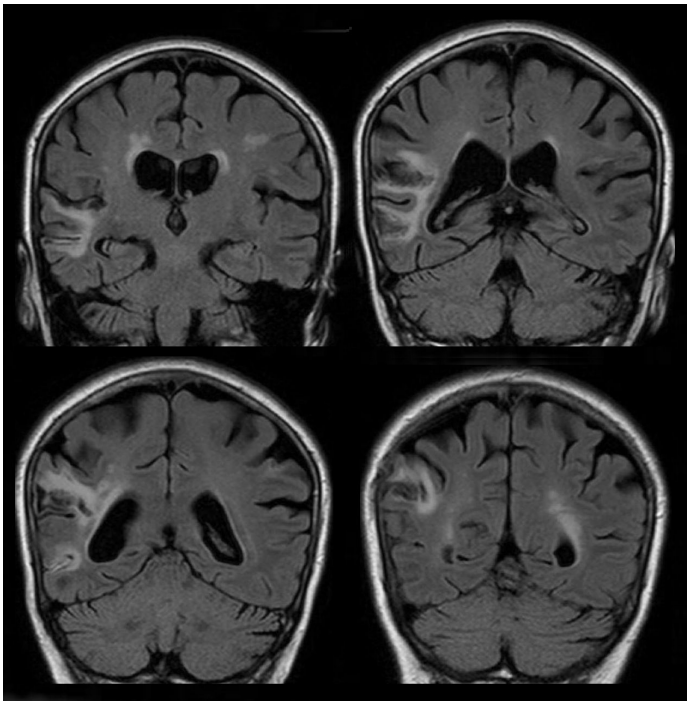

Figure 1. Transient sensory disturbance of the left hand that disappeared entirely within 2 hours, due to a large cardioembolic ischaemic brain infarct in the right cerebral hemisphere in a 72-year-old woman.

This coronal FLAIR-MRI was taken 6 weeks after the incident, showing involvement of the superior temporal gyrus and large parts of the inferior parietal lobule. The somatosensory cortex was spared. Note also the slight bilateral white matter changes typical of vascular encephalopathy probably due to inconsistent antihypertensive treatment.

are advocated, consistent with learning-dependent plasticity, and with the speciality of neurorehabilitation and its focus on the restoration and maximisation of functions.[19] It needs to be realised, however, that activities of daily living usually recover within 26 weeks after the stroke insult and are often accompanied by compensatory hand use.[20,21] This adaptation of the brain is functionally relevant but essentially not equivalent to cerebral plasticity affording restitution of function. Accordingly, the recovery potential of a stroke patient includes compensatory adaptation as well as functional restitution in the optimal and true sense of cerebral plasticity. The impact of the lesion on brain networks and knowledge of viable brain networks with capacity for plasticity is critical to target restorative stroke rehabilitation to the individual.[22]

RECOVERY POTENTIAL AFTER STROKE

The recovery potential is determined largely by the location and the volume of ischaemia and the cerebral infarct as determined on MRI.[3,23-28] Large brain lesions or small subcortical white matter lesions may affect multiple brain systems, resulting in complex neurological syndromes such as apraxia, spatial neglect or Gerstmann syndrome.[29-31] In particular, measures of fibre tract damage or cortical activations have been found to explain the recovery of motor,[23,32-35] language, somatosensory, and visual functions.[36-39] For example, the extent to which an individual patient will achieve good recovery of the upper limb function depends, in part, on the integrity of the corticospinal tract (CST) as determined by transcranial magnetic stimulation (TMS), on MRI, or with diffusion tensor imaging (DTI).[35,40,41] On clinical grounds, the degree of residual proximal arm movements determines the degree of recovery of hand function.[42] However, using clinical, neurophysiological and neuroimaging measures of CST integrity, a stepwise algorithm has been developed to predict upper limb function at the subacute phase.[40]

Beyond structural changes there are also functional changes in the brain following stroke. Regardless of subcortical or cortical location of infarction, these changes affect the perilesional tissue and the interhemispheric balance of activity.[43-45] Using paired-pulse TMS it was found that, within the first 7 days after a brain infarction, there is an enhanced cortical excitability in the cortex adjacent to the brain lesion but also in the contralateral hemisphere.[46-48] Notably, the enhanced perilesional excitability was transmitted to the intact motor cortex in the contralesional hemisphere. In keeping with these observations, functional MRI (fMRI), performed approximately 2 days after stroke, revealed an area in the ipsilesional postcentral gyrus and posterior cingulate gyrus that correlated with motor recovery approximately 3 months after stroke.[49] Furthermore, restoration of hand function, 3 months after stroke, was associated with highly lateralised activation of the affected sensorimotor cortex in fMRI, which developed over time.[50,51] In patients with a stable deficit in the chronic stage after stroke, a reduced strength of the precision grip of the affected hand was associated with an enhanced activation of the contralateral motor cortex in a demanding task involving the affected hand, while more severely

affected patients had greater motor cortex activation in the affected hemisphere.[52]

Apart from local activations, there is a pathological interhemispheric interaction between the ipsi and contralesional motor cortex as well as between the ipsilesional supplementary motor area (SMA) and contralesional motor cortex in patients with a single infarct lesion. This was shown by network type of analysis of functional imaging data.[53,54] In unilateral movements of the affected hand there was an inhibitory influence from the contralesional to the ipsilesional motor cortex, which correlated with the degree of motor impairment.[54] The importance of interhemispheric interactions and functional brain networks is further highlighted by evidence that disruption of interhemispheric connectivity predicts attention and motor performance deficits after stroke.[55]

Motor network connectivity strength was shown to correlate with motor outcome after stroke.[56] In chronic stroke patients, DTI-derived measures of transcallosal motor fibres, as well as the components of the ipsilesional corticospinal tract, could be used to explain the therapeutic response to rehabilitation: the more the diffusivity profiles resembled those observed in healthy subjects, the greater a patient's potential for functional recovery.[57] While these findings need to be substantiated by further investigations, they accord with the evidence from functional imaging, suggesting that the concerted action of both cerebral hemispheres is required for recovery. It is worthy of note that upper limb function is governed by a largely lateralised sensorimotor system, which allows identifications of the contribution of ipsilesional and contralesional changes in the motor and sensory system as well as network related changes in the brain contributing to recovery.

APPROACHES OF NEUROREHABILITATION

There are numerous reports about rehabilitative approaches to improve the neurological deficit following stroke.[58-60] By these measures, cortical and cortico-subcortical reorganisation (cerebral plasticity) is aimed at being enforced. The behavioural effects and neural mechanisms underlying evidence-based movement rehabilitation have been reviewed.[40] To date, most studies have been conducted in the chronic phase of recovery. Interventions that have been shown to improve motor function in the upper limbs and to influence brain activation in functional brain imaging and reorganisation, include constraint-induced movement therapy and task-specific interventions.[58,61,62] Notably, the intensity of the training rather than the type of targeted training appears to determine long-term improvement of motor function of the upper limbs.[63,64] Treadmill training was found to improve walking velocity, which correlated with brain activity in the posterior cerebellum in fMRI related to movement of the paretic limb.[65] Successful hand shaping and grasping of objects did not occur unless there was sufficient volitional control of finger and thumb extensions.[66] An important and largely neglected aspect of hemiparesis is the presence of spasticity that typically builds up progressively after stroke-counteracting voluntary movement. If botulinum toxin was combined with repetitive bilateral arm cycling training in chronic stroke patients, spasticity could be reduced. This was reflected clinically by a profound reduction of spasticity and a change of the cerebral activation pattern as evident from fMRI.[67]

The concept of 'learned non-use' was implemented in the so-called 'constraint-induced' therapy. It has been shown to be successful particularly when applied in the chronic state to moderately affected patients.[68,69] This beneficial effect of constraint-induced movement therapy is likely to be composed of focussing the patient's attention to the affected side. Imposing repetitive training results in improved motor function and enhanced functional brain activation in the partially damaged sensorimotor cortex.[32,69] Similar effects were achieved with bihemispheric direct cortical stimulation (DCS), which activated the affected motor cortex and inhibited the contralesional motor cortex.[70]

Mental training can also result in better functionality of the upper extremity and in greater gains of activities of daily living than standard physiotherapy.[71,72] FMRI revealed that motor imagery activated a widespread network of cerebral areas in motor, premotor and parietal cortex in both cerebral hemispheres.[56,72] In controlled trials, early after stroke, mirror therapy was found to improve the neurological status immediately after the intervention and at long-term follow-up.[73,74] Also, there is a transfer effect of the highly skilled hand to the affected hand in stroke patients.[75]

Based on the knowledge of postlesional pathophysiology it has been hypothesised that

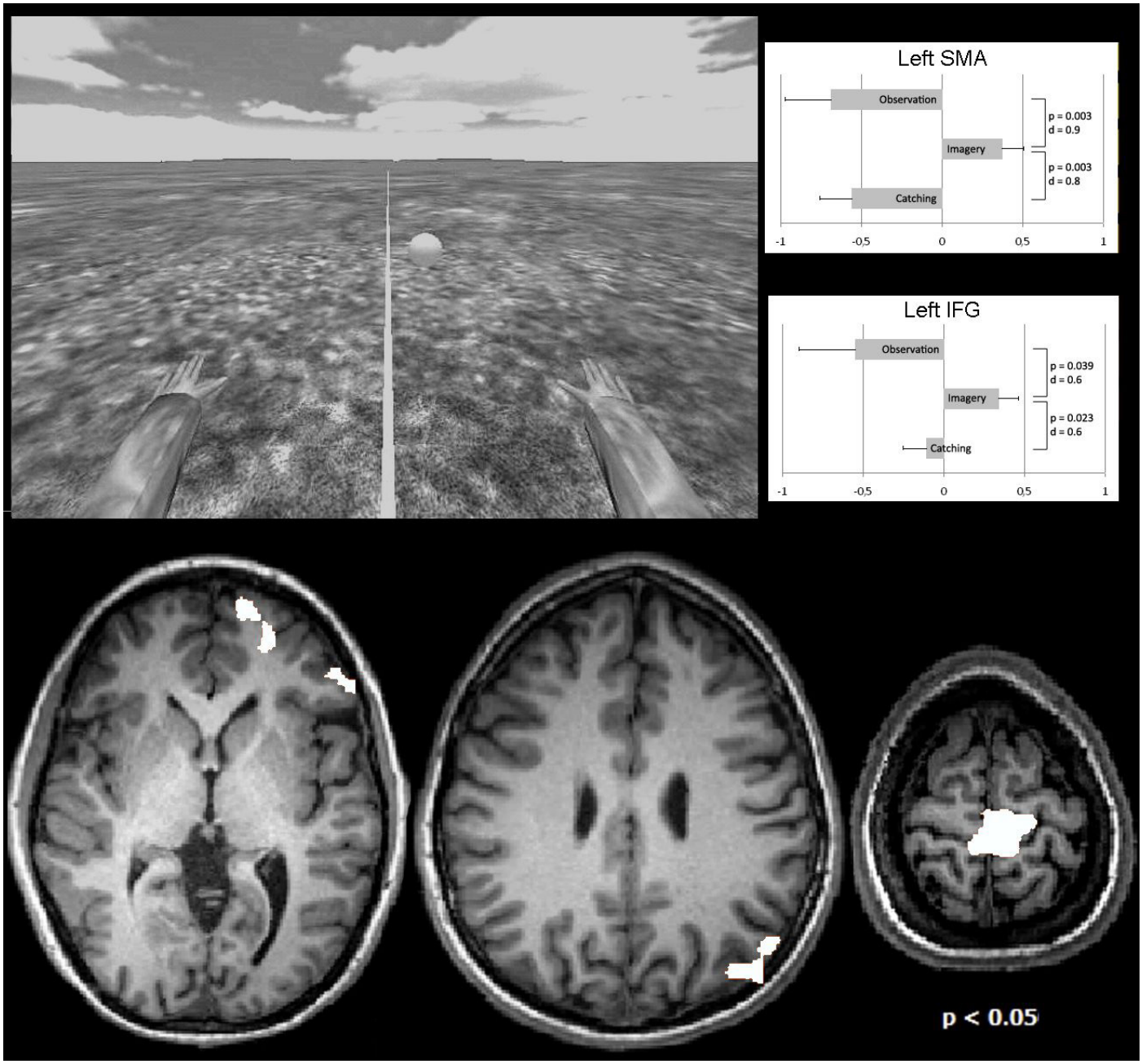

Figure 2. The Rehabilitation Gaming System.
Upper left panel: Virtual reality environment showing the two arms of the avatar and a sphere flying towards the viewer.
Lower panel (from left to right): Activation areas related to movement imagery in healthy volunteers located in the left anterior prefrontal cortex, the left inferior frontal gyrus (IFG), the left inferior parietal lobule, and the supplementary motor area (SMA).
Upper right panel: Strong activations during imagery in the left SMA and left IFG, no activation during simple observation, no change during actual catching in the left IFG.

the stimulation of the human brain can augment the effect of rehabilitation. The idea is to affect the threshold of cortical excitability which is abnormal after stroke. In fact, anodal stimulation of the affected motor cortex was found to augment motor skill acquisition.[76] Conversely, application of 1 Hz repetitive TMS of 10 minutes duration to the contralesional motor cortex, which down-regulates the contralesional motor cortex, improved the kinematics of finger and grasp movements in the affected hand.[77] This resulted in overactivity in the contralesional motor and

premotor cortical areas as found with fMRI. The combination of electrical stimulation of finger extensor muscles and tracking training over 2-3 weeks did not result in a greater improvement of dexterity of the affected hand, as assessed with the Jebson-Taylor Hand Function Test, than each intervention alone.[78] Subjects with an intact motor cortex showed a greater improvement than those who had direct involvement of the motor cortex. Similarly, in chronic stroke-induced aphasia, repetitive TMS over the left inferior frontal gyrus resulted in an increase of reaction time or error rate in a semantic task, suggesting restoration of a perilesional tissue in the left hemisphere.[79,80]

Also, to enhance the effect of rehabilitation, individually-tailored and adaptive robot-based rehabilitation techniques have been developed to provide a means for extended long-term training sessions.[81] The goal of these approaches is to maximise the effect of repetitive training while simultaneously limiting the demand of personal support per session and, thus, the economic expenditure.[82] For example, the Rehabilitation Gaming System (RGS) has been designed as a flexible, virtual reality-based device for rehabilitation of neurological patients. Recently, training of visuomotor processing with RGS was shown to effectively improve arm functions in acute and chronic stroke patients.[83,84] It was postulated that the RGS-based training protocol creates conditions that aid recovery by virtue of the human mirror neuron system. To test this hypothesis behind RGS, an fMRI study was performed which allowed identification of the brain areas engaged during performance of RGS.[85] The activation of a number of brain areas in the imagination condition including the left SMA, the left inferior frontal gyrus (IFG), the left posterior insula, the left postcentral gyrus, the left inferior parietal lobule (IPL), and the right cerebellum was observed (Figure 2). In fact, these areas constitute a widespread circuit of sensorimotor areas including key cortical areas of the human mirror neuron system.[86-88] This is consistent with earlier observations showing that the IFG and IPL are candidate areas for sensory control of action, movement imagery and imitation.[86-88]

Goal-driven attention and working memory are important in learning-based rehabilitation.[60] Rehabilitation may be viewed as 'an active process focused on facilitation of adaptive learning'.[60] Attention modulates neural plasticity and is involved in new learning.[89] Motivation and emotion help drive and prioritise attention.[90] Furthermore, attention and working memory share similar regions of activation in the brain.[91] The process of learning or relearning requires access to these functions and the brain networks that support them. It is therefore important to understand not only the focal brain lesion but also residual brain networks that can support recovery and learning. Interruption to these networks will impact on the process of recovery and ability to benefit from rehabilitation.

CONCLUSION

In summary, neurorehabilitation is a clinical subspecialty focused on the 'restoration and maximisation of functions' that have been lost due to brain injury.[92] The potential for recovery and ability to benefit from rehabilitation is impacted by interruption to brain networks as well as remote changes in the brain. Various rehabilitative approaches have been developed and tested. A learning-based approach is advocated to facilitate neural plastic changes and outcomes of restoration. Given individual variability in recovery and the interaction between brain networks involved in recovery, it is critical to identify not only the impact of the focal lesion but also viable brain networks that may be accessed during the recovery process.

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CURRENT ESSENTIALS IN INFLAMMATORY MYOPATHIES

Maren Breithaupt,[1] Jens Schmidt[1,2]

1. Clinic for Neurology, University Medical Center Göttingen, Göttingen, Germany
2. Department of Neuroimmunology, Institute for Multiple Sclerosis Research and Hertie Foundation, University Medical Center Göttingen, Göttingen, Germany

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ABSTRACT

Inflammatory myopathies are a heterogeneous group of acquired systemic diseases, which include dermatomyositis (DM), polymyositis (PM), necrotising myopathy (NM) and inclusion body myositis (IBM). All four disease entities share certain clinical characteristics, such as progressive muscle weakness and elevated muscle enzymes. Other characteristic-associated features such as skin involvement in DM or the detection of myositis-specific antibodies, may be indicative of a particular subtype. However, muscle biopsy is still essential for the diagnosis and shows distinct histopathological characteristics for each subtype of myositis. Treatment of inflammatory myopathies is still based on clinical experience, since placebo-controlled trials are scarce. While DM, PM and NM respond well to immunosuppressive treatment, IBM is usually resistant to immunotherapy. This review aims to give a concise overview and provide guidance for general management of myositis.

Keywords: Myositis, muscle inflammation, polymyositis, dermatomyositis, necrotising myopathy, inclusion body myositis.

INTRODUCTION

Inflammatory myopathies are a heterogeneous group of acquired systemic diseases which result in muscle weakness and disability. The four most common subtypes include dermatomyositis (DM), polymyositis (PM), necrotising myopathy (NM) and inclusion body myositis (IBM). They are characterised by distinct clinical presentations, histopathology and response to treatment. They all share certain clinical features such as progressive muscle weakness over a period spanning from weeks to years, elevated muscle enzymes and inflammation in muscle biopsy. In the sera of many patients, myositis-specific antibodies can be detected, some of which are associated with a specific phenotype.[1,2] Pathological examination on muscle biopsy is the key diagnostic tool to establish the diagnosis of myositis. Muscle magnetic resonance imaging (MRI) can be a useful tool to identify a target muscle for biopsy. There is a lack of evidence-based treatment guidelines for myositis due to the rarity of the disease. Expert opinions on treatment options are reviewed in this article.

DERMATOMYOSITIS

Dermatomyositis (DM) is a multisystem autoimmune disease, which presents with proximal muscle weakness and typical skin manifestations. It affects adults and children alike, and is referred to as juvenile DM (JDM) when patients are under the age of 18 years old. Women are more often affected than men. JDM is the most common form of inflammatory myopathy among children. The average age of onset in JDM is 7 years old, and girls are affected more often than boys with a ratio of 5 to 1.[3] In adults, the age of onset is usually between 45 and 65 years old.

The majority of patients present with painless, symmetric proximal muscle weakness, which evolves over a period of weeks to months, and usually shows elevated muscle enzymes such as creatine kinase (CK). Involvement of oropharyngeal

muscles can be present, resulting in dysphagia and dysarthria. In addition to muscle weakness, typical skin manifestations such as an erythematous rash, a heliotrope rash and oedema around the eyes, periungual telangiectasia or Gottron's papules are present. Skin features can accompany or even precede muscular symptoms. The rash is usually located in the face, neck, torso, and extensor surfaces of the extremities. Infrequently, adult patients also show subcutaneous calcifications, ulcerations and skin atrophy, although those features are more common in JDM.[4,5]

Some patients present with typical skin features, but lack muscle involvement. This specific subtype is referred to as amyopathic dermatomyositis (ADM).[6]

DM is frequently associated with other medical conditions, two of which are: interstitial lung disease (ILD) and malignancies.[7-9] In the past, different myositis specific antibodies have been identified, which are associated with specific phenotypes. Anti-Mi-2 autoantibodies can be found in about 20% of patients and are associated with the typical phenotype of DM. In ADM, an antibody (Anti-CAMD-14) acting against melanoma differentiation-associated gene 5 (MDA5) has been identified. The presence of these antibodies is associated with the development of a rapid progressive ILD and poor prognosis.[10] Anti-P155/140 has been reported in 13-21% of the patients with DM and is associated with an increased risk for malignancy.[11]

Electromyography (EMG) in patients with DM typically shows polyphasic motor units of small amplitude and of short duration, as well as spontaneous activity (positive sharp waves and fibrillations). MRI may detect signal abnormality or oedema, while in the later stages of the disease muscle atrophy or fatty transformation is more evident.

Muscle pathology in DM is marked by perifascicular atrophy, degeneration and regeneration of muscle fibres and perivascular inflammation. Complement activation and formation of the membranolytic attack complex may lead to damage of endothelial cells and capillaries, thereby causing muscle fibre ischaemia.[12,13] It has recently been proposed that type I interferons might play the leading role in the pathogenesis of DM.[14,15]

POLYMYOSITIS

Polymyositis (PM) is a rare disease, which usually begins after the age of 18. Past diagnostic criteria differentiate PM from DM only by lack of skin alterations. As in DM, symptoms in PM include a subacute onset of proximal muscle weakness and elevated muscle enzymes. In addition, patients frequently complain of myalgia and tenderness, particularly upon examination. Studies suggest that PM has been over diagnosed in the past, since muscle biopsy was not considered, and the lack of specific clinical characteristics make it difficult to distinguish PM from other forms of myositis.[16]

EMG and MRI findings are the same as those in DM, and cannot be used to discriminate between the two disease entities.

Muscle biopsy is essential to differentiate PM from other inflammatory myopathies. Histopathological features of PM include endomysial inflammatory infiltrates, necrosis and regenerating muscle fibres of different size. The inflammatory infiltrates consist of macrophages and mononuclear CD8+ T cells, which invade non-necrotic muscle fibres expressing the MHC class I antigen.[17,18]

As in DM, PM patients can develop complicating extramuscular syndromes such as ILD and myocarditis. Previous studies state that cardiological complications account for 10-20% of deaths in PM patients.[19]

NECROTISING MYOPATHY

Several years ago, immune-mediated necrotising myopathy (NM) has been identified as a specific subtype of myositis.[18,20] Clinical symptoms are indistinguishable from PM and include proximal muscle weakness, myalgia, and considerably elevated muscle enzymes. EMG and MRI yield similar results as in other inflammatory myopathies. Its aetiology is multifactorial and NM can be associated with malignancies, intake of statins or connective tissues diseases. Myositis-specific antibodies against the signal recognition particle (anti-SRP) are frequently found in the blood of NM patients with an average age at disease onset of 48 years, and seem to be associated with an unfavourable prognosis concerning the disease progression.[21,22] Recently, another antibody reacting against 3-hydroxy-3-methylglutaryl-

coenzyme A reductase (HMGCR) has been described.[23,24] HMGCR is the key enzyme in cholesterol biosynthesis and can be inhibited by statins. Anti-HMGCR antibodies have been identified in statin-exposed patients above the age of 50, while non-exposed patients tend to be younger.[24] Recently, it has been recognised that statins may not only cause a toxic myopathy, but can also trigger an autoimmune necrotic myopathy. Statins lead to an up-regulation of HMGCR-expression. Therefore, one hypothesis is that in presence of other risk factors such as environmental influences of genetic susceptibility, statins might activate an autoimmune process if anti-HMGC-antibodies are present.[24]

The pathological features of NM are distinct from PM and DM because the muscle biopsy lacks endomysial inflammation. Muscle fibre necrosis is the main characteristic finding on muscle biopsy.[25] In some patients perivascular deposits of complement can be found. Inflammatory cells are scarce and are mainly represented by macrophages. The exact pathogenesis of NM is still unclear. Several studies suggest a humoural autoimmune process, which is supported by the fact that complement deposits and autoantibodies are present.[18]

TREATMENT STRATEGIES IN DM, PM AND NM

Since inflammatory myopathies are autoimmune-mediated disorders, therapeutic options include immunosuppressants and immunomodulatory drugs. Treatment goals are to suppress inflammation, stop muscle necrosis and regain muscle strength. Controlled trials are scarce and are difficult to carry out due to the rarity of these diseases.

Empiric data show that corticosteroids are effective in the treatment of DM, PM and NM. Based on experience, high-dose corticosteroids are the initial treatment of choice. Patients are usually treated with a standard dosage of 1 mg/kg body-weight per day for at least 2-4 weeks. If severe symptoms are present, treatment may be initiated with an intravenous application of 500 to 1,000 mg prednisolone daily over a period of 3-5 days, followed by high-dose oral treatment as mentioned above.[27] Depending on the clinical stabilisation, prednisone dose is tapered slowly until the maintenance dose of usually 5 to 10 mg per day is reached. However, upon initial clinical stabilisation, many patients deteriorate when the prednisolone dose is lowered. Frequently, the use of immunosuppressant drugs such as azathioprine, methotrexate or mycophenolate mofetil, are needed as a steroid-sparing agent. The most recent Cochrane Review found four studies comparing different immunosuppressant with each other. None of the studies could find significant variation between the different drugs.[27] Patience is needed since the clinical effect of these drugs may takes 3-6 months to evolve. Methotrexate may cause pneumonitis as a severe side effect, which can be difficult to distinguish from the ILD seen in myositis patients.

CK levels do not always reflect disease activity, but may be decreased under the immunosuppressant therapy.

In rapidly progressive cases or when steroid-response is poor, intravenously applied immunoglobulins (IVIG) are the treatment of choice.[28-30] The initial dosage is 2 g/kg body weight every 4-8 weeks, depending on the clinical response.

Etanercept, a TNF-α inhibitor, has been investigated in a double-blind, placebo-controlled study of 16 patients with DM. Results did not demonstrate a benefit regarding muscle strength, but a steroid-sparing effect was observed.[31] After several promising case series,[32,33] recently, the results of a randomised, double-blind, placebo-controlled trial of rituximab in the treatment of adult and juvenile myositis have been published.[34] 83% of the patients, who had been unresponsive to prior immunosuppressive treatment, showed improvement of muscle strength during the 44 weeks of the trial.

INCLUSION BODY MYOSITIS

Sporadic inclusion body myositis (IBM) is the most common form of inflammatory myopathies above the age of 50 years.[35] In contrast to PM and DM, men are more often affected than women.

IBM is characterised by slowly progressive, often asymmetric muscle weakness, which can affect proximal and distal muscle groups and relentlessly leads to disability. Frequently, hand and finger flexors and knee extensors are affected early during the course of the disease, accompanied by severe muscle atrophy. In contrast to other forms of

myositis, involvement of oropharyngeal muscles is present in more than 60% of IBM patients, which leads to dysphagia and complications such as aspiration pneumonia.[36] CK levels may only be mildly elevated. EMG findings are similar to those found in other myositis; in addition, nerve conduction may show peripheral sensory axonal neuropathy. Muscle MRI yields similar findings as in DM, but can emphasise asymmetrical distribution of muscle involvement. Recently, an auto-antibody in IBM has been demonstrated: anti-Mup44 targets the cytosolic 5'-nucleotidase 1A, an enzyme highly abundant in skeletal muscle, which seems to play a role in DNA repair metabolism.[37,38] Larger series are awaited to confirm the sensitivity and specificity of this antibody.

Histopathology shows endomysial inflammation mediated by CD8+ T cells and macrophages similar to PM. In addition, MHC class I up-regulation is present on necrotic and non-necrotic muscle fibres as a surrogate marker of inflammation. In addition, degenerative features are present and include protein accumulation with intrafibre deposition of β-amyloid as well as vacuolar transformation, which clearly distinguish IBM from other forms of myositis.[39] The pathogenesis of IBM is still unclear.

Past diagnostic criteria for IBM defined by Griggs et al.[40] do not rely much on clinical features. Since not all characteristic histopathological findings may be present at the beginning of the disease, criteria, which include clinical features, are needed in order to allow early diagnosis. Revised diagnostic criteria have been compiled at a recent ENMC International Workshop.[41] According to these criteria, the classifications include clinico-pathologically defined IBM, clinically defined IBM, and probable IBM. Clinical and laboratory features include: a duration over 12 months, age at onset >45 years, CK no higher than 15-fold above the upper limit of normal, and knee extension weakness ≥hip flexion weakness and/or finger flexion weakness ≥shoulder abduction weakness. Pathological features include: endomysial inflammatory infiltrate, up-regulation of MHC class I, rimmed vacuoles and protein accumulation or 15-18 nm filaments.

THERAPEUTIC STRATEGIES IN IBM

Although the role of degeneration in the pathogenesis of IBM is still unclear, it might be one explanation why IBM seems to be resistant to immunosuppressive treatment. Unlike other forms of myositis, glucocorticosteroids have no, or only a transient effect on the disease progression and might even lead to deterioration.[42,43] Several studies on different immunosuppressants such as MTX, anti-T lymphocyte globulin, azathioprine, MMF, cyclosporine A and tacrolimus, did not show a beneficial effect on muscle strength or disease progression.[44-47] A pilot trial of etanercept and a small open trial of alemtuzumab could not show sustained improvement regarding muscle strength or function.[48,49]

Clinical trials with IVIG failed to demonstrate efficacy, except for some improvement of the dysphagia in one of the studies.[50,51] Since dysphagia is frequent in IBM and associated with a high mortality due to aspiration and malnutrition, IVIG presents a therapeutic option in patients with dysphagia. In addition, physical therapy and logopaedic training are advisable early in the course of the disease.[52,53]

CONCLUSION

Inflammatory myopathies comprises of four disease entities; DM, PM, NM and IBM, which usually can be distinguished by characteristic clinical, histological or pathological features. Treatment management is still based on clinical experience since large, controlled trials are lacking, mostly due to the rarity of these diseases. While DM and PM respond well to immunosuppressants, the treatment of IBM remains challenging. Further understanding of the pathogenesis is needed in order to identify suitable therapeutic targets.

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MOTOmed Movement Therapy mobilises sufferers of neurological disease

THE LOSS of independence is often the most distressing outcome following neurological trauma. Side-effects of diseases such as multiple sclerosis, stroke, paraplegia, tetraplegia, spasticity, Parkinson's disease and other neurological and geriatric conditions, can have a catastrophic effect on a person's mobility, and therefore their quality of life.

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Much-needed training can also be made accessible for both those confined to bed, or for children, with the MOTOmed letto2 and gracile12 systems respectively, without compromising on any special features or therapy options. All three models offer passive movement of the legs and arms, via integrated motor, and ServoCycling, a motor-assisted active training technique.

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'Mini-brains' grown from stem cells

"This is one of the cases where size doesn't really matter."

Dr Juergen Knoblich, Institute of Molecular Biotechnology, Austria

MINIATURE human brain cells have been grown in a laboratory for the first time, with researchers extremely positive that this can open new areas of research into treating disorders such as schizophrenia and autism.

Initially cultured as human stem cells, these were eventually developed into 'cerebral organoids', or mini-brains, comprising of several distinct brain regions. This is the first time that scientists have managed to replicate the development of brain tissue in three dimensions.

Doctors Juergen Knoblich and Madeline Lancaster, from Austria's Institute of Molecular Biotechnology, and fellow researchers at the Edinburgh University Human Genetics Unit in the UK, began with human stem cells, growing them using a unique combination of nutrients designed to get the most out of the cell's innate ability to organise into complex structures.

The tissue first developed into neuroectoderm, the layer of cells in the embryo from which all components of the brain and nervous system develop. Portions of tissue were then embedded in a scaffold and placed into a spinning bioreactor, which provided oxygen and nutrients for cerebral organoids development.

Primitive structures that could be recognised as developing brain regions include the retina, choroid plexus and cerebral cortex. After 2 months, the organoids reached their maximum size of approximately 4 mm. Though still small and quite far from becoming a functional brain, the important factor, according to Dr Knoblich, is that they contain neurons and distinct types of neutral tissue.

"This is one of the cases where size doesn't really matter," Dr Knoblich told reporters. "Our system is not optimised for generation of an entire brain and that was not at all our goal. Our major goal was to analyse the development of human brain [tissue] and generate a model system we can use to transfer knowledge from animal models to a human setting."

The study of the miniature brains holds potential in the further understanding of neurological disorders, with Dr Knoblich's team already able to model the development and cause of the rare condition, microcephaly.

Human brain-to-brain interface: New era of mind control

HUMAN-TO-HUMAN brain interface, in which one researcher was able to transmit a brain signal through the internet to control the hand of another, has been developed at the University of Washington, USA.

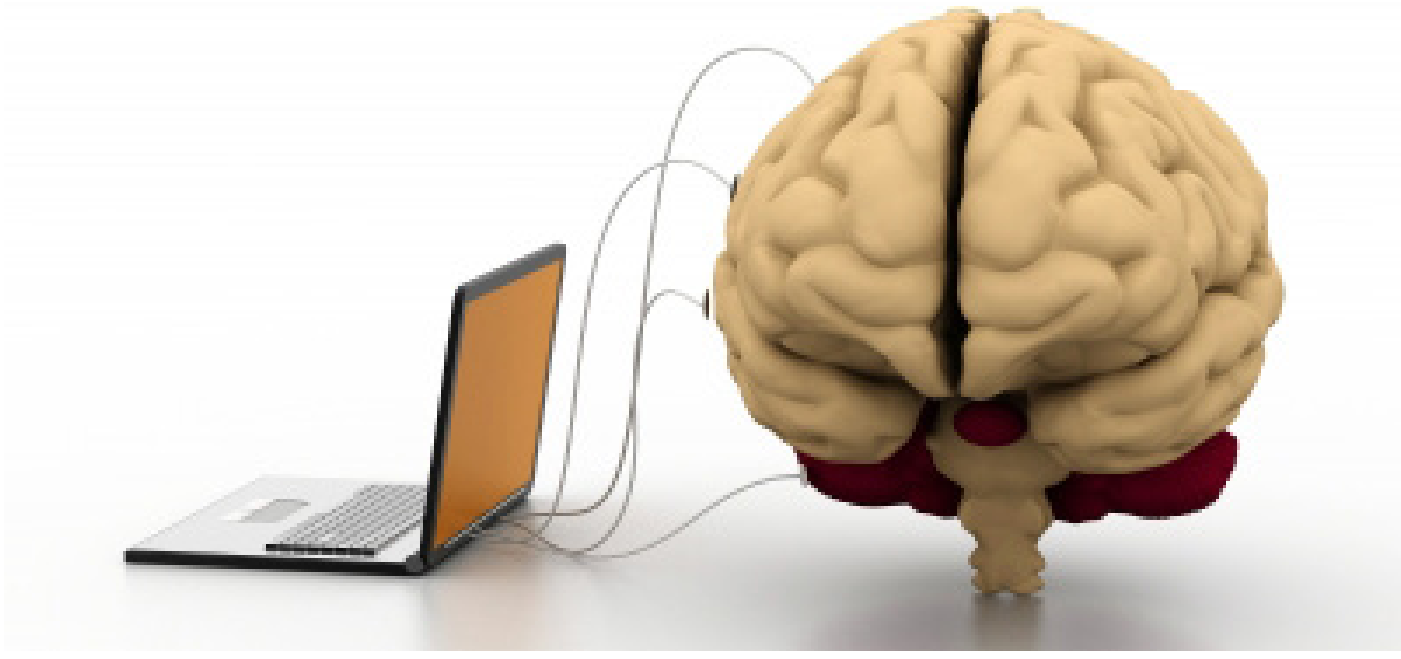
Prof Rajesh Rao has been working on brain-computer interface over the past decade, collaborating with Prof Andrea Stocco at the University of Washington's Institute for Learning and Brain Sciences.

Prof Rao was wearing a cap with electrodes connected to an electroencephalography machine, which reads electrical activity in the brain. Prof Stocco was in another lab across campus, wearing a purple swim cap marked with the stimulation site for the transcranial magnetic stimulation coil directly placed over his left motor cortex, which controls hand movement.

Prof Rao was playing a videogame and as he looked at a screen at the point where he was supposed to fire a virtual cannon at a target, he visualised himself moving his right hand to press the cursor. Prof Stocco instantaneously moved his right finger to press the space bar on the keyboard in front him, despite wearing noise reduction earplugs not looking at a computer screen, describing the feeling as an involuntary twitch.

Brain signals from the sender are recorded, so when the computer detects imagined hand movements, a command is transmitted over the internet to the transcranial magnetic stimulation (TMS) machine. This causes the receiver's right hand to move.

"It was both exciting and eerie to watch an imagined action from my brain get translated into actual action by another brain," Prof Rao said. "This was basically a one-way flow of information from my brain to his. The next step is having a more equitable two-way conversation directly between the two brains."



New hope for multiple sclerosis patients

AN EXPERIMENTAL therapy could potentially treat multiple sclerosis without compromising the immune system, with the full study published in *Science Translational Medicine.*

In the Phase I study, white blood cells were used to transport myelin antigens into nine patients, reducing the immune reaction to the myelin by 50-75%. The intravenous injection, consisting of 3 billion white blood cells with myelin antigens, also did not produce any adverse effects.

"Our approach leaves the function of the normal immune system intact," senior author, Prof Stephen Miller of Northwestern University, Illinois, USA, said. "The therapy stops autoimmune responses that are already activated and prevents the activation of new autoimmune cells."

"In the Phase II trial, we want to treat patients as early as possible in the disease before they have paralysis due to myelin damage," Prof Miller noted.

This treatment also shows promise in treating other autoimmune and allergic diseases, with Prof Miller having previously shown that the therapy was effective at treating type 1 diabetes, asthma, and peanut allergies.

Genetic sequencing project finds new mutations

MUTATIONS which are responsible for a significant amount of low-grade gliomas (LGGs), and are vulnerable to current drugs in development, have been identified.

According to results published in *Nature Genetics*, researchers used whole genome sequencing on 39 paired tumours and normal tissue samples from 38 children and adolescents with different subtypes of LGG and related tumours called low-grade glioneuronal tumours (LGGNTs).

There were alterations present in two genes that occurred in a subtype called diffused LGG, the mutations accounting for approximately 53% of diffused LGG.

"We can now account for the genetic errors responsible for more than 90% of low-grade gliomas," said the study's corresponding author, Dr David Ellison, Chair of the St. Jude Children's Research Hospital, Department of Pathology, USA. "The discovery that FGFR1 and MYB play a central role in childhood diffuse LGG also serves to distinguish the paediatric and adult forms of the disease."

Amongst the findings, researchers also demonstrated that one of the mutations, FGFR1, caused tumours when introduced into the glial brain cells of mice that lacked the tumour suppressor gene Trp53.

"The finding suggests a potential opportunity for using targeted therapies in patients whose tumours cannot be surgically removed," added Dr Ellison.

Amino acids make brain cancer more aggressive

AN ENZYME involved in amino acid catabolism increases the aggressiveness of brain cancer, according to data published in *Nature Medicine*.

Tumours generally require significantly higher levels of energy to build cellular components, which are obtained from the consumption of sugar and amino acids. A number of tumours can catabolise glutamine, which is a vital building block of proteins while isocitrate dehydrogenase (IDH) is a key enzyme in amino acid decomposition.

"The study of the IDH gene currently is one of the most important diagnostic criteria for differentiating glioblastomas from other brain cancers that grow more slowly," Dr Bernhard Radlwimmer from the German Cancer Research Center said, speaking to *Science Daily*. "We wanted to find out what spurs the aggressive growth of glioblastomas."

In collaboration with scientists from other institutes including Heidelberg University Hospital, Dr Martje Tönjes and Dr Sebastian Barbus from Dr Radlwimmer's team, compared gene activity profiles from several hundred brain tumours. They aimed to find whether either altered or intact IDH show further specific genetic characteristics which might help explain the aggressiveness of the disease.

Radlwimmer's team made a significant observation where tumour cells with intact IDH genes produce BCAT1. The activity of the BCAT1 enzyme under normal conditions is responsible for breaking down branched chain amino acids.

When pharmacological therapies were used to block the BCAT1's effects, it was shown that the tumour cells lost their invasive capacity and released less glutamate neurotransmitter. The increase of glutamate is responsible for severe neurological symptoms such as epileptic seizures. When glioblastoma cells with blocked BCAT1 genes were transferred into mice, they no longer progressed into tumours.

"Altogether, we can see that overexpression of BCAT1 contributes to the aggressiveness of glioblastoma cells," Dr Radlwimmer said.

"The good news is that we have found another target for therapies in BCAT1. In collaboration with Bayer Healthcare, we have already started searching for agents that might be specifically directed against this enzyme."

Blood pressure drugs delay dementia

PATIENTS taking angiotensin-converting enzyme (ACE) inhibitors have a reduced rate of deterioration caused by certain types of dementia, it was reported in *BMJ Open.*

Records of 361 patients with dementia were analysed, and initial observations show that those who were taking ACE inhibitors showed a smaller decrease in their cognitive abilities compared to their counterparts who are not prescribed the drugs.

Scores on one cognitive test fell 1.8 points in those suffering from vascular dementia and Alzheimer's disease who took the drugs, compared with 2.1 points in those who did not take them.

According to the lead researcher Prof William Molloy, Professor of Gerontology and Rehabilitation at the University College Cork, Ireland, these significant findings hold an inexpensive way to ease the burden of dementia, with the effect potentially due to the drugs acting against brain tissue swelling, or improving the blood flow to the brain.

microRNA helps to diagnose Alzheimer's disease

CIRCULATING molecules, called microRNA (miRNA), can be a potential indicator for Alzheimer's disease, according to research published in *Genome Biology.*

There is a need to develop more sensitive methods of detection, as Alzheimer's disease can currently only be confirmed through either a brain biopsy, or a post-mortem.

Changes in the level of miRNA were analysed from blood samples of 48 people with Alzheimer's, and 22 unaffected controls. The results found 140 altered miRNAs levels in those who have Alzheimer's, 12 of which were made into a panel for testing. The 12 chosen miRNA were thought to be responsible for the regulation of 2,000 genes, including genes responsible for nerve cell development and the projection of nerve cells across the brain.

Another 202 blood samples from volunteers were also tested using the panel. The group of volunteers consisted of people both with and without Alzheimer's, as well as including patients with mild cognitive impairment, or other neurological conditions including multiple sclerosis, Parkinson's and schizophrenia.

Dr Eric Karran, Director of Research at Alzheimer's Research UK, said: "This is an interesting approach to studying changes in blood in Alzheimer's and suggests that miRNAs could be playing a role in the disease. The findings highlight the importance of continuing research efforts to understand the contribution of miRNAs to Alzheimer's, but the translation of this into a blood test for Alzheimer's in the clinic is still some way off.

"A blood test to help detect Alzheimer's could be a useful addition to a doctor's diagnostic armoury, but such a test must be well-validated before it's considered for use. We need to see these findings confirmed in larger samples and more work is needed to improve the test's ability to distinguish Alzheimer's from other neurological conditions."

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Recognising and responding to the growing need for innovative treatments related to the ageing global population, EVER Neuro Pharma strives to maintain its ethical conduct in all areas of business and human relations.

11th National Neuroscience Conference: Multiple Sclerosis 2013

2nd Dec 2013

London, United Kingdom

An opportunity to hear about emerging areas of research into the causes and risk factors of MS, to learn about MS clinical trials and current and emerging therapies. You will be kept up to date with treatment options for MS including relapsing emitting MS and progressive MS and gain insights into the management of some of the complications of MS including spasticity management as well as exchange ideas with leading practitioners in the field.

XX World Federation of Neurology World Congress on Parkinson's disease and Related Disorders

8th–11th Dec 2013

Geneva, Switzerland

The XX World Congress on Parkinson's disease and Related Disorders is an innovative educational forum for learning about the latest research and discoveries in aetiology, pathogenesis, potential diagnostic markers, and treatment modalities of Parkinson's disease and its related disorders.

The 2nd International Conference on Heart & Brain (ICHB 2014)

27th–1st Mar 2014

Paris, France

A unique meeting that unites cardiologists and neurologists in order to pursue a holistic approach to understanding the connection between the heart and the brain. As a leader in the emerging multidisciplinary field of neurocardiology, the biennial ICHB conference has set the standard in the rapidly growing field of integrated medicine that encourages a broad spectrum of knowledge for improved practice and patient care.

The 8th World Congress on Controversies in Neurology (CONy 2014)

8th–11th May 2014

Berlin, Germany

CONy Congress will raise the most dynamic and controversial topics facing clinicians in the fields of neurology in an exciting debate forum. The Congress will promote excellence in the field by seeking to shed light on ongoing and challenging debates and to bridge gaps between the expansion of information and its consolidation in clinical practice.

Joint Congress of European Neurology (EFNS/ENS 2014)

31st May-3rd Jun 2014

Istanbul, Turkey

The joint European Federation of Neurological Societies/European Neurological Society Congress will include 8 symposia, 23 workshops, 5 special sessions, 3 practical sessions and 3 interactive sessions. The topics will range from preclinical neuroscience to mechanisms of disease, treatment, and practical training.

The 4th International Conference Advances in Clinical Neuroimmunology (ACN 2014)

27th–28th Jun 2014

Krakow, Poland

The Conference will be devoted to recent advances in pathogenesis, diagnosis, and therapy of neuroimmunological disorders. The main topics include multiple sclerosis, GBS, CIDP, myasthenia gratis, immunological aspects of stroke, and neurodegenerative disorders of the CNS, paraneoplastic syndromes.

9th World Stroke Congress (WSC 2014)

22nd–25th Oct 2014

Istanbul, Turkey

WSC 2014 will present the latest research and techniques in treating and preventing stroke. Renowned experts along with the best and brightest young clinicians will have the opportunity to exchange ideas and information and lay the groundwork for future collaborations.

10th International Congress on Non-Motor Dysfunctions in Parkinson's disease and Related Disorders (NMDPD 2014)

4th-7th Dec 2014

Nice, France

NMDPD 2014 is a leading annual educational forum offering a unique opportunity to deliberate on brain diseases and how they contribute to cognitive decline, and to identify the specific psychological markers, biochemical and genetic factors of Parkinson's dementia and of dementia with Lewy bodies.


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