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NEUROLOGY

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INSIDE

Review of

JOINT CONGRESS OF EUROPEAN NEUROLOGY 2014

Istanbul, Turkey

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NEUROLOGY

Editorial Board

Neurology

Editor-in-Chief: Dr Rita Krishnamurthi

Senior Research Fellow, Programme Leader, Cerebrovascular Diseases Research Team, National Institute for Stroke and Applied Neurosciences, Auckland University of Technology, Auckland, New Zealand.

Welcome

I am pleased to introduce to you this second edition of the *European Medical Journal – Neurology*, in which the most important, game-changing, and groundbreaking discoveries are presented.

One of the hardest things to teach is experience, but to encourage the idea of thoughtful learning Dr Sue Yin Lim has presented two case studies of neurological dysfunction, in her paper: '*A scarlet enemy of the brain – a practical approach to diagnosis and management of cerebral amyloid angiopathy*.' In this paper, Dr Lim describes two patients, one who was admitted due to isolated focal cortical subarachnoid bleeding, and another who was admitted due to an intracerebral lobar haemorrhage. Dr Lim discusses the features which lead to the diagnosis of probable cerebral amyloid angiopathy, and also designed a series of questions and answers to explain the pathways and management of this condition.

According to the European Brain Council neurological disorders affect around 220.7 million people worldwide; this number is expected to rise in the future. For this reason there is an ever-growing need for new discoveries to be made and more research to be done within this area. This also demonstrates why meetings such as the Joint Congress of Neurology, which included the European Federation of Neurological Societies (EFNS) and the European Neurological Society (ENS), are so important.

In our 'Congress Review' section we have reported on some of the most important findings presented at the Congress. It was discovered that neuropsychiatric disorders, such as anxiety and depression, were common conditions in people who suffer from epilepsy. The study concluded that in order to detect these conditions early, the neurologist will need to test for these specifically and treat them accordingly; thus, benefitting and improving the quality of life for patients.

With regards to stroke: depression and psychosocial distress can both be independent risk factors; after stroke, patients can become depressed or develop post-stroke depression. These are very challenging conditions for these patients. Dr Dirk Sander wrote a very illuminating paper on the subject: '*Depression and psychological distress as risk factors for stroke and worse stroke recovery: clinical implications and therapeutic options*,' which suggests new treatment options that are available to stroke patients who experience depression, and the preventative strategies which can be implemented to prevent post-stroke depression.

The aim of this journal is to disseminate up-to-date knowledge and techniques, which will hopefully influence your daily practice as well as benefitting and improving the lives of your patients. We hope that this edition proves to be an invaluable source of information.

Spencer Gore
Director, European Medical Journal

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Foreword

Dr Rita Krishnamurthi

Senior Research Fellow
Auckland University of Technology, New Zealand.

Dear Colleagues,

Welcome to the second edition of the *European Medical Journal - Neurology*. This journal is aimed towards those with an interest in the discipline of neurology, from postgraduate level upwards, with peer-reviewed articles addressing various aspects of neurological disorders' aetiology, prevention, treatment, and management.

This journal features articles written by internationally renowned academics and researchers, addressing the most important and chief developments within the field of neurology. This issue includes: an interesting article concerning imaging and treatment decisions in seizures and epilepsy, an insightful paper detailing how depression and psychological distress can be risk factors for a stroke, and a paper discussing the practical approaches that should be taken when diagnosing and managing cerebral amyloid angiopathy.

This issue reports on the highlights of the European Federation of Neurological Societies and European Neurological Society (EFNS-ENS) Joint Congress of European Neurology, 31st May-3rd June, 2014, which was held in Istanbul, Turkey. This scientific meeting offered the ideal platform for continuing education in all fields of neurology, covering a broad spectrum of topics with state-of-the-art lectures by acknowledged experts. EFNS and ENS are dedicated to providing the highest quality of continuing medical education, as well as to encourage professional education opportunities.

> "The EFNS-ENS merge into the European Academy of Neurology, set out in Istanbul, leads us into a new era in the field of neurology in Europe."

Plenary session presenters included Professors V. Hachinski, W.D. Heiss, G.L. Lenzi, R.A.C. Hughes, J. Olesen, S. Davis, and M. Brainin, to name but a few. There were also a number of teaching sessions covering various aspects of diagnosis and management of neurological disorders. The EFNS-ENS merge into the European Academy of Neurology, set out in Istanbul, leads us into a new era in the field of neurology in Europe. After such a success, I hope you will join us for the First Congress of the European Academy of Neurology, Berlin, Germany, 2015.

I hope you will benefit from reading this issue of *EMJ-Neurology* with articles and news features covering some of the most exciting and promising areas in neurology.

Kind regards,

Rita Krishnamurthi

Senior Research Fellow, Programme Lead, Cerebrovascular Diseases Research Team, National Institute for Stroke and Applied Neurosciences, AUT University, Auckland, New Zealand.

JOINT CONGRESS OF EUROPEAN NEUROLOGY 2014

ISTANBUL CONVENTION CENTER, ISTANBUL, TURKEY

31ST MAY – 3RD JUNE 2014

Welcome to the *European Medical Journal* review of the Joint Congress of European Neurology (EFNS-ENS)

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ISTANBUL CONVENTION CENTER, ISTANBUL, TURKEY
31ST MAY – 3RD JUNE 2014

Welcome to the *European Medical Journal* review of the Joint Congress of European Neurology 2014

This year's Joint Congress of European Neurology, hosted by the European Federation of Neurological Societies (EFNS) and the European Neurological Society (ENS), witnessed the end of an era for these two societies, but the beginning of a new age in neurological studies, by merging the two under the European Academy of Neurology (EAN).

To continue education in the field of neurology was the aim of this Congress, and it not only achieved this aim, it surpassed it. More than 8,000 European and non-European delegates attended this event, which consisted of 120 sessions presented by international experts and discussed the latest and most important trends and highlights of modern neurological research and therapy. The topics discussed included dementia, epilepsy, stroke prevention and treatment, multiple sclerosis (MS), headaches, and neuropathies. The most important and game-changing scientific findings were reported in more than 1,800 abstracts.

Istanbul, Turkey provided an excellent backdrop to this Congress which ran from the 31st May - 3rd June, 2014. Istanbul truly represents a country of diversity, discovery, and change; on the one hand it harbours Asian influences, while on the other it embraces its European partners, and as such, it is a city which constitutes a mosaic of many civilisations and cultures combined.

Mirroring the city in which it was based, this unique Congress presented some of the most ground-breaking discoveries made to date, especially with regards to the early detection and prevention of Alzheimer's and Parkinson's disease. A study from Milan, conducted by Dr Daniela Galimberti, highlighted that circulating microRNAs could be the future of diagnosing

"Tackling major challenges has to involve everyone – not just researchers, not just participants, not just funders, not just governments."

Prof Martin Rossor, University College London Hospitals, London, UK

Alzheimer's disease (AD). Another study suggested that a combination of amyloidosis and neuronal injury biomarkers could be potential signatures of AD.

With regards to Parkinson's disease, it was shown that olfactory testing or transcranial ultrasound could help to detect the disease earlier than before, and when diagnosing the disease, neuropsychiatric comorbidities and non-motor symptoms are very important.

Within this field, discoveries such as these are important to the clinician, the patient, and their families. "Tackling major challenges has to involve everyone – not just researchers, not just participants, not just funders, not just governments. Patients will always be central to research, not only as participants but as sources of unique knowledge around the disease and increasingly as active researchers themselves as has been evidenced by examples of Citizen Science," said Prof Martin Rossor, University College London Hospitals, London, United Kingdom.

While a very difficult undertaking, new studies showing the benefits of personalised therapies and treatments for MS were presented. As current MS treatments can have many adverse effects, the drugs need to be targeted so that they can truly bring benefits to the patient. Although MS is still incurable, the use of biomarkers is helpful in advancing our knowledge and understanding of the disease.

It is through research, such as that presented at the Congress, that these diseases can become less of a burden for patients, and even possibly a thing of the past.

No longer ignoring those with epilepsy

PSYCHIATRIC comorbidities such as anxiety or depression have been shown to be common conditions in patients suffering with epilepsy. There is now a call for adequate treatment and testing of these conditions, which should improve the early detection of anxiety disorders.

"Up to 60% of people with epilepsy suffer from psychiatric comorbidities such as anxiety or depression, but the situation is still not getting the attention it deserves. This is very unfortunate because the insufficient awareness ultimately impedes the development of appropriate assistance for the group of people affected, and frequently results in inadequate care," said Dr Hannah Cock, St George's University, London, United Kingdom.

A British study highlighted that the 'Neurological Disorders Depression Inventory for Epilepsy' and the 'Emotional Thermometers' have proven to be effective screening questionnaires for depression, and they can also be applied in this setting to detect anxiety.

Dr Cock stated: "We have tested these conventional analogue tools on more than 200 people with epilepsy, but without depression, and conclude that both tests should be used as screening tools as an initial first step to rule out patients who are unlikely to have anxiety, as we are now using routinely in our service."

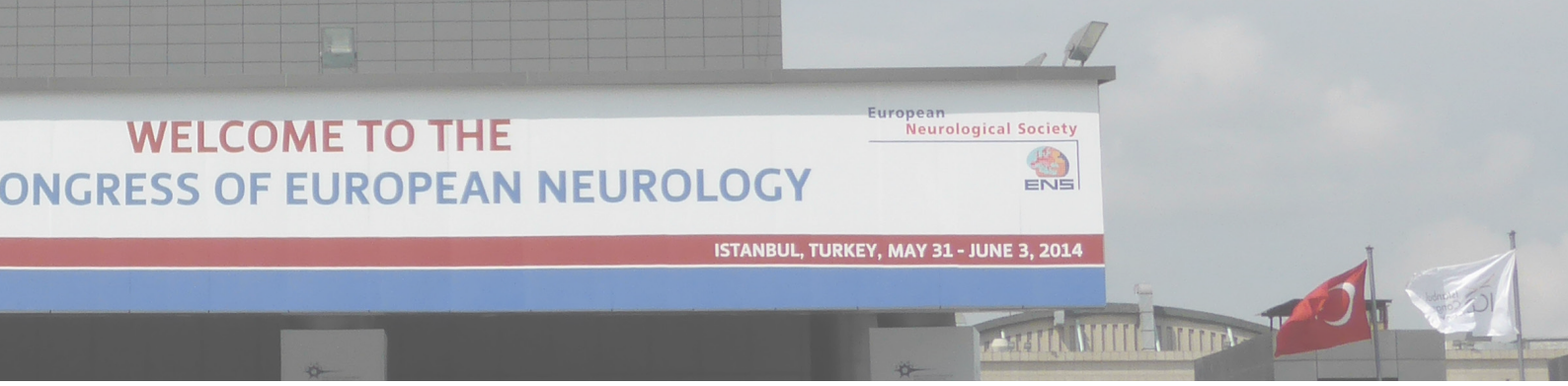
It was demonstrated, in a Norwegian study, that young men with epilepsy (mean age of 31.8 years) suffer significantly more with depression compared to healthy men in their age group (3.9% versus 2.5%, respectively). In another study comprising of 71,000 men, 650 of whom had epilepsy, 36.9% took antiepileptic drugs while the remainder were left untreated. Prof Nils Erik Gilhus, University of Bergen, Bergen, Norway, said: "That has unfortunate consequences. In all aspects related to mental health, untreated men with epilepsy fared worse than those treated."

It was also shown that epileptic women suffer more frequently from depression during pregnancy but are seldom treated. At the 18th week of pregnancy and during the third trimester, the prevalence of depression was higher in women with epilepsy than in non-sufferers.

A Turkish study demonstrated that over 40% of epileptic patients claimed to feel 'different' compared to non-epileptics, and 45% found it difficult getting a job because of their condition.

In light of these findings, there is a need not only to educate society about epilepsy, but to raise awareness of the problems among those affected.

> "Up to 60% of people with epilepsy suffer from psychiatric comorbidities such as anxiety or depression, but the situation is still not getting the attention it deserves."
>
> *Dr Hannah Cock, St George's University, London, UK*



One biomarker more for multiple sclerosis

> "With the increasing identification and use of biomarkers, a new and very promising chapter is opening in the management of MS."
>
> *Prof Aksel Siva, Istanbul University, Istanbul, Turkey*

PERSONALISED and more targeted therapies are being developed to treat patients affected by multiple sclerosis (MS) more efficiently and effectively.

Developing personalised therapy approaches for MS patients is a difficult challenge; the individual's response rate has to be monitored, and also, current MS treatments can have wide adverse effects, for instance bradycardia, immune mediated thyroid disease, or progressive multifocal leukoencephalopathy.

"This is why these drugs should be used in a targeted way, in patients for whom they can really bring benefits," said Prof Aksel Siva, Istanbul University, Istanbul, Turkey. "A lot of work therefore is being done to identify biomarkers that can reliably predict not only the efficacy of treatment, but also the side-effects that can be expected, so that the risks and benefits can be weighed up for each case."

A study from the Czech Republic showed that significantly higher levels of beta-2-microglobulin and interleukin-8 in cerebrospinal fluid (CSF) were found in MS patients compared to the control group. These findings are significant, as Prof Siva suggests: "With the increasing identification and use of biomarkers, a new and very promising chapter is opening in the management of MS."

According to an Austrian study, another aspect that should be analysed is the amount of iron detected in the brain. As iron accumulation increases rapidly, especially in the early phases of the disease, this should be monitored in patients, as well as sIFNAR2. Prof Siva proposes that biomarkers: "Help us greatly to quickly and non-invasively confirm or reject a diagnosis, to anticipate the outcome, and to check whether or not the chosen therapy is effective in a particular patient."

This expanding field of MS research has led us to many interesting and exciting prospects for the future, and discoveries such as these are helpful for patients and clinicians alike. "These are big steps towards personalised therapies that can be customised to a specific patient's situation," said Prof Siva.

"MS is currently still incurable. Timely, accurate diagnosis, and targeted early treatment using a growing number of modern drugs have been crucial factors behind the progress made recently in improving patients' quality of life," concluded Prof Siva.

Age worse than illness for driver reactions

NEUROLOGICALLY-impaired patients face a number of stigmas concerning road-worthiness; namely, are they fit to drive? Answers to such doubts hail from major trials at Greek universities, which have helped to clear the mists of confusion surrounding this sensitive issue.

87 subjects of differing age were put behind a driving simulator in a study designed to test driver reaction times, which was led by Dr Alexandra Economou, University of Athens, Athens, Greece, and colleagues. The total sample included 49 healthy control subjects, 14 drivers with mild cognitive impairment, 13 others with a mild form of dementia, and 11 patients with Parkinson's disease (PD). Simulated urban and rural driving conditions were used to test subjects' reaction times.

"When only one factor was considered, namely age, the test results showed that reaction times in both city as well as country driving depended mainly on how old the participants were, regardless of whether they were healthy or sick," said Dr Economou. "When the various groups of patients were compared to the healthy control group, however, dementia patients 'driving' on rural roads fared the worst."

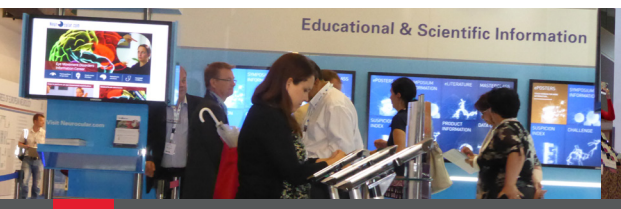
"When only one factor was considered, namely age, the test results showed that reaction times in both city as well as country driving depended mainly on how old the participants were, regardless of whether they were healthy or sick."

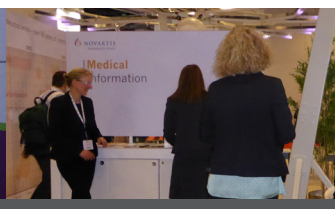
Dr Alexandra Economou, University of Athens, Athens, Greece

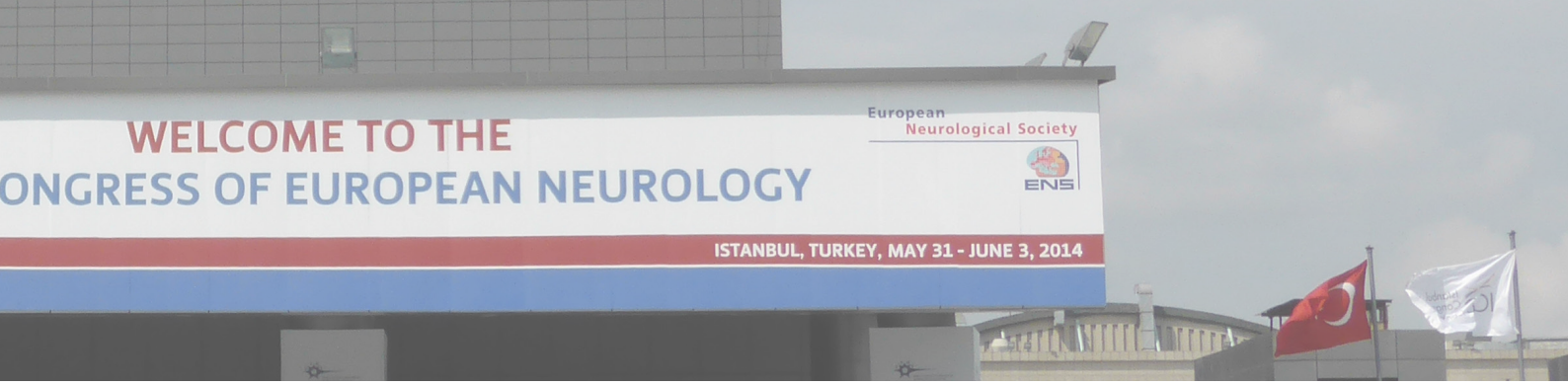
For checking brain function performance, the Trail Making Test (TMT) is used internationally for predicting the driving ability of PD sufferers. Scientists from Attikon University, Athens, established the Comprehensive Trail Making Test (CTMT), which builds on the TMT by broadening the range of cognitive functions tested.

The team of the study said: "A group of patients with PD completed a comprehensive medical and neuropsychological assessment as well as a driving simulator evaluation. Our latest findings indicate the importance of using diverse measures for checking the roadworthiness of PD patients.

"In particular, the CTMT has shown itself very useful in that respect. When compared to the classical TMT it appears to be a better predictor of various [indices] of driving performance, namely average speed, speed variation, and reaction time to unexpected incidents."





Calling for change in European regulations

OPTIMUM therapies for treating patients with multiple sclerosis (MS) should be given to patients first, argues Prof Gavin Giovannoni, Professor of Neurology, Barts and The London School of Medicine and Dentistry, London, UK.

"Unfortunately, access to the most effective therapies is delayed through licensing and reimbursement so patients only get the drugs they really need too late, only after they fail first-line therapies," said Prof Giovannoni. "By the time they can access more effective therapies, patients have already acquired a lot of damage, which is irreversible."

Currently, there is a 'pyramid structure' in place that determines which treatment patients with MS receive. A majority of patients fail first-line therapies such typical injection therapies, which contain a disease-modifying agent, or a drug known as teriflunomide.

Prof Giovannoni said: "According to current regulations, a patient needs to fail badly on one of the first-line agents to access the next tier." Many neurologists believe that this is not the most effective way to treat these patients as they have to be monitored for 18-24 months before accurate clinical assessment can be made.

"We want these more effective therapies used earlier because patients who acquire damage on first-line drugs never actually catch up because once it has happened it is irreversible," argues Prof Giovannoni.

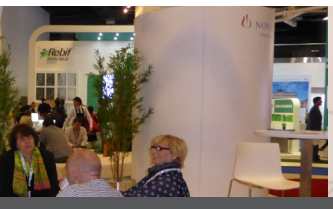
If there was a revision of the guidelines from the European Union and payer policies this would enable clinicians to prescribe the optimum treatment in a timely way, which would ultimately benefit patients over the long term. Prof Giovannoni believes that if the pyramid was inverted then more aggressive treatment could be prescribed earlier during the disease course.

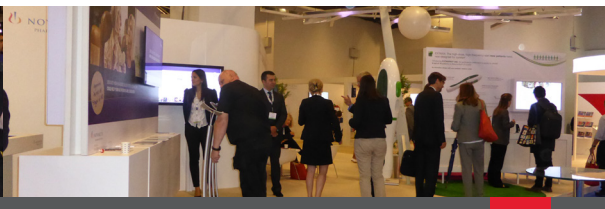
"Neurologists welcome this, but we find our prescribing restricted by existing licences and the confines of payer policies that forbid first-line use of these powerful and more effective drugs.

"We want to enable use of the most active therapies first-line," Prof Giovannoni concluded.

"Unfortunately, access to the most effective therapies is delayed through licensing and reimbursement so patients only get the drugs they really need too late, only after they fail first-line therapies."

Prof Gavin Giovannoni,
Barts and The London School of Medicine and Dentistry,
London, UK





Locked-in patients: steering in the right direction

> "Our hope is that it will be possible to use this method, say, to manoeuvre a wheelchair."
>
> *Prof Steven Laureys, University of Liège, Liège, Belgium*

LOCKED-IN syndrome sufferers may be able to communicate with others through the use of an electroencephalography (EEG).

EEG is a harmless, pain-free procedure. Brain activity can be measured in patients suffering from locked-in syndrome or those who have survived a coma.

An EEG can measure electrical signals in the brain, and determine if they can be classified as communication signals. If a person was to raise their arm an electrical signal is produced in the brain; this signal can occur whether the person is able to do this action or not.

Prof Steven Laureys, Coma Science Group, University of Liège, Liège, Belgium, said: "The basic action is for a patient to say 'yes', for example by concentrating on their left arm. The next step is to expand their vocabulary to include 'yes' and 'no'. Gradually, progress is made until the patient is able to move the cursor on a screen in this way."

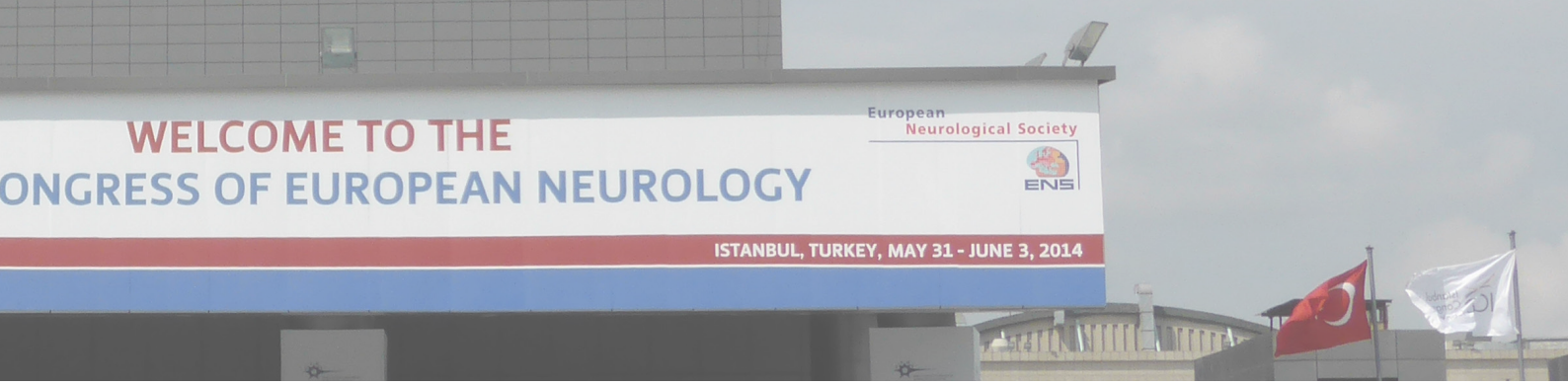
To determine the level of consciousness the patient possesses required for communication the researchers used auditory and tactile cues and motor imagery – a tact used to help patients to imagine themselves raising their arm.

The methods achieved 80% accuracy; the remaining 20% accounted for factors such as individual variations in EEG readings from the test subjects.

"Our hope is that it will be possible to use this method, say, to manoeuvre a wheelchair. At present though, there are still significant limits to the method since the experiments achieved excellent results with healthy subjects but, in patients with severe brain damage, other problems have to be overcome; for example, patients often have problems concentrating for extended periods, or have impaired intellectual capacity," said Prof Laureys.

Although there are still many difficulties to overcome, discoveries such as this are monumental. This research highlights that we are one step closer to achieving this reality for these patients.





Fruit flies: the key to Parkinson's disease

FRUIT flies could hold the potential to understanding the biological process which occurs in the brain in connection with Parkinson's disease (PD). This discovery could hold the key for new methods to be developed. It could change not only the way the disease is diagnosed, but it may result in the disease being delayed or never breaking out.

"This new research may prove to be ground-breaking in the understanding and treatment of PD. Science does not currently have answers for what happens in the brain before and during the disease, but these discoveries may bring us closer to this understanding. This may also give us the opportunity to revolutionise the diagnosis and treatment of PD for the benefit of patients and their families," said Mr Kim Andersen, Senior Vice President, Research at Lundbeck, Valby, Denmark.

The research indicated that, as in humans, overactivity in the brains of fruit flies can lead to cell death, which ultimately leads to PD. It was noted that in fruit flies with this gene mutation the communication process in the brain changed dramatically; visual signals were amplified resulting in a loss of vision in later life.

"This technique forms a remarkable bridge between human clinical science and animal research. If it proves successful in the future, it could open the door to a new way of studying a whole range of neurological diseases," said Dr Alex Wade, Department of Psychology, University of York, York, United Kingdom.

To prevent the occurrence of cell death, a drug with a dampening effect on gene mutation was used. This caused a reduction in overactivity, preventing occurrence of abnormal changes in the flies' visual function while cells and processes in the brain were normalised.

Dr Chris Elliott, Department of Biology, University of York, said: "If this kind of drug proves to be successful in clinical trials, it would have the potential to bring long-lasting relief from PD symptoms and fewer side-effects than existing levadopa therapy."

If the treatment can also be used in humans, it may pave the way for people with the specific gene mutation, and possibly PD patients in general. This may lead to patients being diagnosed and receiving preventive treatment earlier, which, in turn, may lead to them never developing the disease.

"This new research may prove to be ground-breaking in the understanding and treatment of PD."

Mr Kim Andersen, Research at Lundbeck, Valby, Denmark

Anxiety low for recurrent brain tumour patients

RECURRENT brain tumour may cripple a patient's daily life rhythm, but it seems less able to cripple a patient's spirit.

An often unexplored region of brain tumour research concerns the quality of life (QoL) and mental state of patients and relatives providing care, with caregivers shown to experience a boost in self-esteem having given their all for family members.

Lower psychological distress is recorded in patients with the neurological disorder than in people suffering from other cancers, although QoL remains poor due to functional impairments in everyday life. This is according to two recent studies on psychosocial aspects led by Dr Alessandra Petruzzi, The Foundation of the Carlo Besta Neurological Institute, Milan, Italy.

81 recurrent brain tumour patients were tested for psychological stress, anxiety, and depression in the first study; subjects' functional status, and resultantly the degree of disease-related limitations in daily activity, self-sufficiency, and self-determination, were then evaluated. The subjects demonstrated far inferior functional limitations in everyday life compared to primary brain tumour patients while also suffering greater disruption in their social and family wellbeing.

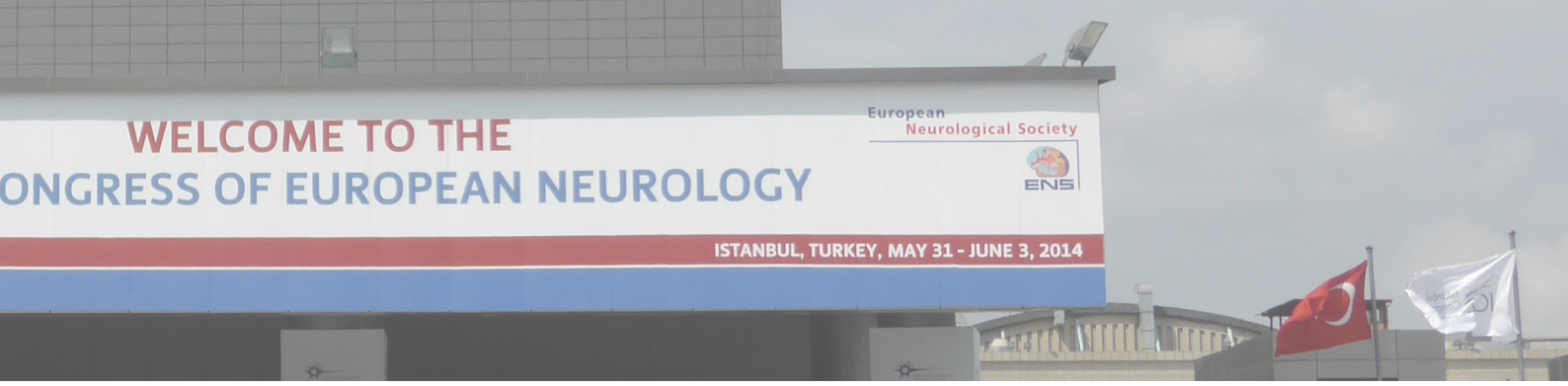
"Despite all this, they demonstrated significantly lower psychological distress compared to patients with other tumours. Quite surprisingly, test group patients additionally showed far better average values for emotional wellbeing than had patients with primary brain tumour," Dr Petruzzi said.

Commenting on the results Dr Petruzzi said: "The fact that a brain tumour recurs can play a greater role in the condition of the patient than the actual functional limitations itself. The psychological response is understandably strong. The disjuncture between the almost universally detected poor life quality on the one hand and the low rated psychological distress on the other hand is certainly the most striking result of this study.

"It leads to the conclusion that those affected can nevertheless call up extremely well-preserved coping strategies in the emotional sphere, while managing to clearly assess their comprehensive situation and be well informed about their illness."

Caregivers invest outstanding positive physical energy to a suffering family member, according to the second study; the boost in their self-esteem attributed to their loyalty to loved ones during commanding situations.

"Both studies clearly indicate that in the diagnosis of a brain tumour, a comprehensive approach must be adopted, including the mental health of victims and family members," Dr Petruzzi added.



Neurological disorders: the underestimated threat

> "To counter the growing burden from neurological diseases in a suitable way, a well-coordinated general plan is needed at international level for basic research and clinically applied research."
>
> *Prof Gustave Moonen, University of Liège, Liège, Belgium*

IMPACTING both healthcare and social services, the affliction from neurological diseases continues to be an underestimated threat.

There are approximately 220.7 million European sufferers according to clinical data from the European Brain Council. These diseases create a significant impact on individuals, their families, societies, and healthcare systems.

"Disorders such as strokes, Parkinson's disease or Alzheimer's disease (AD) all occur more often in old age. With life expectancy on the rise, the incidence of many neurological diseases will therefore skyrocket. The healthcare systems must start making preparations now to meet this challenge," said Prof Jacques L. De Reuck, Department of Neurology, Ghent University Clinic, Ghent, Belgium.

Disability-adjusted life years (DALYs) are used by the WHO as a measure to quantify the burden, taking into account both mortality and morbidity rates. It is the number of years of life lost due to early death combined with the number of years of life lost as a result of disability, whereby the years are multiplied by a given factor based on the severity of the disability. The DALYs for neurological diseases were calculated by the WHO to rise from 95 million in 2015 to 103 million cases in 2030, an increase of more than 9%. AD and other forms of dementia (increasing 37% from 2015 to 2030) or cerebrovascular diseases (increasing 13%) may be the main causes of this overall increase.

"To counter the growing burden from neurological diseases in a suitable way, a well-coordinated general plan is needed at international level for basic research and clinically applied research. One way to promote joint efforts is to network at European level, just as this congress is encouraging everyone to do. We can expect to see progress for the affected patients from this approach and from international collaboration in studies and clinical trials," said Prof Gustave Moonen, Professor Emeritus of Neurology, University of Liège, Liège, Belgium.

Bluetooth gatecrashes multiple sclerosis scene

FIRST ever Bluetooth-enabled injection management system has been introduced to boost the administration and monitoring of Betaferon® (interferon β-1a), a globally popular multiple sclerosis (MS)-combatting drug.

A fully electronic autoinjector designed by Bayer to make Betaferon injections more comfortable, BETACONNECT™ delivers visual and audible injection reminders as well as allowing the patient to set injection preferences including the needle depth, as recommended by an MS nurse, and injection speed.

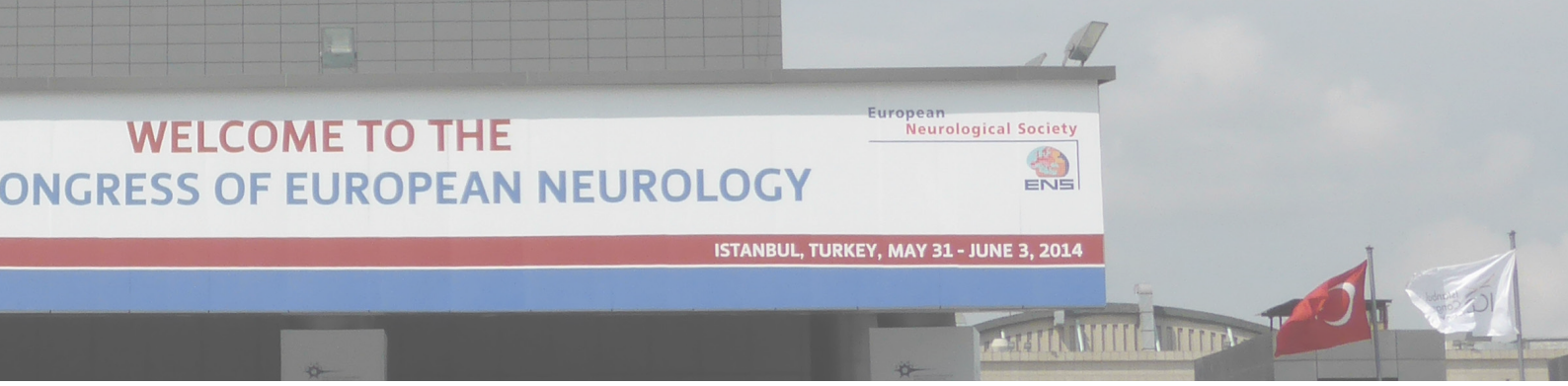
The technology has been touted as a potential way for patients to improve MS treatment, with patients able to upload injection details including injection date/time, speed/depth, and volume to a computer or Smartphone via an application, called myBETAapp™, using a Bluetooth or USB connection.

32 patients and 30 caregivers were involved in a major study evaluating the performance of the BETACONNECT autoinjector. Here, subjects answered a 13-question survey on the device following a human factors test involving a simulated injection, while half of the subjects were given training for using the device prior to the session. Feedback was very positive across both groups, who overall found performing injections to be very easy and expressed great confidence in completing the procedure. Increased patient satisfaction with treatment and a potential increase in adherence of patients on Betaferon therapy were among the main conclusions drawn from the study.

"By introducing the first MS autoinjector with Bluetooth capabilities, Bayer is helping patients who use Betaferon with a true innovation to gather – in real time – important information on their MS treatment and, if they choose, to seamlessly share the data with their healthcare providers. This new innovative technology enables the healthcare providers to optimise the recommendation for the treatment to patients," said Prof. V. Limmroth, Chairman, Department of Neurology, Cologne General Hospital, University of Cologne, Cologne, Germany.

A well-established worldwide MS treatment, Betaferon is the only disease-modifying drug that has demonstrated beneficial effect for early versus delayed treatment initiation over 8 years, demonstrated by the BENEFIT trial. Improved cognitive performance was recorded in early treatment subjects, who showed the earliest signs of MS, compared to late treatment subjects.

BENEFIT 8-year data also displayed long-term disease stabilisation and a low rate of escalation to second-line therapy in most patients.



One small step in the early detection of Parkinson's disease

> "It is high time for new integrated treatment options that provide better and faster help to PD patients."
>
> *Prof Heinz Reichmann, University Hospital Carl Gustav Carus, Dresden, Germany*

NEUROPSYCHIATRIC comorbidities and non-motor symptoms are highly important when diagnosing Parkinson's disease (PD). However new methods, for example olfactory testing or transcranial ultrasound, could help to detect the disease earlier.

"Despite 20 years of intensive research, we have still not reached our goal of being able to identify potential candidates for PD as early as possible before the disease breaks out. We must put more emphasis on early diagnosis and take new approaches in this area," said Prof Werner Poewe, Innsbruck Medical University, Innsbruck, Austria.

By offering interventions at an earlier stage, there is greater potential for slowing down the progression of the disease. Procedures for improved early detection such as imagining, genome-wide association studies - which have identified several PD risk alleles - and olfactory testing have all proved their worth.

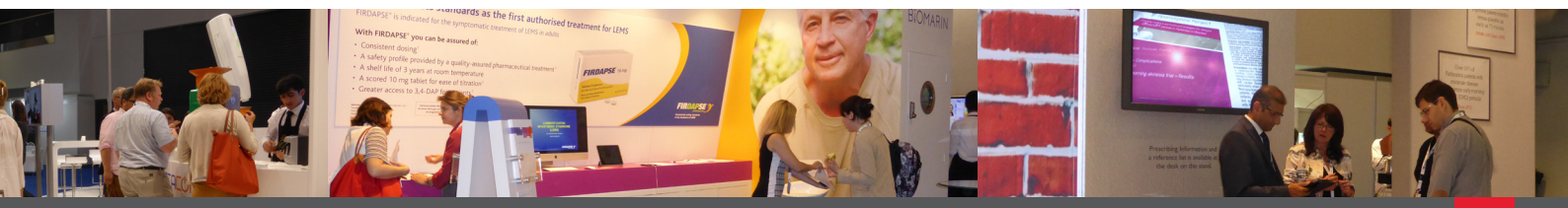
Currently, potential proteomic markers for PD are being investigated and evidence has suggested that a certain combination of biomarkers could define populations who are at risk of PD. 35 patients with rapid eye movement sleep behaviour disorder underwent olfactory testing; as a result, it was found that olfactory impairment was a predictor for PD.

Since at least 40-50% of PD patients battle with depression, this is another factor which should be analysed. Research has shown that depression often manifests itself before the motor symptoms of PD; in 30% of all patients, depression is observed before motor symptoms occur. Nocturnal sleep disturbances are another major issue for patients, occurring in 60-98% of patients.

Prof Heinz Reichmann, University Hospital Carl Gustav Carus, Dresden, Germany, said: "The high incidence of depression shows yet again that diagnosis and treatment must not be allowed to focus solely on the classical motor signs of PD."

Although PD remains an incurable disease, research such as this brings us one step closer to understanding the disease while also helping to delay its devastating effects.

As Prof Reichmann highlighted: "It is high time for new integrated treatment options that provide better and faster help to PD patients."



New weapons to battle against multiple sclerosis

RELAPSING multiple sclerosis (MS) is under fresh attack by self-dosing interferon beta therapy and first-of-its-kind evaluation software, which will together bolster therapeutic outcomes and patient engagement.

Designed by Merck Serono, RebiSmart® allows patients to self-inject the company's disease-modifying drug Rebif® (interferon β-1a), which is very similar to the naturally-occurring modulating cytokine interferon β (IFN-β). Being the first injection device in MS to record the date, time, and dosage of each injection, RebiSmart allows open discussion of an accurate dosing history with a patient, enabling the physician to monitor and enhance patient adherence to therapy.

Data recorded by RebiSmart are sent to Merck's secure web-based software system, MSdialog, which allows MS patients to engage with management of their disease through a series of periodic health report questionnaires while giving physicians a platform to monitor patients' adherence to treatment and trends of their health status.

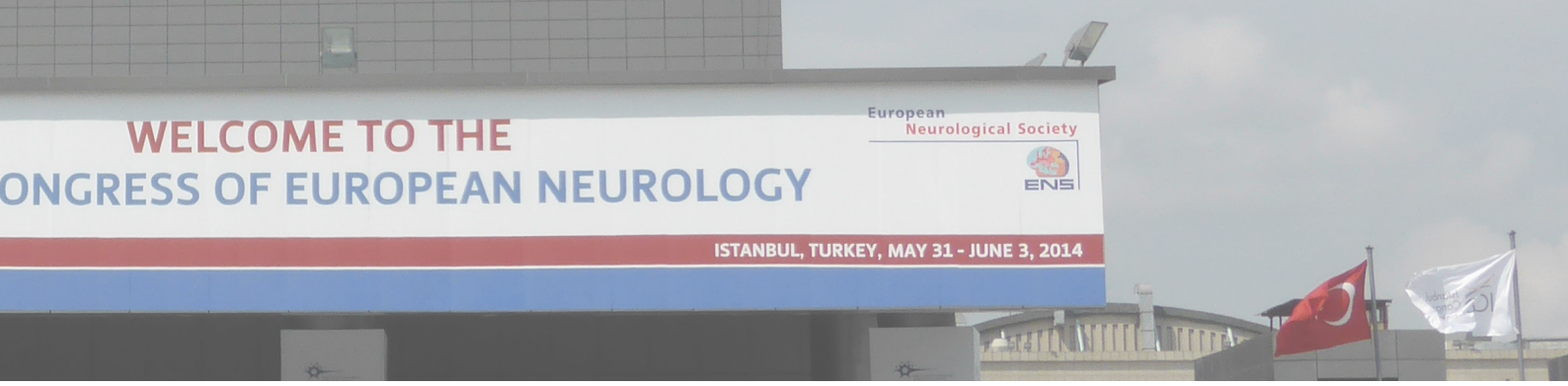
Already registered in over 90 countries worldwide, Rebif was the first licensed disease-modifying drug and has positive effects on relapses and disability progression, as well as decreasing magnetic resonance imaging lesion activity and area.

An ideal choice for MS therapy, IFN-β, upon which the therapy is based, is central to immune regulation. Among the protein's numerous anti-inflammatory effects is its ability to prevent T cell activation and the migration and adhesion of myelin-reactive T cells, active players in MS occurrence, to the blood-brain barrier.

The latest RebiSmart and MSdialog were made available across much of Europe in May 2014, while two strengths of the multi-dose cartridge – 132 μg (3 doses of 44 μg) and 66 μg (3 doses of 22 μg) –received EMA approval in January 2009.

"Engaging and empowering patients through knowledge and technology may have the potential to improve outcomes by allowing patients to monitor their own disease," said Dr Gavin Giovannoni, Professor of Neurology, Barts and The London School of Medicine and Dentistry, London, UK. "The new RebiSmart and the MSdialog platform can provide physicians with access to certain treatment information as it happens, allowing for time during visits to discuss relevant, patient-specific issues. And patients using these technologies may be more in touch with their own disease."

Scientists still do not completely understand how IFN-β benefits MS patients, and so further research into MS and IFN-β is required.



Women suffer worse outcomes than men after stroke

> "The task must be to understand and assess the causes and mechanisms that attack mental health and prevent them."
>
> *Prof Franz Fazekas, University Clinic of Neurology, Graz, Austria*

WOMEN receiving the same treatment as men post-stroke are likely to suffer a worse functional outcome. The same study also highlighted that mental deterioration and dementia are often a result of lacunar strokes, which themselves are underestimated.

Although progress has been made within this area, there are still many unmet challenges, for example in prevention, rehabilitation, and treatment. The current Austrian study found that there was not only a difference in men and women that suffer strokes, but it also highlighted new ways of treating patients who experience such conditions.

The study, which was conducted from 2005-2012, included more than 47,000 individuals, 47% of whom were women. Although women have different requirements compared to men if they have experienced an acute stroke or a transient ischaemic attack, they were treated no differently. The results indicated that when this happened the functional treatment outcome was worse for women; however, their death rate was lower.

Prof Franz Fazekas, University Clinic of Neurology, Graz, Austria, said: "Although further studies should be conducted to illuminate the socioeconomic situation of patients after a stroke, these data indicate that gender-specific treatment approaches could make therapy more successful."

80-90% of strokes occur due to an inadequate supply of blood to the brain, mostly due to thrombi; these are often accompanied by sudden neurological deficiency symptoms. The most common consequences of lacunar strokes, for example, include mental deterioration and dementia.

The severity of lacunar strokes has often been underestimated, but the effects of such a condition can be detrimental. Until now it has been unclear whether the risks differ depending on the type of ischaemic stroke involved.

Prof Fazekas suggested: "As the chances of survival after a stroke increase so too does the significance of quality of life as an issue following survival. The task must be to understand and assess the causes and mechanisms that attack mental health and prevent them."

Biomarkers beating Alzheimer's disease

IDENTIFICATION of meaningful biomarkers has led to great improvements in early detection, prevention, and diagnosis of Alzheimer's disease (AD).

AD is the most common form of dementia, responsible for 60-80% of all dementia disorders. In Europe alone 6.3 million people suffer from the condition, costing the European economies more than €100 billion annually.

Prof Philip Scheltens, VU University, Amsterdam, the Netherlands, said: "Dementia will be the fastest growing health problem over the next 30 years. This poses a challenge for all heath systems in Europe and will affect neurology to a major extent since dementia will be the most significant brain disease in the future."

Mild cognitive impairment (MCI), causing a slight but noticeable decline in cognitive abilities, is considered a transitional stage of the aging process. According to the European AD Consortium (EADC) study, the use of biomarkers to identify the aetiological diagnosis is widespread.

The findings of the study indicated that a combination of amyloidosis and neuronal injury biomarkers were signatures of AD. Visual readings of the atrophy of the medical temporal lobe on magnetic resonance imaging was most frequently used to identify the aetiological diagnosis of MCI.

Another study suggested that diagnosing AD in the future may lie with circulating microRNAs (miRNA). Dr Daniela Galimberti, University of Milan, Milan, Italy, explained: "Our results suggest a potential use of circulating miRNAs, together with other markers, as non-invasive, relatively inexpensive, and peripheral biomarkers for Alzheimer's diagnosis."

In Alzheimer's patients and control subjects, a specific PCR array with 84 miRNAs was used to screen miRNA serum levels. Alzheimer's patients showed significantly lower scores on the number of tested RNAs.

Research such as this is invaluable. As more biomarkers for the various forms of dementia become known, there is more chance of detecting the disease earlier and preventing it from progressing, saving both the patient and their families.

Prof Scheltens said: "These are exciting but challenging times in AD research. At many levels, a more detailed picture of the disease is being refined and advanced. Long-hoped-for advances in the development of disease-modifying therapy remain unfulfilled. Prevention will therefore be given greater attention. In recent dementia research, important progress has been observed particularly in the diagnosis of the disorder."

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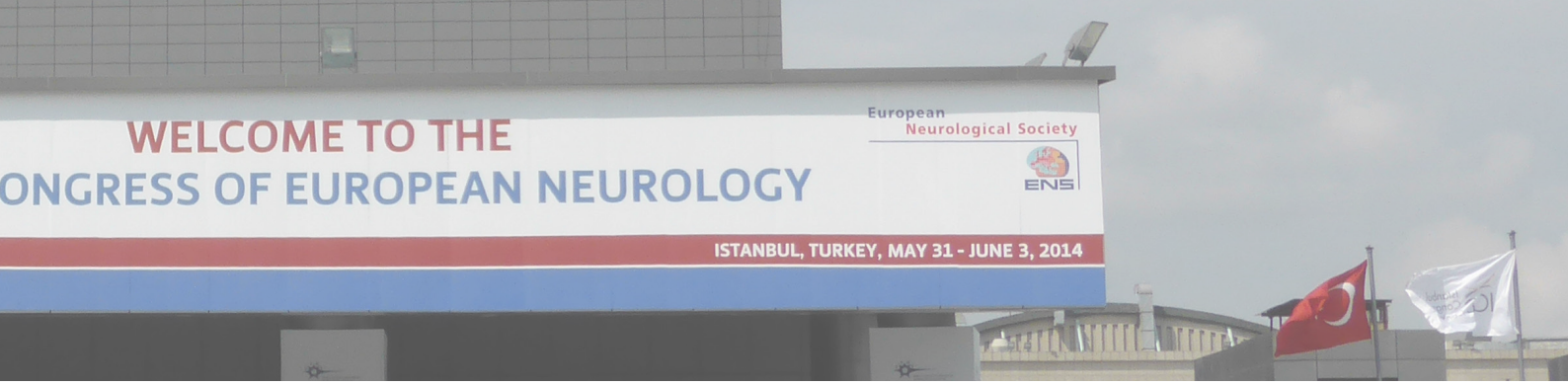

Drug overuse furthers headache nightmare

> "The results show that the changeover from self-medication to specialised medical care may reduce the frequency of symptomatic treatment and the number of headache attacks per month, and improve the quality of life in patients with headache."
>
> *Prof Fabio Antonaci, C. Mondino National Institute of Neurology Foundation, Pavia, Italy*

MEDICATION overuse has been highlighted as a key risk factor for migraine and tension headache, although a structured detoxification programme can successfully treat more than three-quarters of cases.

Potentially triggering a downward spiral in sufferers of headache and migraine, uncontrolled use of painkillers itself results in headaches. Among the most numerous neurological complaints, headache and migraine are affecting increasing numbers of people, particularly across the more industrialised countries.

Lifetime prevalence of episodic headache is 70% and episodic migraine is 15% according to the WHO, with headache being one of the top ten conditions responsible for the most functional disability worldwide.

Professional medical treatment of headache has proved to be more effective than self-medication. Duration of headaches was halved within the first 3 months of professional treatment in patients who had previously been self-medicating in a University of Pavia-led study, while the intensity of headaches and monthly dose of analgesics also went down.

"The results show that the changeover from self-medication to specialised medical care may reduce the frequency of symptomatic treatment and the number of headache attacks per month, and improve the quality of life in patients with headache," said study author Prof Fabio Antonaci, Headache Center, C. Mondino National Institute of Neurology Foundation, IRCCS, University of Pavia, Pavia, Italy.

Medication overuse headache (MOH) can be successfully treated by a structured detoxification programme. In a recent study by the Katip Celebi University, Izmir, Turkey, 77% of patients remained free of MOH 12 years after treatment, while there was a more than 50% drop in headache frequency in 20% of patients.

"This long-term follow-up study revealed a marked decline in the frequency of MOH. Patients who were previously regarded as treatment-resistant, benefited considerably from multidisciplinary treatment and close follow-up," said study author Dr Yesim Beckmann, Department of Neurology, Atatürk Training and Research Hospital, Izmir, Turkey.

ELECTION OF THE BOARD OF THE EUROPEAN ACADEMY OF NEUROLOGY (EAN)

The European Federation of Neurological Societies and the European Neurological Society have joined together to make one neurological society; the European Academy of Neurology (EAN). The aim of the EAN is to promote excellence in neurology in Europe. They hope to raise awareness concerning the burden and cost of neurological disorders, and to promote the benefits which clinical neurology can bring. This unified society will act as one voice representing all healthcare professionals with an interest in this field.

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APOMORPHINE PENJECT – EMERGING EVIDENCE AND TREATMENT STRATEGIES FOR DELAYED ON AND OFF PERIODS IN PARKINSON'S DISEASE

Summary of Presentations from the Britannia-sponsored Symposium, held at the Joint Congress of European Neurology (EFNS–ENS), Istanbul, Turkey, on 1st June 2014

Chairperson

Olivier Rascol[1]

Speakers

Fabrizio Stocchi,[2] Stuart Isaacson,[3] William Ondo[4]

1. Professor, Toulouse University Hospital Clinical Investigation Centre, Toulouse, France
2. Professor, Institute of Research and Medical Care, IRCCS San Raffaele, Rome, Italy
3. Associate Professor, Florida International University, Herbert Wertheim College School of Medicine, Miami; Director, Parkinson's Disease and Movement Disorders Center of Boca Raton; Research Director, Marcus Neuroscience Institute, Boca Raton Regional Hospital, Florida, USA
4. Professor, University of Texas Health Science Center, Houston, Texas, USA

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MEETING SUMMARY

This educational symposium was held during the Joint Congress of European Neurology (EFNS–ENS), which took place from 31st May to 3rd June 2014 in Istanbul, Turkey, and was sponsored by Britannia Pharmaceuticals Limited. The symposium debated the problem of delayed ON and OFF periods in Parkinson's disease that can occur even in patients optimised on oral medication. Emerging evidence for the rapid and effective resolution of such complications using apomorphine intermittent injection (penject) was reviewed with particular reference to the positive results of the recent AM IMPAKT trial in patients with morning akinaesia. The discussions were illustrated with examples of 'real life' patient case studies to help determine which patients might be best suited for treatment with apomorphine injection.

Delayed ON and Wearing OFF – Complications

Professor Fabrizio Stocchi

Prof Stocchi described how the management of patients with Parkinson's disease (PD) is frequently complicated by the development of motor fluctuations and dyskinaesias, which occur as a result of alterations in levodopa responsiveness following long-term therapy. Prof Stocchi considered that these motor complications represented a therapeutic challenge to the effective long-term treatment of PD and had a significant negative impact on the patient's quality of life (QoL).[1] Motor fluctuations comprise end-of-dose 'wearing-off' phenomena, peripheral problems such as 'delayed ON' (for example morning akinaesia) or 'no ON' (dose failure), and unpredictable 'ON–OFF' periods. Dyskinaesias may be peak-dose effects, distressing and painful diphasic dyskinaesias, or painful OFF-period dystonia. Prof Stocchi presented compelling

video evidence of real patient cases showing just how debilitating and distressing these different motor complications could be, underlining the need for effective management.

Prof Stocchi highlighted the results of the recent DEEP Study (Early DEtection of wEaring off in Parkinson disease), which had been undertaken to assess the frequency of wearing off in PD patients and its impact on QoL using a validated screening tool, WOQ-19.[2] These results showed that the frequency of wearing off increased with duration of disease such that, after 10 years, around 80% of PD patients experienced wearing-off phenomena.

Prof Stocchi outlined the results of a secondary analysis of the STalevo Reduction In Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) study that had investigated the effect of levodopa dose and other risk factors on the development of dyskinaesias and wearing off. The results demonstrated that time to the development of dyskinaesias and time to wearing off both correlated with the dose of oral levodopa.[3] Multivariate analyses showed that factors predictive of dyskinaesia included young age at onset, higher levodopa dose, low body weight, female gender, and more severe Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores. Predictors of wearing off included baseline UPDRS scores but excluded weight.

Evidence suggests that many of these motor complications directly reflect variations in levodopa plasma levels and the rate of levodopa transport to the brain. Standard oral formulations of levodopa result in pulsatile dopaminergic stimulation and are not able to maintain steady plasma levels throughout the day. Within the basal ganglia, striatal dopamine concentrations are normally maintained at a relatively constant level and dopamine receptors are continuously activated.[4] Continuous dopaminergic stimulation (CDS) is therefore thought to more closely mimic the physiological situation, and has been proposed to help overcome the motor complications that occur with standard oral therapy.[5-8]

The benefits of the CDS approach compared with oral levodopa were initially demonstrated with the dopamine agonist lisuride.[9] This double-blind, double-dummy, randomised, controlled trial comparing levodopa + lisuride subcutaneous infusion versus levodopa + high-dose oral pramipexole confirmed the benefits of infusion therapy on UPDRS motor scores and in reducing OFF time and ON time with troublesome dyskinaesias in PD patients.

Prof Stocchi also recognised the contribution of peripheral factors to delayed ON and dose failure with oral levodopa. He illustrated the journey of an oral levodopa dose from mouth to brain and the many possible hurdles it might encounter including swallowing difficulties, delayed emptying from the stomach, absorption in the small intestine, and crossing the blood-brain barrier – a process that takes between 60 and 90 minutes in total. Gastrointestinal (GI) dysfunction, including gastroparesis (delayed gastric emptying), is common in PD, and gastroparesis is a recognised contributing factor to the delay in levodopa time to ON (TTO).[10] Recently, delayed TTO and dose failures have been recognised as a significant proportion of total OFF time, comprising more than twice the duration of wearing off.[11] This was illustrated clearly in a pharmacokinetic study, undertaken by Prof Stocchi, of levodopa given every 4 hours, which revealed a substantial proportion of OFF time over the day, particularly delayed ON (Figure 1) [unpublished data].

Prof Stocchi went on to discuss the role of apomorphine in the management of PD. Apomorphine is a non-ergot dopamine agonist first synthesised in 1845 by heating morphine with hydrochloric acid. Unlike morphine, it has no opioid analgesic effects. It is predominantly a dopamine D1 and D2 receptor agonist, in contrast to most other dopamine agonists which are of the D2 family. The D1 agonist effects of apomorphine are thought to result in less psychosis and less dyskinaesia compared with other dopamine agonist compounds. When injected subcutaneously, apomorphine has a very rapid onset of action within 7.5–10 minutes and duration of effect of around 90 minutes. Subcutaneous apomorphine is available in two formulations for clinical use – an intermittent injection (penject) and a continuous infusion – giving the clinician different therapeutic options depending on the patient's symptoms.

The apomorphine penject is an easy to use injection device that has been shown in a range of clinical studies to reduce OFF time by as much as 65% in PD patients with motor fluctuations when used as an adjunct to the patient's usual oral medication. Patients with more advanced or complex disease who require frequent daily apomorphine injections to control their OFF periods may be more suited

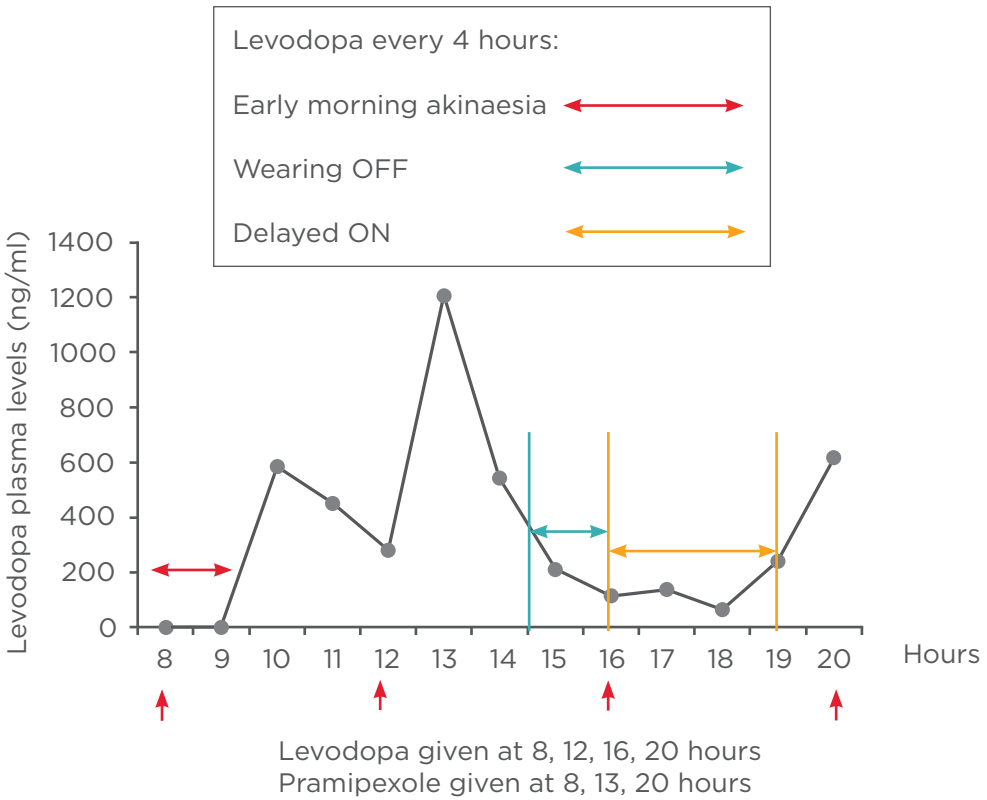


Figure 1: Proportion of OFF time following oral doses of levodopa [unpublished data].

to apomorphine continuous infusion which provide CDS. The efficacy of the infusion formulation has also been demonstrated in clinical trials with reductions in OFF time, oral levodopa dose, and the severity of dyskinaesia being reported.[12-16] In addition, the efficacy of apomorphine in PD patients has been shown to be sustained over several years without the development of tolerance.[13]

Prof Stocchi noted that in addition to classical motor fluctuations, many PD patients also experience non-motor fluctuations, such as anxiety, panic attacks, pain, fatigue, mood changes, urinary urgency, and swallowing difficulties,[17] which, in his clinical experience, could also be resolved rapidly with apomorphine intermittent injection.

Prof Stocchi considered that the types of PD patient most suited to apomorphine penject were generally those with disabling motor and non-motor fluctuations despite optimised oral therapy, and those (or those with carers) who can clearly recognise their OFF periods and who are able to inject themselves (with help if it is available). It might not be suitable for those who have a poor response to levodopa, those with severe cognitive impairment, or those with excessive skin problems.

In clinical studies apomorphine had been shown to be well tolerated, but there were commonly-reported adverse events in the form of local reactions and skin nodules at the injection site. However, these rarely necessitate cessation of apomorphine therapy and can be easily managed.

Prof Stocchi concluded that apomorphine is a very effective treatment for PD patients with motor and non-motor fluctuations, in particular for those with advanced PD whose motor fluctuations are uncontrolled by conventional oral or transdermal medication. Apomorphine penject offers an effective therapy for the rapid and reliable resolution of delayed ON and no ON phenomena, such as early morning akinaesia.

AM IMPAKT: Apomorphine for Morning Akinaesia Trial – Results

Professor Stuart Isaacson

Prof Isaacson continued to debate the problem faced by many clinicians: getting oral levodopa, acknowledged as the mainstay of PD therapy, to work reliably in their patients. Initially, the

therapeutic effect of each levodopa dose is rapid, reliable, and sustained with an onset of around 20 minutes and a long duration response. However, after several years of levodopa treatment the long duration response is replaced by a short duration response and OFF periods emerge, comprising both end-of-dose wearing off and delayed TTO. Despite attempts to optimise oral therapy and the use of multiple medications, many patients still experience OFF time. Both motor and non-motor symptoms are frequent during these OFF periods, especially when the next levodopa dose has a delayed onset of action; when this occurs upon awakening it is known as morning akinaesia. Morning akinaesia is in fact a very common but under-recognised symptom of PD for which treatment appears to be suboptimal despite the availability of a rapid and effective therapy in the form of subcutaneous apomorphine pen injection. Prof Isaacson considered that there should be a renewed focus on the importance of delayed TTO and its management, including not only morning akinaesia but also nocturnal akinaesia and postprandial akinaesia. Studies have shown that delayed TTO is a major contributor to OFF time, being more than twice the duration of wearing off.[11]

There is increasing evidence in PD that the GI system is dysfunctional and that this can occur almost a decade or more before PD is clinically diagnosed. Medications used to treat PD may also contribute to GI dysfunction, including levodopa, dopamine agonists, anticholinergics, amantadine, and inhibitors of monoamine oxidase B (MAO-B) and catechol-O-methyltransferase (COMT). A survey of PD patients found that 24% reported nausea and 45% reported bloating, both symptoms of gastroparesis.[18] The most common gastroparesis symptoms comprise postprandial bloating, early satiety, nausea, vomiting, weight loss, and malnutrition; however, Prof Isaacson considered that in PD patients delayed ON and dose failure, manifesting as OFF periods such as morning akinaesia, were also suggestive of gastroparesis. Studies of the incidence of motor fluctuations in PD patients show that morning akinaesia is indeed extremely common, occurring in around 58% of subjects.[1]

Treatment strategies to improve morning akinaesia focus on reducing early morning OFF time through the use of long-acting dopamine agonists or by inhibiting MAO-B, or on attempts to hasten TTO by enhancing delivery of levodopa to the proximal small intestine (through the use of liquid, dispersible, modified, or higher-dose levodopa). However, in PD patients who have gastroparesis, emptying of both solids and liquids may be impaired[19] so delayed TTO may still occur. The phenomenon of delayed TTO is one that may not always be well described by patients in the clinic but it is important that clinicians try to identify it to be able to effectively manage it.

Recently, the EUROPAR Study Group investigated the prevalence and characteristics of early morning OFF (EMO) periods in 320 PD patients.[20] EMO periods were present in 59.7% of patients, and of these, 88.0% had EMO with mixed motor and non-motor symptoms while 12.0% had pure motor EMO. EMO also occurred throughout the course of the disease in mild, moderate, and severe PD patients. The motor component of these EMO periods was morning akinaesia, while the most common non-motor symptoms comprised urinary urgency, anxiety, pain, dribbling, low mood, and paresthaesia. Many of the patients in the EUROPAR study were taking dopaminergic therapy but although the addition of prolonged release dopamine agonists appeared to result in less EMO periods compared with levodopa alone, EMO periods still occurred.

Having identified the inherent problems with levodopa therapy, Prof Isaacson considered that it was important to find an effective solution. Since subcutaneous injection avoids the oral route of administration with its associated challenges, apomorphine penject may be a valuable option for the management of morning akinaesia; TTO will not be affected by delayed gastric emptying or impaired intestinal absorption. Prof Isaacson described how this hypothesis formed the rationale for the ongoing Phase IV, multicentre (12 sites), open-label, efficacy and safety study - AM IMPAKT (Apokyn for Motor IMProvement of Morning AKinesia Trial).[21-23] AM IMPAKT is investigating whether subcutaneous apomorphine injection upon awakening can provide rapid and reliable improvement in motor symptoms in PD patients with morning akinaesia. Enrolment is now complete (10 patients) and the full results are expected towards the end of 2014.

Interim analysis of the initial 50 patients in the AM IMPAKT trial has revealed that morning akinaesia is common and occurs throughout the course of PD, even in the early stages; many patients in the study had experienced it for an average of four years even though they were taking adjunctive

therapies. In addition, they had never been offered apomorphine injection to manage their symptoms despite it having been available for decades.

Optimal apomorphine doses were identified by the investigator as the dose replicating the levodopa effect after 15 minutes. In 38% of patients, the optimal dose level was 4 mg but around 18% needed a higher dose. Patients recorded their time to ON after their first morning levodopa or apomorphine injection dose in a diary every 5 minutes by checking boxes either 'yes' or 'no' until onset of ON up to 60 minutes.

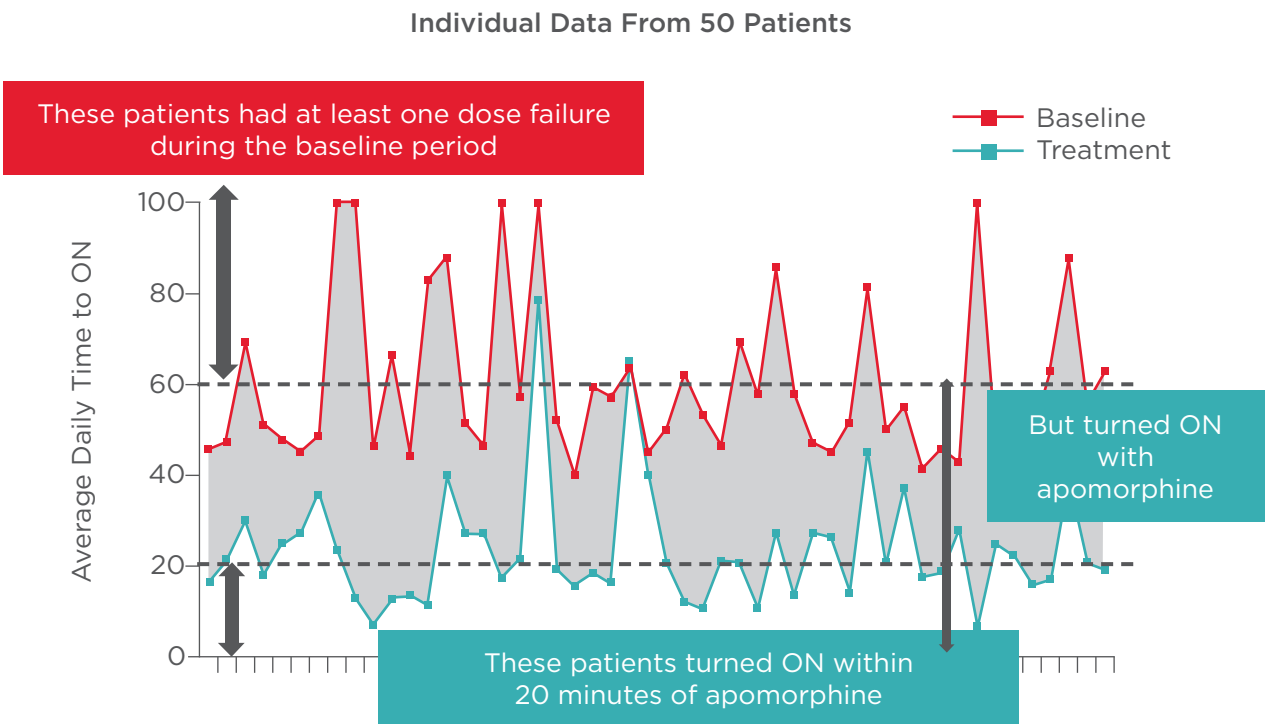
The results of the study so far have found that apomorphine pen injection significantly improved the primary endpoint of TTO, and was rapid and reliable with 95% of patients achieving at least a 20-minute reduction in TTO with an average reduction of 40 minutes. Mean baseline TTO with levodopa was 60.26 minutes which reduced significantly to 23.59 minutes with apomorphine injection.

Analysis of individual data for each patient clearly illustrates the reliability of the response to apomorphine; 48 of the 50 patients had a rapid and reliable clinical improvement in TTO. Surprisingly, when patients were taking their usual levodopa dose, dose failures were found to be common with 40% having at least one during the study period. In contrast, with apomorphine penject all but two patients achieved an ON state, 60% of these within 20 minutes (Figure 2).

UPDRS motor scores were also significantly reduced within 15 minutes of apomorphine compared with baseline (33.6 versus 14.9; $p<0.0001$) as was the Hoehn and Yahr (H&Y) Stage (2.8 versus 2.3; $p<0.0001$). Prof Isaacson considered that the H&Y Stage was an indicator of postural instability and the risk of falling so this change represented an improvement in balance.

Patients and investigators were asked to rate their global impression of severity of illness relative to akinaesia/motor function before and after apomorphine therapy, measured on a 7-point scale from 'normal' to 'extremely ill'. In both cases significant improvements were recorded.

Motor symptom improvements were also reflected in measures of health-related QoL. EQ-5D-3L index scores were significantly reduced from a mean of



Subject recorded their time to "ON" after their L-dopa or APOKYN dose in a diary every 5 minutes by checking boxes either "yes" or "no" until onset of "ON," up to 60 minutes. A value of 100 was imputed for subjects that did not report turning "ON" within 60 minutes.

Figure 2: Reliable reduction in average daily time-to-ON in individual patients following apomorphine injection.

3.50 at baseline to a mean of 2.31 at the end of the 1-week apomorphine treatment period (p<0.0001). EQ-5D-3L is a patient-reported health outcome scale related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, in which each dimension is ranked from 1 (no problem) to 5 (extreme problem), so lower scores indicate a more favourable rating. Similarly, EQ-5D VAS scores significantly improved from a mean of 48.02 at baseline to 65.25 at the end of the treatment period (p=0.0001). Using this scale, subjects rate their health state relative to akinaesia on a scale of 0 (worst imaginable] to 100 (best imaginable) so higher scores indicate a more favourable rating. Overall, apomorphine pen injection was well tolerated, the most common side-effects being nausea and somnolence. As expected, more adverse effects were seen at higher doses.

Prof Isaacson concluded that the interim results from the AM IMPAKT study suggest that morning akinaesia is a common but under-recognised symptom of PD and that subcutaneous apomorphine pen injection results in a rapid and reliable TTO in such patients. Importantly, the reduction in TTO is clinically relevant – significant improvements were observed in motor score, H&Y Stage, measures of QoL, and global impression of severity.

Clinical Case Considerations

Professor William Ondo

Prof Ondo reviewed several PD patient cases, illustrated with videos, to determine what type of patient or disease features could potentially benefit from subcutaneous apomorphine injection, and also where it might not be an appropriate therapy.

Case 1

- 54-year-old working male with an 8-year history of PD
- Has been taking levodopa for 6 years: 150 mg, 4–5 times/day with entacapone
- Latency to onset 60 minutes despite crushing and taking with orange juice
- He experiences painful dystonia in the morning
- Duration of levodopa action was 3–4 hours with variable wearing off and unpredictable dose failures
- He experiences mild dyskinaesia, usually when under stress
- Modest non-motor signs: constipation
- No dementia, psychosis, depression, or postural problems
- No fear of needles

Prof Ondo illustrated this case with a video of the patient commenting that painful OFF-period dystonia was often a common presenting feature of young-onset PD. The majority of the audience considered that this patient would be a good candidate for apomorphine injection. Prof Ondo agreed that this was very much a 'typical' apomorphine pen injection patient – relatively young and needs to be turned ON rapidly, particularly as he is working.

Case 2

- 84-year-old female with a 22-year history of PD
- Advanced PD: H&Y Stage 4 (not ambulating); no tremor
- Moderate-to-severely demented: MMSE 14/30
- Positive visual hallucinations
- Marked sialorrhoea, urinary incontinence
- Lives in nursing facility
- Takes levodopa 25/250, 1.5 tablets, 4 times/day
- Has difficulty determining if her medication is helping or not but feels worse when not taking it
- ON examination: has mild dyskinaesia with some doses but still has severe gait/balance issues, marked dysarthria/dysphagia, and dementia

Prof Ondo commented that the fact that this patient has dyskinaesia when she is turned ON demonstrates that the levodopa is in fact being absorbed. He noted that many cases of levodopa non-responsiveness are due to the fact the patient is not taking a sufficient dose, but in this case the dyskinaesias show that the dose is adequate. In this patient, even in the ON state she experiences significant non-levodopa responsive morbidity and is unable to walk easily. The majority of the audience considered that for this reason she was not a suitable candidate for apomorphine penject. Prof Ondo agreed that using apomorphine injection might give the patient a longer ON time but due to the disability she experiences when ON, it is unlikely to improve her overall QoL.

Case 3

- 78-year-old male with an 18-year history of PD
- Fluctuations for 14 years
- Takes levodopa 25/250, 6 times/day
- 30–40 minutes to onset of levodopa effect
- Frequent dose failures
- When OFF, unable to walk
- Marked benefit complicated by mild dyskinaesia
- History of marked nausea and mild hallucinations with trials of dopamine agonists in the past
- Mild orthostatic hypotension
- Very bad constipation
- Cognitively good

The audience was somewhat divided about whether this patient would be a suitable candidate for apomorphine injection – about 60/40 in favour. Prof Ondo illustrated the case with a video of the patient showing rapid resolution of his OFF symptoms with apomorphine injection within about 10 minutes highlighting that it can be an extremely beneficial therapy even in relatively advanced disease presenting with complex symptoms.

Prof Ondo went on to discuss two studies of possible predictors of response to apomorphine injection. A single-site study had prospectively assessed orthostatic blood pressure, nausea (assessed using a visual analogue scale), and other adverse events (AEs), while a sub-analysis of a recent clinical trial for PD subjects with problematic morning akinaesia had assessed all AEs and apomorphine dose.[24,25]

In terms of AEs, there was very limited correlation with previous response to other dopaminergics: response did not correlate with a history of nausea with dopamine agonists, a history of orthostatic hypotension, age, dose of medications, a history of dyskinaesia, or gender. Younger patients appeared to have more hypotension and, in this study, surprisingly the anti-nausea medication trimethobenzamide was associated with a greater degree of nausea.

In the second study, higher doses of apomorphine were found to be required in patients with a longer duration of disease. However, there was no correlation of response with individual levodopa dose, total daily dose, PD severity, use of dopamine agonists, or gender. There does not appear to be a 'shortcut' to predicting what apomorphine dose will work best to turn a patient ON, so it is important that the clinician titrates the dose in each patient to find what suits that individual. Prof Ondo concluded that the utility of apomorphine injection is greatest in patients who experience OFF periods and need to turn ON rapidly.

Panel Discussion – Apomorphine Injection in PD: When, Who, Why?

The Panel considered that it was not possible to predict the response to apomorphine injection based on a patient's response to other dopamine agonists. Prof Stocchi noted that apomorphine was associated with fewer psychiatric AEs than other dopamine agonists; however, the experience of nausea might vary between compounds. Prof Isaacson commented that patients already taking a dopamine agonist when they start apomorphine might have some degree of peripheral dopaminergic tolerance, and therefore fewer AEs might be expected, but this had not been investigated in clinical trials. He added that the relatively short half-life of apomorphine meant that any AEs also tended to be short-lived and tolerable.

It was agreed that doses of apomorphine needed to be titrated individually for each patient – a higher dose was not necessarily better and some patients might have symptoms that were not responsive to levodopa therapy. Prof Isaacson commented that clinical data show that apomorphine injection is effective almost every time in suitable patients, and often it is the case of adjusting therapy to find the right dose.

Prof Rascol considered that apomorphine injection should be considered as a suitable treatment much earlier in the disease course in patients who experience OFF periods with optimised oral medication, whether early in the morning or during the day. It is able to rapidly and reliably resolve OFF symptoms that occur due to the delay in the levodopa effect. This restored confidence and independence to patients who previously may have been reluctant to socialise for fear of experiencing a debilitating OFF period.

Statement

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Rapid reliable 'on' for Parkinson's disease

APO-go PEN provides rapid and reliable 'on' **for patients with morning akinesia**, reducing time to on by an average of 40 minutes[1]

APO-go® Apomorphine hydrochloride
PRESCRIBING INFORMATION Consult Summary of Product Characteristics before prescribing. **Uses** Treatment of motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication **Dosage and Administration** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used. **Contraindications** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation** Apomorphine should not be used in pregnancy unless clearly necessary. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Apomorphine can increase the antihypertensive effects of domperidone. **Precautions** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly. and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. Contains sodium metabisulphite which rarely causes severe allergic reactions and broncospasm. **Side Effects** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitus. Irritation, itching, bruising and pain may also occur. Rarely injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and light-headedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported as has peripheral oedema. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects* **Presentation and Basic NHS Cost** APO-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers**: APO-go Ampoules: PL 06831/0245 APO-go Pens: PL 06831/0246 APO-go Pre filled syringes: PL 06831/0247 **Legal Category** POM **Date of last revision**: March 2014 For further information please contact: Genus Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK

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THE EVOLVING MS LANDSCAPE: CHALLENGES AND OPPORTUNITIES

Summary of Presentations from the Genzyme-Sponsored Symposium, held at the Joint Congress of European Neurology (EFNS-ENS), Istanbul, Turkey, on 2nd June 2014

Chairperson

Mefkûre Eraksoy[1]

Speakers

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Unmet Medical Needs in Multiple Sclerosis: Patient and Healthcare Perspectives

Professor Mefkûre Eraksoy

Historically, multiple sclerosis (MS) treatment goals have focused on clinical endpoints, delaying disability, and reducing relapse frequency, and magnetic resonance imaging (MRI) goals have focused on reducing and preventing new lesions.[1,2] Current treatments are preventive rather than restorative,[3] have limited impact on the accumulation of disability, and are only partially effective in preventing relapse.[4]

New treatments offer the opportunity to delay disability progression and relapses, but to address unmet needs one must consider the perspective of both the patient and the healthcare provider.[5-8] Patients require more tolerable therapies[9] that are easier to take,[10] and reduce the frequency of intravenous interventions.[10] They require customised treatments based on disease prognosis and individual needs[9,10-14] that provide quality of life (QoL) benefits.[12] Patients also require greater knowledge of the overall benefit/risk balance of the available treatments.[13] Health status deteriorates with increasing disability in a non-linear manner.[15-17] The initial steep progression as the patient moves from 0.5 to 2.5 on the expanded disability status scale (EDSS) slows between EDSS 2.5 and 6.0 before a rapid decline leading to EDSS 9.0. Early intervention is therefore important to limit disability and preserve health status.

Treatment can be better individualised by understanding what impacts a patient's QoL.[16] QoL is not based on function alone; it involves social, mental, and emotional aspects.[14,16,18-20] Treatment adherence is a major challenge. A survey of 2,648 patients revealed that adherence to injectable disease-modifying treatments (DMTs) declined the longer the patients received therapy.[9] Lack of adherence is largely due to injection-related issues, principally injection site pain, injection anxiety, and patients becoming tired of taking injections.[9] Furthermore, many patients simply forget to administer their drugs.[9]

Adherence plays a crucial role in long-term outcomes; adherent patients have a 60–70% risk reduction in relation to reaching EDSS 6; EDSS 6 combined with secondary progressive MS (SPMS), SPMS alone, or being confined to a wheelchair.[21]

Better involvement of patients in treatment decisions can improve adherence; however, physicians and patients place different emphasis on the importance of clinical attributes.[22] Physicians are primarily concerned with long-term outcomes, whereas patients are more concerned with the immediate impact of daily treatments on their disease and their QoL.[22] Importantly, patients may be more willing than their physicians to take risks in exchange for efficacy benefits.[13]

The course of MS is driven by inflammatory events, occurring early on, which predict long-term disability progression and highlight the need for early intervention rather than a 'wait and see' approach to optimise long-term outcomes.[23-29] Thus, early in the disease there is a therapeutic window when the greatest benefit can be obtained from the most appropriate intervention.[30] Individualising therapy relies on understanding the optimal patient prognosis to select the most appropriate treatment. Factors associated with good prognosis are younger age of onset, white ethnicity, female gender, isolated sensory systems, long interval to the second relapse, and low MRI lesion load at onset. Conversely, older age of onset, male gender, non-white ethnicity, involvement of efferent systems, large MRI lesion load at onset, and a rapid rate of accumulation of MRI lesions during the first 5 years are predictors of poor prognosis.[31] Not only is there considerable variation in the course of the disease but the response to treatment is heterogeneous. Up to 50% of patients have a suboptimal response to injectable therapies,[26] highlighting the need for markers of efficacy and safety to enable better individualised treatment. Switching treatment based on clinical and MRI disease activity is feasible and clinicians should strive for a disease activity-free response in patients with relapsing-remitting multiple sclerosis (RRMS).

Currently, there are no standardised guidelines or algorithms for choosing between the increasing number of DMTs available (11 as of 2014[32]). For many patients, the first treatment choice will not be the last; treatment is an ongoing decision requiring close monitoring. Consideration of the patients' needs, clinical presentation, prognosis, and the ultimate treatment goal offers a practical approach that can be implemented as individualised treatment. The traditional approach of starting all patients on the same moderate efficacy treatment options then cycling and escalating these as the disease progresses ignores the heterogeneities of the disease course or treatment response,[26,33,34] and is not appropriate for all patients.[26] Individualised treatment based on projected disease course is the basis of an evolving treatment paradigm;[33,35] one that considers the needs, disability and disease status, prognosis, and adherence potential of a patient from the outset,[35-37] and involves the patient in treatment decision-making. Individualised treatment relies on close and ongoing assessment to achieve freedom from disease activity.[36,37]

In summary, traditional treatment goals in MS have been strictly limited by the treatment available. New therapies can address the unmet needs of both physicians and patients, allowing a redefinition of treatment goals to include improving existing disability, reducing new MRI activity, and freedom from disease activity. Consideration of the patient's perspective allows individualised treatment, taking into account the willingness of patients to accept risks in exchange for greater efficacy, reduced treatment burden, and improved QoL.

New Oral Opportunities in First-Line MS Therapy: Teriflunomide

Professor Matthias Mäurer

Teriflunomide is the primary active metabolite of leflunomide, a drug used for the treatment of rheumatoid arthritis. Following an extensive clinical study programme,[8,38,39] a once-daily 14 mg dose of the novel formulation, teriflunomide, has been licensed for the treatment of RRMS in the European Union (EU)[22,40] and is under regulatory review in Turkey.[22] Teriflunomide inhibits a key enzyme of pyrimidine synthesis, thereby interrupting the pyrimidine supply of rapidly proliferating cells. Particularly, rapidly proliferating T and B cells are depleted of dihydro-orotate dehydrogenase (DHODH), a compound vital for RNA and DNA synthesis, cell membrane molecules, and second messengers.[41] In this regard, teriflunomide can be viewed as a selective immunomodulator rather than an immunosuppressive drug. Resting T cells and non-lymphoid cells are unaffected because they utilise the 'salvage pathway' to supply their pyrimidine pool.[41]

To date there have been ten clinical trials involving teriflunomide.[8,11,39,42-48] The TEMSO[8] and

the TOWER[42] studies examined teriflunomide at 7 mg and 14 mg versus placebo. The TENERE trial[43] examined teriflunomide versus the established MS treatment, Rebif. The TOPIC study[49] examined the efficacy of teriflunomide in clinically isolated syndrome. TERIPRO[46] is a multinational study evaluating the effect of teriflunomide on patient-related outcomes in clinical practice. The TERIKIDS trial[48] is evaluating the effect of teriflunomide in children and adolescents. TERIVA[44] and the Rabies neoantigen study[45] are examining vaccination with teriflunomide. These trials measure efficacy in three key areas: relapse rate, progression of disability accumulation, and MRI activity. Annualised relapse rate (ARR), the primary endpoint of TEMSO[8,38] and TOWER,[38,42] was significantly reduced by both the 7 mg and 14 mg doses of teriflunomide, with the latter reducing risk by 32-36%. Furthermore, unlike the 7 mg dose, the 14 mg dose significantly reduced disability accumulation in both trials.[8,38,42] Both doses produced significant reductions in gadolinium-enhancing (Gd) lesion loads of 57% and 80%, respectively.[8] In addition, the 14 mg dose significantly reduced total lesion volume by 67%.[8]

Data from the TEMSO and the TOWER populations were pooled to create a larger subgroup of patients with highly-active disease, defined as two or more relapses in the year before study entry. Both doses of teriflunomide significantly reduced severe relapses leading to hospitalisation, requiring IV corticosteroids, had sequelae, or were defined by Panlich's rules, with the greatest reductions associated with the 14 mg dose.[50] Such relapses have a significant impact on a patient's QoL as assessed by the SF-36 questionnaire.[49] Based on these data, the European Medicines Agency licensed teriflunomide for the treatment of MS for patients with RRMS without any restriction. Data from the TOPIC trial,[49] evaluating the effect of teriflunomide in patients with early MS or clinically isolated syndrome (CIS), show a 43% risk reduction for a further relapse in CIS. Despite failing to meet its primary endpoint - time-to-failure versus Rebif - the TENERE study[43] showed similar rates of relapse/treatment discontinuation for both drugs. Furthermore, there was no significant difference in ARR between subcutaneous interferon preparation and teriflunomide 14 mg.[43] Nevertheless, treatment satisfaction questionnaire for medication (TSQM) scores at week 48 demonstrated a clear advantage for teriflunomide in terms of side-effects and convenience, which may have important implications for adherence.[43]

Many patients do not want injectable therapies. Take for instance the case of a 28-year-old female who experienced a right optic neuritis, had complete remission after IV steroids and an EDSS of 0.0. Her MRI shows dissemination in time and space and she fits McDonald's 2010 criteria for definite MS. The patient needs a convenient and tolerable medication and wants children eventually. Therefore, teriflunomide meets all the criteria required for an individualised MS therapy. Pooled safety data show no difference between placebo and teriflunomide in the rates of serious infections and malignancies.[51] Side-effects include nausea, diarrhoea, hair thinning, and reduced neutrophil and lymphocyte counts that remain within the normal range.[8,42,51,52] Teriflunomide causes a slight elevation of liver enzymes and regular monitoring is mandatory.[51] Ongoing blood pressure and total blood count testing is also required, and women of child bearing age need to use contraception. Whilst there have been 26 live births with no malformations or structural or functional abnormalities of children exposed during gestation,[53] teriflunomide is contraindicated in pregnancy. Should a patient fall pregnant accidentally or wish to become pregnant, an accelerated elimination procedure using charcoal or cholestyramine can reduce teriflunomide concentrations by 98% in 11 days.[54] Two studies have addressed the effects of teriflunomide on vaccinations and demonstrated a normal seroprotective response to neoantigens (rabies)[44] and recall antigens (influenza).[39]

In summary, teriflunomide has a consistent efficacy in clinical and MRI outcomes across a broad spectrum of MS patients. Teriflunomide demonstrated significant benefits on disability in two separate placebo-controlled Phase III trials (TOWER and TEMSO). An extensive clinical programme with long-term follow-up provides a consistent and well characterised safety profile of teriflunomide. Taken together, the overall benefit/risk profile supports teriflunomide's use as an initial therapy for RRMS patients.

New Opportunities with Alemtuzumab: a Mechanism-Based Therapy for MS

Professor Alastair Compston

Alemtuzumab (Lemtrada) began life 23 years ago as Campath-1H. The original name reflects the fact that it was produced at the University of Cambridge and was the first humanised monoclonal

antibody. Based on the knowledge of the pathogenesis of MS in the late 1980s it was hypothesised that targeting the circulatory immune system might provide a viable treatment option. The hypothesis was first tested in a patient in 1991. Observations over the next decade led to the realisation that drugs targeting the immune system need to be given early in the course of the disease. Alemtuzumab performed well in the CAMMS223 Phase II study of patients with early MS designed in conjunction with Ilex, subsequently purchased by Genzyme. Data at 3 and 5 years were extremely positive and led to the Genzyme 2 Phase III studies, CARE-MS I and CARE-MS II. All trials have entered into extension phases and data are continuing to be gathered. Based on these trials, the EU granted a product licence on 17th September 2013 for the use of alemtuzumab in the treatment of adults with active RRMS as a first-line therapy. Alemtuzumab is also approved in Australia, Brazil, Canada, Guatemala, and Mexico.[22] An FDA licencing decision is due in December 2014 and reviews are taking place in several other countries; however, Turkey has not approved alemtuzumab.[22]

Alemtuzumab binds to CD52, a protein of unknown function, which is abundant on the surface of B and T lymphocytes.[55] Alemtuzumab is administered in two courses by IV infusion at 12 mg/day. The first course runs over 5 consecutive days and, 1 year later, the second course runs over 3 consecutive days.[56] Blood levels initially reach a high concentration that falls following the infusion. The drug is undetectable after 30 days following the first course and 14 days following the second.[57] Once the treatment is complete there is no withdrawal or requirement to reverse the drug. On the first 3 days of each course patients should be pretreated with conventional IV corticosteroids to avoid cytokine release syndrome leading to acute infusion reactions.[56] Patients should also be given acyclovir antiviral therapy for the first month of each treatment course.[56]

Alemtuzumab is a cytotoxic antibody that selectively targets the adaptive immune system by depleting T and B cells in the circulation,[55,58,59] sparing the neutrophils and monocytes of the innate immune system.[7] Following treatment, levels of CD4 T cells drop rapidly before recovering slowly; however, they remain below the lower limits of normal during the treatment period and for many years after that.[7] Depletion of the adaptive immune system creates an 'immunological space' that is repopulated to form an immune system with entirely different properties.[55,58-60] During repopulation there is a surge of regulatory T cells and the immunological space is filled by an expansion of surviving memory clones. This preferential memory cell expansion may bring back some old immunological memories that are probably responsible for alemtuzumab's main side-effect, secondary autoimmunity.

The initial treatment cohort treated between 1991 and 1997 consisted of 36 patients with relatively advanced secondary progressive MS who were already disabled. Following suboptimal results from these first patients, the next trial commenced in 1999 focusing on a cohort of 22 people with early RRMS.[61] Data from the secondary progressive MS and RRMS cohorts show that alemtuzumab reduced relapse rates by 98% and 91%, respectively.[61,62] Disability in the progressive MS cohort, as measured by EDSS, increased in the years following the course of alemtuzumab. Conversely, EDSS scores in the RRMS cohort actually fell in the majority of patients.[61] These results highlighted the need to treat patients early on in the course of the disease to achieve the best possible reduction in disability and this rationale was the basis of the subsequent multicentre international clinical trials.

The Phase II study, CAMMS223, and the Phase III studies, CARE-MS I and CARE-MS II, are randomised, comparator-controlled trials comparing alemtuzumab against a high dose of interferon beta-1a (Rebif) in patients with active RRMS. CAMMS223 and CARE-MS I focused on drug-naïve patients whereas patients in CARE-MS II had already relapsed on another therapy.[6,63,64] Over 94% of patients from CARE-MS I and II entered the extension study, and as of June 2014, patients have been followed for at least 4 years, representing over 6,500 patient-years of exposure.[6,63,64] CARE-MS I and II are well balanced in terms of disease duration, gender, number of attacks, and number of enhancing lesions. However, CARE-MS II includes higher levels of disability and longer disease durations.[64] CARE-MS I and II both reached their co-primary endpoint of ARR. Both trials achieved treatment effect over and above that achieved with Rebif, namely 55% for CARE-MS I and 49% for CARE-MS II.[6,64] Moreover, alemtuzumab proved superior in reducing the rate of severe relapse.[65,66]

The other co-primary endpoint concerned disability; alemtuzumab produced highly significantly lower rates of sustained accumulation of disability in CARE-MS II[64] and a pooled analysis of CARE-MS I

and CAMMS223.[67] Patients receiving alemtuzumab in CARE-MS II were more than twice as likely to have a sustained improvement in disability over 6 months.[6] Furthermore, mean EDSS scores at 2 years improved from baseline in patients receiving alemtuzumab and worsened in patients receiving Rebif.[64] Alemtuzumab also demonstrated significant reductions over Rebif in the proportion of patients with Gd-enhancing lesions, new or enlarged T2 and new T1 lesions.[68,69] However, reductions in T2 lesion volumes were not significant in CARE-MS I or II.[6,64] The proportion of patients free from disease activity, either measured using MRI or clinical parameters is - with the exception of MRI activity in CARE-MS I - significantly higher in both CARE-MS I and II.[6,70,71] Alemtuzumab-treated patients had significantly improved QoL at all time points.[72,73] Overall, approximately 80% of patients did not require a third alemtuzumab dose; <2% changed therapy.[65] Both ARRs remained low[6,7,65] and disability scores continued to improve after 3 years.[60] 12 year follow-up of the initial 87 patients shows 80% of the cumulative experience led to stability or improvement.[74]

The majority of adverse effects were mild-to-moderate and patients responded to conventional therapies; serious infections were rare.[22,64,75] The overall incidence of adverse effects and infections declined over 3 years.[76] The safety profile was similar in treatment-naïve patients and those who had received prior therapy. Acute infusion effects coincided with the two courses of treatment, and were fewer with the second course.[77,78] In addition to acute infusion reactions, alemtuzumab's main side-effect is secondary autoimmunity affecting the thyroid, with very rare cases of idiopathic thrombocytopaenic purpura and renal immunity.[79] As a result, there is a compulsory risk management plan to anticipate such complications.[56]

In summary, alemtuzumab demonstrates superior and durable efficacy (both clinical and MRI measures) and improvements of pre-existing disability. The drug has a consistent, well characterised safety profile with early detection and management of identified risk managed via a comprehensive safety monitoring programme. These data support a favourable benefit/risk profile for alemtuzumab in RRMS patients.

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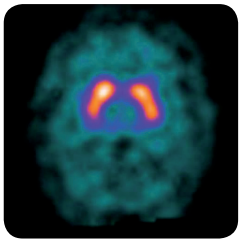
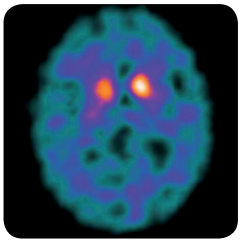


Probable dementia with Lewy Bodies (DLB)



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DaTSCAN™ ioflupane (^{123}I) 74 MBq/ml solution for injection
Please refer to full Summary of Product Characteristics (SPC) before prescribing. Further information available on request.
PRESENTATION Single dose vials containing 185 MBq or 370 MBq ioflupane (^{123}I) at reference time.
INDICATIONS Detecting loss of functional dopaminergic neuron terminals in the striatum. **i)** in adult patients with clinically uncertain Parkinsonian Syndromes, for example those with early symptoms, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP). DaTSCAN is unable to discriminate between PD, MSA and PSP. **ii)** in adult patients to help differentiate probable dementia with Lewy bodies (DLB) from Alzheimer's disease. DaTSCAN is unable to discriminate between DLB and Parkinson's Disease dementia.
DOSAGE AND METHOD OF ADMINISTRATION Prior to administration appropriate resuscitation equipment should be available. For use in patients referred by physicians experienced in the management of movement disorders/dementia. Clinical efficiency has been demonstrated across the range of 111-185 MBq; do not use outside this range. Appropriate thyroid blocking treatment must be given prior to injection of DaTSCAN. The safety and efficacy of DaTSCAN in children 0 to 18 years has not been established. No data are available in patients with significant renal or hepatic impairment. DaTSCAN should be used without dilution. Slow intravenous injection (15-20 seconds) via an arm vein is recommended. SPECT imaging should take place 3-6 hours after injection of DaTSCAN.
CONTRAINDICATIONS Pregnancy and hypersensitivity to the active substance or any of the excipients.
WARNINGS AND PRECAUTIONS If hypersensitivity reactions occur, the administration of the medicinal product must be discontinued immediately and, if necessary, intravenous treatment initiated. Resuscitative medicinal products and equipment (e.g. endotracheal tube and ventilator) have to be readily available. Radiopharmaceuticals should only be used by qualified personnel with appropriate government authorisation and should be prepared using aseptic and radiological precautions. For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic result. DaTSCAN is not recommended in cases of moderate to severe renal or hepatic impairment. Contains 39.5 g/l (5% volume) ethanol, up to 197mg per dose, harmful for those suffering from alcoholism. To be taken into account in high-risk groups such as patients with liver disease or epilepsy.
INTERACTIONS Consider current medication. Medicines that bind to the dopamine transporter with high affinity may interfere with diagnosis; these include amfetamine, benzatropine, buproprion, cocaine, mazindol, methylphenidate, phentermine and sertraline. Medicines shown during clinical trials not to interfere with DaTSCAN imaging include amantadine, trihexyphenidyl, budipine, levodopa, metoprolol, primidone, propranolol and selegiline. Dopamine agonists and antagonists acting on the postsynaptic dopamine receptors are not expected to interfere with DaTSCAN imaging and can therefore be continued if desired. In animal studies pergolide does not interfere with DaTSCAN imaging.
PREGNANCY AND LACTATION Contraindicated in pregnancy. Information should be sought about pregnancy from women of child bearing potential. A woman who has missed her period should be assumed to be pregnant. If uncertain, radiation exposure should be the minimum needed for satisfactory imaging. Consider alternative techniques. If administration to a breast feeding woman is necessary, substitute formula feeding for breast feeding for 3 days.
UNDESIRABLE EFFECTS No serious adverse effects have been reported. Common side effects include headache. Uncommon side effects include vertigo, increased appetite, formication, dizziness, dysgeusia, nausea and dry mouth. Intense pain on injection has been reported uncommonly following administration into small veins. Hypersensitivity occurs with unknown frequency. Exposure to ionising radiation is linked with cancer induction and a potential for hereditary defects. Because of the low radiation dose incurred these adverse events are expected to occur with a low probability.
DOSIMETRY Effective dose from 185 MBq is 4.35 mSv.
OVERDOSE Encourage frequent micturition and defecation.
MARKETING AUTHORISATION HOLDER *GE Healthcare Limited, Amersham Place, Little Chalfont, Buckinghamshire, HP7 9NA, UK.*
CLASSIFICATION FOR SUPPLY Subject to medical prescription.
MARKETING AUTHORISATION NUMBERS EU/1/00/135/001 (2.5ml) and EU/1/00/135/002 (5.0ml).
DATE OF REVISION OF TEXT 22 March 2013.
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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to GE Healthcare.

GE Healthcare Limited, Amersham Place, Little Chalfont, Buckinghamshire, England HP7 9NA www.gehealthcare.com

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1. Warr L, Walker Z. QJ Nucl Med Imaging 2012; 56: 39–54.
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Images courtesy of Southampton General Hospital, UK

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PARADIGMS: A NEW INITIATIVE TO CUT THROUGH THE NOISE ON MULTIPLE SCLEROSIS
A CONVERSATION WITH DR ANDREAS LYSANDROPOULOS

Interview of Andreas Lysandropoulos[1] by Caroline Charles[2]

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About Dr Andreas Lysandropoulos

- Andreas Lysandropoulos is a neurologist specialised in multiple sclerosis and neuroimmunology working at the University Hospital Erasme in Brussels, Belgium.
- He received his M.D. in Greece and completed his internship in Neuroimmunology in Lausanne, Switzerland.
- He is actively involved as a principal investigator in major clinical studies and has published many peer-reviewed articles.

INTRODUCTION

ParadigMS is a new, independent peer-group of multiple sclerosis (MS) experts, aiming to provide a high level of science and insight to healthcare practitioners (Table 1). The project is sponsored by Genzyme EMEA for logistic and organisational purposes.

During one or two international meetings a year, the experts will discuss between six and nine topics, and identify evidence-based approaches and strategies, but always in interactive and pragmatic ways. Then, each participant will disseminate the information through national symposia in order to reach out to neurologists and healthcare practitioners in their own language and with information tailored to each country's characteristics.

One of the members of ParadigMS, Dr Andreas Lysandropoulos, tells us more about this exciting new venture and the topic he presented at the second meeting - quality of life (QoL) – and the general wellbeing of patients living with MS.

You are part of ParadigMS, and it seems that this programme comes at a time when we know so much about MS, yet many questions remain unanswered and some paradigms have shifted, disrupting in the process some certainties. What are the main challenges physicians are facing today regarding MS?

MS is a topic that is currently 'exploding' because a lot of new data are constantly flowing in from everywhere and new products are regularly added to the therapeutic armamentarium. Our peer-group recognised the need to review this amount of data in an objective way and with a high scientific level. Thus, we will be able to focus on evidence-based knowledge that we can summarise then disseminate to our colleagues also working with MS patients. We are aiming to provide a collection of scientific data they can actually use and broadcast to others. Hopefully, we will help physicians position themselves in this rapidly changing environment.

You are then aiming to address one of the main weaknesses of congresses and medical education:

Table 1: The members of ParadigMS.

Position	Name	Country
Chair	Otto Van Eikema Hommes	the Netherlands
Co-Chair	Bernd Kieseier	Germany
Member	Paolo Gallo	Italy
Member	Nikolaos Grigoriadis	Greece
Member	Eva Havrdova	Czech Republic
Member	Raymond Hupperts	the Netherlands
Member	Ralf Linker	Germany
Member	Andreas Lysandropoulos	Belgium
Member	Celia Oreja Guevara	Spain
Member	Carlo Pozzilli	Italy
Member	Maura Pugliatti	Italy
Member	Sven Schippling	Switzerland
Member	Vincent Van Pesch	Belgium
Member	Bart Van Wijmeersch	Belgium

sometimes the information can be impractical or impossible to implement locally.

Yes, some physicians who are not specialised in certain areas may feel drowned by the information provided at congresses, sometimes after only 15 minutes. Our objective here is to provide practical knowledge without getting lost in incomprehensive and complicated algorithms. That said, our goal is to always give information that everyone will be able to select and use: our documents will be developed at different levels so that each doctor can decide whether he/she is interested in basic or advanced information.

The ParadigMS project thus acts as a filter?

Sometimes the word 'filter' can imply negative aspects: we do not pretend to know or choose what information is useful or not, we will simply offer core evidence-based medicine. We will not present scientific hypotheses that have not yet been confirmed, we will only focus on evidence, and we will provide it in a structured and practical way, so that doctors will be able to use it.

What sets your programme apart is the extremely pragmatic approach.

Yes, in most areas, including MS, treatment algorithms are developed, but this is not real medicine. Instead of this, our ambition is to deliver a framework and a philosophy so that physicians can 'feel' how to treat a patient with MS. Certainly, we will present information related to the disease, its evolution, and hands-on aspects ('how to evaluate a patient', 'how long should we wait between two magnetic resonance imaging (MRI) scans', 'which clinical scales should we use'), but we will never introduce information rigidly.

How many meetings are scheduled per year?

At least once or twice a year; this year, we had two meetings. The current project is to create an online Cloud where we can share our presentations at two levels: one for members of ParadigMS, so we can collaborate all year long and suggest some changes along with new research developments, and the other level for healthcare practitioners as a learning platform. We had a very nice experience during both meetings, our approach is very modern, and we have a very relaxed atmosphere. By including experts who still practice and see patients every day, we continue to have a feeling of 'everyday life' while discussing at a very high scientific level.

How do you ensure impartiality throughout the process as a pharmaceutical company is sponsoring the project?

It is clear that we need organisational support for several reasons; it is an international project, MS specialists are coming from everywhere, and it is obvious that this kind of project is difficult to

organise by the academy or by an independent team. The pharmaceutical company supports us in terms of logistics, organising our meetings, and our presentations, but it was very clear from the start that the firm is not involved at any stage of production, maintenance or evaluation of what we provide. The presence of the pharmaceutical company is very restrained, and the proof is that during the first two meetings, we did not speak at any time about specific products from Genzyme or another company.

The topic that you presented at the first meeting focused on QoL for MS patients, could you provide a brief overview of what was discussed?

QoL should be the main focus when evaluating a patient and the main objective of MS management. Clinical studies on new drugs or new therapeutic approaches usually rely on clinical aspects or MRI results, but this is not reality. Some patients can be stable when you consider these criteria, yet their QoL scores are catastrophic and the patient can be in a lot of pain, psychologically speaking. On the other hand, a patient can present disastrous clinical results but his/her QoL can be close to normal. As you can see, there is a discrepancy between what is objectively measured and what happens in real life. QoL can comprise fatigue, sexual dysfunction (for psychological or physical reasons), and cognitive impairment. Public perception of MS is often linked to the wheelchair stigma. At the time of diagnosis, many patients feel lost and betrayed by their bodies; they isolate themselves and abandon professional or personal projects.

Furthermore, QoL must be measured. We have scales at our disposal but there is no consensus on which scale can perfectly assess QoL. We have to work on this by applying scales, collecting data, and evaluating them in cohort studies.

On another level, to detect issues related to QoL, physicians must have sufficient time to spend with their patients. This is crucial and this belief is shared by all of my colleagues from ParadigMS. Nowadays, time is consumed for very practical aspects of disease management; we miss things that are much more crucial to our patients, things that they do not usually admit to right away, so we have to work with them and discuss sensitive issues.

This is extremely relevant since some studies have shown that QoL can directly influence clinical aspects of MS and be a prognostic tool for the evolution of the disease.

There are even studies that are very impressive and discuss the effect of the psychological state of mind of patients, and how they see themselves in our society and in the lives of others. Some other results show that psychological support may have a direct influence on the brain's inflammatory lesions, and it shows on MRI readings. This is the proof that psychological care is not just theoretical; it has a direct impact on the biology at the core of the disease.

Additionally, cognitive impairment is more and more recognised as it is an issue from disease onset and mainly concerns rapid processing of complex information. We know that cognitive reserve is not only influenced by genetics, but also by cognitive leisure activities and life experiences. This is very important with respect to QoL; we must encourage patients to remain active on a cognitive level.

These are topics that seem very basic but are quite new to MS. 10 years ago, people with MS were people with physical disabilities. Now we know that MS patients experience fatigue and cognitive impairment, but we can implement useful approaches and they do not necessarily have to be pharmacologic strategies.

Could you give us some principles to further close the gap between medical rationalism and patient insight?

I would advise to spend more time with patients, apply scales, and take advantage of the internet. If you ask your patient to fill a scale on QoL for 10 minutes, you lose valuable time. It does not help either to ask a patient to fill the scale at home and return it for next time because the patient might forget. Now, if the patient prints a scale at home and fills the information in real-time, the results will be much more accurate and closer to the historical reality than to ask a patient to recall the last 3 months during a consultation. MS patients are connected - there are a lot of discussion forums and patient associations - and we can turn this into a very useful tool.

How can multidisciplinary care help with issues related to QoL such as sexual dysfunction?

Many problems of this disease should be managed by a multidisciplinary approach. As an example, dynamic physiotherapy has a beneficial effect; exercise with a physiotherapist influences brain plasticity and helps to create new networks. Psychological care, alone or in working groups, is essential. Studies also have shown benefits for

patients who are part of a group who meet along with healthcare practitioners to discuss together many aspects of the disease.

How do you address these sensitive issues?

These issues should be discussed privately with the patient by taking the time to let the patient confide in us during a consultation; we should not take our patient by surprise. At first, it is important to find the root of the problem. Sexual dysfunction may be related to self-image, psychological or organic issues, directly or indirectly related to MS. A good patient-doctor relationship built on trust is of crucial importance to ensure good communication and proper care. While we may have psychologists in our multidisciplinary teams in hospitals, private care neurologists should not hesitate to address a patient to a psychologist if they feel the issue requires further help.

What about pregnancy? How can we manage female patients before, during, and after pregnancy, and ensure acceptable QoL?

In the last decades, pregnancy was believed to have a negative effect on MS because in the first 3-6 months after delivery, the patient might present resurgence of inflammatory disease activity, even if the third trimester was quiet. We must not avert our patients from becoming pregnant as pregnancy is only contraindicated in extremely severe cases. Pregnancy is a project that is important in the life of a woman so we must benevolently assist, advise, and manage our patients during this important stage of their lives.

We know now that the idea to stop any treatment for 3 months before a pregnancy is questionable for interferons and glatiramer acetate, which are traditional treatments of MS, so we can tell our patients to continue therapy until pregnancy is confirmed. This is an important development for QoL because patients who interrupt their treatment in order to attempt a pregnancy are often anxious. With anxiety, pregnancy will not happen right away and sometimes patients will experience a slight relapse, which will discourage them and make them give up their plans for pregnancy.

We have a supportive role to play in collaboration with the obstetrician/gynaecologist. The latter do not often see MS patients and may have questions on whether these patients can deliver vaginally or receive anaesthesia; the answer to both is: Yes!

Breastfeeding is important for the mother-child relationship, but as MS drugs are not recommended during lactation, we may - with the help of clinical evaluation and MRI results - determine the ideal timeframe and ask the patient to stop breastfeeding earlier or later than anticipated.

Let's go back to ParadigMS - what are the next steps?

Currently, we are finalising the presentations of the second meeting and uploading them online on our Cloud. Then we will go to the local level; each member of ParadigMS, with support from Genzyme, will organise a national meeting in his/her country in order to disseminate the information and share our thoughts with healthcare professionals.

The next meeting in 2015 will review failures and successes of our national meetings; we will share the feedback we received and address things that need to be improved. This project is not an autistic project and we will listen to what our colleagues suggest. To date, there are no specific topics defined for the next meeting as this collaborative approach will actually use the feedback from the last, and we are waiting to see which topics our colleagues want us to refine or address.

We want to be useful above and beyond theoretical aspects, so then we will move on to more practical things such as building tools to evaluate QoL.

What are the long-term ambitions of this programme?

All the participants were very enthusiastic during both meetings and ideas are flowing in! We shall discuss the possibility of developing online learning platforms and tools for physicians alongside mobile educational solutions for patients, although we must work step-by-step in this direction and not go too fast.

I would like to highlight the participation of Prof Van Eikema Hommes in this project; he has been intensely involved with MS for a very long time, despite his career level and age, and has retained a very modern and pragmatic vision for MS management. He is very charismatic and inspires us a lot, and we believe this is crucial to the project. He is the best example of a doctor who, through all the years, has kept the patient at the core of his interest. That is actually the first thing he insisted on when we started working together; before us, as physicians, we have a human being and we must consider the patient as a whole.

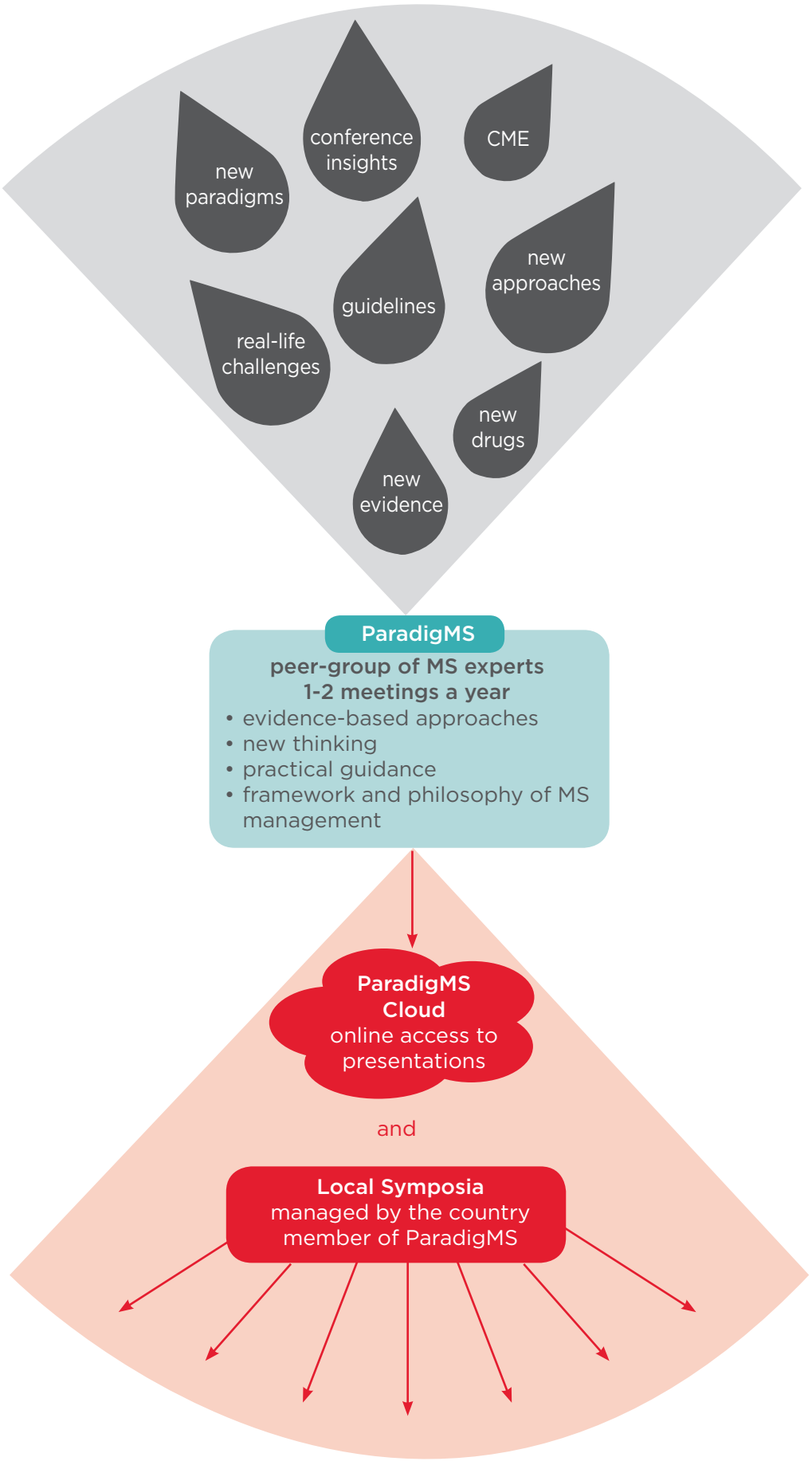

Figure 1: ParadigMS, a new independent peer-group of multiple sclerosis (MS) experts.

NEUROIMAGING OF ACUTE ISCHAEMIC STROKE: CURRENT CHALLENGES

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ABSTRACT

Over the last decade, neuroimaging methods have been refined to improve clinical decisions regarding acute stroke treatment. Computed tomography and magnetic resonance imaging are routinely used to rule out intracerebral haemorrhage or other contraindications of thrombolysis, to detect stroke mimics and to estimate the time of stroke onset. With the availability of fast and advanced imaging methods, there is a growing interest in expanding their application for the prediction of success and risks of specific therapies. The mismatch concept, which has long been controversial, has now experienced a breakthrough due to further development and standardisation of imaging parameters, and a separation of different, clinically relevant mismatch patterns. In this review, we will highlight existing neuroimaging modalities for acute stroke. To interpret neuroimaging results, knowledge about the clinical situation is essential. Furthermore, the factors of time since stroke onset and collateral blood supply need to be incorporated into existing imaging-based therapeutic strategies.

Keywords: Stroke, cerebral blood flow, mismatch, magnetic resonance imaging (MRI), computed tomography (CT), neuroimaging.

COMPUTED TOMOGRAPHY (CT) IN ACUTE STROKE

A plain non-contrast CT scan is sufficient to perform thrombolysis in acute stroke patients if all contraindications can be excluded.[1] Since the European Cooperative Acute Stroke Study (ECASS) III trial, intravenous thrombolysis with recombinant tissue-type plasminogen activator (rtPA) has been approved in Europe for up to 4.5 hours from symptom onset, and appears to be safe within this time frame.[2,3] Despite this extended therapeutic window, rtPA can only be given to a small fraction of stroke patients.[4] This is because the potential benefit of treatment has to be balanced against the risk of haemorrhage in the individual patient. There is an inverse relationship between time from stroke onset and successful recanalisation with thrombolysis.[5]

Non-contrast brain CT is fast and easily available, helping to minimise delays within the hospital ('door-to-needle times'), and therefore still the preferred primary imaging modality in many stroke centres.[6] In addition to non-contrast CT, CT angiography (CTA) and/or CT perfusion (CTP) imaging are increasingly available for stroke patients.[7] They allow visualisation of extra and intra-cranial arteries, including plaque characteristics as well as collateral flow.[8,9] Earlier drawbacks of a significantly increased radiation dose have been overcome by improved hardware and post-processing capabilities in new-generation CT scanners.[10] CTP allows imaging of brain tissue perfusion through sequential CT acquisitions following an intravenous bolus of an iodinated contrast agent. The following parameters are derived in most CTP applications: cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP).[11] After deconvolution of a reference arterial input function, MTT is derived. CBV is the area under the time contrast-enhancement curve, the TTP contrast enhancement, and CBF is calculated as CBF=CBV/MTT.[12]

MAGNETIC RESONANCE IMAGING (MRI) IN ACUTE STROKE

MRI is increasingly available as an alternative imaging modality in acute stroke and allows several non-contrast image acquisition modalities as well as magnetic resonance (MR) angiography (MRA) and MR-based perfusion-weighted imaging (MRI-PWI). From the latter, and similar to CTP, the parameters CBF, CBV, and MTT can be derived.[10,13,14] In addition to bolus-tracking techniques that rely on the application of an MRI contrast agent, arterial spin labelling MRI measures perfusion by non-invasively, magnetically labelling endogenous water protons.[15,16] The method is gaining access to clinical MRI protocols and has the unique potential to selectively analyse blood supply from a single, magnetically labelled vessel ('vessel encoded imaging') or with blood flow of a pre-defined velocity ('velocity selective imaging'), which is not feasible with bolus-tracking CTP or MRI-PWI methods.[17,18]

The MRI sequence parameter which revolutionised stroke imaging in the 1990s was the non-contrast application diffusion-weighted imaging (DWI).[19] DWI can readily depict even small ischaemic lesions within the first minutes/hours of stroke onset, and has proven to be more sensitive in ischaemic lesion detection than CT.[20] MRI is at least as good as CT with respect to the detection of acute intracranial haemorrhage.[21] Stroke mimics such as seizures, migraines, or encephalopathy are typically not discerned on a non-contrast CT.[22] Although the complication rate of thrombolysis in stroke mimics is low, patients would receive a potentially harmful therapy unnecessarily. In patients presenting with ambiguous clinical symptoms raising doubt about an ischaemic cause, MRI would be the preferred imaging modality.

Another challenge for the physician is stroke occurring during the night ('wake-up stroke') or in other situations when the onset is unknown; these patients were previously excluded from thrombolysis. Using DWI and fluid-attenuated inversion recovery (FLAIR) MRI, it is now possible to estimate the onset of stroke into <6 or >6 hours earlier.[23] Patients with wake-up stroke, who have a DWI positive lesion that is not demarcated on FLAIR, are very likely to be within a time window where thrombolysis can still be performed. Both sequences can be acquired within 5-10 minutes. Since stroke occurs during the night in approximately 25% of patients, this concept may significantly increase the eligibility of acute stroke patients for thrombolysis. Despite these advantages of MRI, the applicability to acute stroke patients is often limited due to the required head restrain, difficulties in patient monitoring, and exclusion of patients with pacemakers or claustrophobia.

THE TARGET MISMATCH

Initially described by Astrup in 1981,[24] the penumbra is tissue at risk of infarction due to a reduction in blood flow, hypoxia, and loss of functionality that has not yet caused irreversible failure of energy metabolism and necrosis.[25] The concept of 'mismatch' is an attempt to define this area by imaging, with the goal to search for tissue that is hypoperfused but still salvageable by recanalisation even beyond the approved treatment time window or to select patients for endovascular treatment. It was initially used in the context of a MRI-PWI and DWI mismatch for MRI assessment in acute stroke patients.[26] The infarct core is the area where MRI-PWI and DWI lesions are overlapping, indicating that hypoperfusion in these areas have already progressed to infarction. With time and persistence of the vascular occlusion, the core is expected to grow.

After results from smaller studies indicated that the PWI-DWI mismatch may indeed help to select patients for safe thrombolysis at treatment times >4.5 hours,[27-29] the concept was introduced into larger clinical trials, where a patient was grouped as having a mismatch when the lesion on MRI-PWI was 20% larger than the DWI lesion.[30-32] These trials (DEFUSE, EPITHET, DIAS-2), although showing a favourable response to thrombolysis with mismatch, could not prove that patient selection for thrombolysis based on the mismatch was beneficial.[2,30,33,34] The results were probably influenced by differences in post-processing of the perfusion maps.[35]

A separate, retrospective analysis of the DEFUSE data showed that the correlation between MRI-PWI lesion and final infarct size depends on the thresholds applied to the calculation of the PWI maps.[36] However, another re-analysis of the pooled DEFUSE-EPITHET data revealed that not only technical aspects might have contributed to the disappointing results regarding the interpretation of the mismatch. In patients between 3 and 6 hours of symptom onset with a mismatch

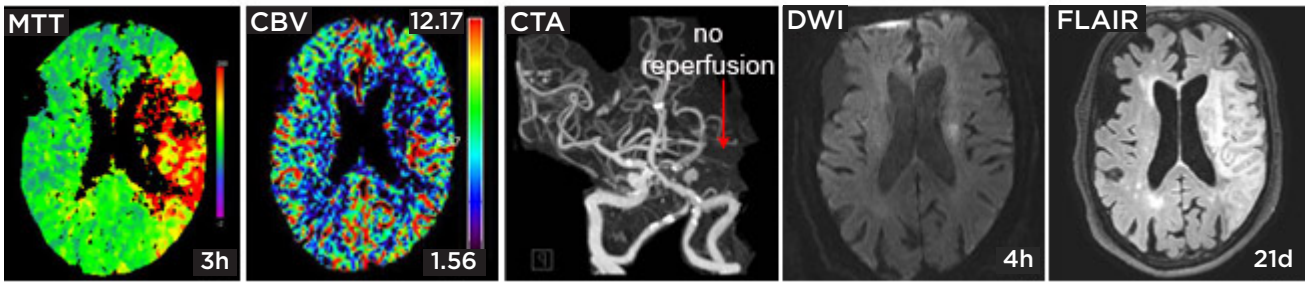

Figure 1: 83-year-old patient presenting with target mismatch without reperfusion, 3 hours after the onset of aphasia and right-sided sensorimotor paralysis.
The computed tomography perfusion (CTP), including mean transit time and cerebral blood volume maps and the diffusion-weighted imaging-magnetic resonance imaging (MRI) acquired 1.5 hours later, show a target mismatch in a MCA-M1 occlusion. Despite timely start of thrombolysis, recanalisation could not be achieved. The FLAIR MRI acquired 3 weeks later demonstrates that, with persisting M1-occlusion, the infarct has grown into the full area of prolonged time to peak on the initial CTP map.

but with a 'malignant' profile, defined as large (>80 ml) DWI and large (>85 ml with Tmax >8 seconds) MRI-PWI lesion, recanalisation caused even worse outcomes due to the increased occurrence of parenchymal haemorrhage.[37] These findings suggest that recanalisation strategies should be pursued with caution in patients presenting at later (>3 hours) time points with a MRI-defined malignant profile. Exclusion of patients with a malignant profile and dichotomising into patients with/without a 'target mismatch' demonstrated that patients with a target mismatch indeed respond better to recanalisation therapies, as in the prospective, randomised DEFUSE2 trial.[38]

Currently, several trials are testing the target mismatch as a selection criterion to extend the thrombolysis time window to up to 9 hours or test endovascular recanalisation.[39] CT has also been used to provide a mismatch, whereby MTT/TTP and CBV/CBF maps are overlaid in analogy to MRI-PWI and DWI, with MTT and CBV probably yielding the best prediction for infarct growth.[7] In this model, the core is the area of decreased CBV embedded into the larger area of prolonged MTT. Although the correlation to the MRI-defined mismatch is fairly good, the approach suffers from the fact that it can assess contrast-based perfusion parameters only and does not measure an independent tissue parameter such as DWI to estimate the core.

CONCLUSION

What is the underlying vascular physiology of a target mismatch versus a malignant profile in similar vascular occlusions? A proficient collateral vascular network might be present in some patients. Such collaterals might maintain perfusion and delay growth of the ischaemic core. It is conceivable that differences in collateral supply or in tissue resistance to ischaemia might contribute to the observed imaging patterns.[40] If different growth dynamics are to be expected, the influence of time should be incorporated into existing models of infarct growth. Recanalisation may still lead to clinical improvement when achieved within the first 3 hours of symptom onset in patients with a malignant profile and/or poor collaterals, but may be beneficial even at much later time points in a target mismatch patient with good collaterals (for an example of a patient with a target mismatch see Figure 1). It is very likely that advanced neuroimaging, including CTP and MRI-PWI, will facilitate the introduction of new and better treatments for acute stroke patients in the near future.

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DEPRESSION AND PSYCHOLOGICAL DISTRESS AS RISK FACTORS FOR STROKE AND WORSE STROKE RECOVERY: CLINICAL IMPLICATIONS AND THERAPEUTIC OPTIONS

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ABSTRACT

Stroke and depression have a strong bidirectional association: on the one hand, depression and psychosocial distress are well known risk factors for stroke; on the other hand, stroke is known to be a strong risk factor for depression. In the first 2 years after a stroke approximately one-third of patients suffer from a post-stroke depression (PSD). PSD aggravates the burden of physical, psychological, and social disability after stroke, and hinders patient participation in rehabilitation. PSD is associated with a poorer outcome and increased mortality. For the treatment of PSD, selective serotonin reuptake inhibitors (SSRIs) were recommended. Interestingly, SSRIs also have positive effects on motor recovery in stroke patients even without depression, but may increase vascular risk.

Keywords: Depression, stroke, psychosocial stress, selective serotonin reuptake inhibitor (SSRI), prevention.

INTRODUCTION

Each year approximately 16 million people worldwide suffer a first ischaemic stroke. About one-third of these people remain disabled.[1] In addition to the well-established risk factors, various studies and meta-analyses during the last years have demonstrated that both depression and psychosocial distress were both independent risk factors for ischaemic stroke. During the first 2 years after stroke, up to 30% of patients developed depression, known as post-stroke depression (PSD). PSD aggravates the burden of physical, psychological, and social disability after a stroke and hinders patient participation in rehabilitation. In these patients, selective serotonin reuptake inhibitors (SSRIs) were recommended. However, less is known about whether the treatment of depression leads towards a stroke risk reduction. Recent studies proved that treatment with SSRI in stroke patients with or without depression leads towards a better outcome. This paper overviews recent studies concerning the bidirectional association between risk of depression in stroke patients as well as depression and psychosocial distress as risk factors for stroke. Moreover, new treatment options in stroke patients and preventing strategies for PSD are described. For this review we searched the PubMed databases and screened references for the items: "stroke", "depression", "psychosocial distress", and "selective serotonin reuptake inhibitor". Only reviews, original articles, and meta-analyses published in English were included.

DEPRESSION, PSYCHOSOCIAL DISTRESS, AND STROKE

Depression is a Risk Factor for Stroke

Depression is known to increase the risk of stroke.[2] Data from the Framingham Heart Study analysing 4,120 patients demonstrated that the risk of stroke

in patients younger than 65 years was 4.2-fold higher in persons with depressive symptoms, even after adjustment for education and other risk factors; in participants older than 65 years this association could not be detected. A large meta-analysis of 17 studies with >200,000 patients determined the association between stroke risk and depression.[3] After adjustment for various risk factors the relative risk of stroke was 1.43 (95% CI: 1.17-1.54), without a significant sex difference. Another systematic review and meta-analysis included 28 prospective cohort studies with a follow-up between 2 and 29 years and described an overall hazard ratio (HR) of 1.45 (95% CI: 1.29-1.63) for total stroke in depressive patients.[4] Jackson et al.[5] recently observed a >2-fold higher risk (odds ratio (OR): 2.41, 95% CI: 1.78-3.27) of stroke in women between the age of 47 and 52 years without a history of stroke during a follow-up of 3 years. After adjustment for several risk factors such as socioeconomic status, lifestyle, and physiological factors the OR was 1.94 (95% CI: 1.37-2.74).

Chronic Psychosocial Stress and Stroke Risk

Surtees and colleagues[6] found in 20,627 stroke-free participants, aged 41-80 years, that increased psychological distress is associated with elevated stroke risk. Episodic major depressive disorder was not associated with incident stroke in this study. A large population-based trial in Sweden analysed chronic psychosocial stress and long-term outcome, cardiovascular morbidity, and mortality in middle-aged men.[7] The OR for cardiovascular events in patients with chronic psychosocial stress was 1.27 (95% CI: 1.15-1.39). Even after adjustment for various risk factors, the difference remained statistically significant. The highest risk was found for fatal stroke in men with an OR of 2.04 (95% CI: 1.07-3.88). According to the results of the INTERSTROKE study[8] both depression and psychosocial distress are risk factors for stroke. This international multicentre study performed in 22 countries defined psychological distress as at least several periods of general stress at work or at home in the past year. Egido et al.[9] observed a gender-independent increased stroke risk in stroke patients with stressful habits and type A behaviour. Henderson et al.[10] analysed the risk of stroke mortality and incident stroke in relation to psychological distress in a population-based cohort in Chicago, including 4,120 persons with a medium age of 77 years and a follow-up of about 6 years. Four psychosocial indicators (depressive symptoms, perceived stress, neuroticism, and life satisfaction) measured psychological distress. The authors found a strong association between psychological distress and stroke mortality even after adjustment for stroke risk factors. Distress was strongly associated with haemorrhagic strokes (HR: 1.0, 95% CI: 1.28-2.25) but not with ischaemic stroke.

Incidence of PSD

The incidence of PSD varies between 25-36%.[11] A recent study analysed the prevalence, incidence, and predictors of depression in a cohort of stroke patients older than 75 years up to 10 years after stroke.[12] The main finding of this hospital-based cohort of survivors of first or recurrent ischaemic stroke was a remaining high prevalence of depression up to 10 years. Moreover, the baseline geriatric depression score was the main predicting factor for depressive symptoms after stroke at all time points. Cognitive impairment was a significant univariate predictor of depression up to 4 years of follow-up. In the first year after stroke, previous stroke and number of vascular risk factors were also predictors for depression. Ayerbe et al.[13] analysed the incidence of PSD in patients registered in the South London Stroke Register between 1995 and 2009 (n=4022 at registration) during a follow-up of 15 years. The authors found a cumulative incidence of 55% and prevalence ranging from 29-39% in their population. Interestingly most episodes of depression started within a year after stroke. Overall, 33% occur within the first 3 months after stroke and none 10 years after stroke. Main predictors for depression in this population were disability, pre-stroke depression, cognitive impairment, stroke severity, and anxiety. A recently published systematic review found that the most frequently cited risk factors were sex (female), history of depression, stroke severity, functional impairments, level of independence, and family/social support.[14]

Prevention of PSD

In the literature, different strategies were discussed to prevent PSD. Palomäki et al.[15] studied the effect of 60 mg mianserin or placebo in a double-blind controlled study for 1 year after acute ischaemic stroke in 100 consecutive patients. They did not find that early initiation of antidepressant therapy is able to prevent PSD. However, the rate of depressive patients was low in the study population, which might have affected the results.

Robinson et al.[16] described that the use of escitalopram or problem-solving therapy resulted in a significantly lower incidence of depression over 12 months of treatment compared with placebo in non-depressed patients with recent stroke. In an intention-to-treat analysis, problem-solving therapy did not achieve significant results over placebo. Rasmussen et al.[17] tested the effect of sertraline in the prevention of PSD. 137 non-depressed patients after experiencing an acute ischaemic stroke were randomly assigned to 12 months of double-blind treatment with either sertraline (n=70) or placebo (n=67). Sertraline was significantly better than placebo. Only 10% of the sertraline-treated patients developed depression, compared to 30% of the placebo group. Another study described the efficiency of fluoxetine in prevention of PSD.[18] The use of duloxetine leads towards a reduction of PSD.[19] In addition, duloxetine is associated with a more rapid rehabilitation from stroke, and was associated with better cognitive function and quality of life (QoL). In conclusion, the prophylactic use of duloxetine not only decreased the incidence of PSD, but also promoted rehabilitation, cognitive function, and QoL. A recent population-based study analysed the effect of stroke rehabilitation within 3 months after stroke on PSD incidence.[20] Over a 10-year follow-up period, 5.8% of the patients with rehabilitation and 8.7% in the control group without rehabilitation developed PSD. Rehabilitation significantly reduced the risk of PSD after 3 months with a HR of 0.57 (95% CI: 0.45-0.73). Recently, Lawrence et al.[21] reviewed the benefit of mindfulness-based intervention after stroke and transient ischaemic attack in 160 participants. The results demonstrated a trend towards the benefit of this intervention in the improvement of psychosocial outcomes.

Outcome of Patients with PSD

PSD is associated with poorer functional outcome.[22] Moreover, the rehabilitation efficacy and the activity of daily living were reduced in depressed patients.[23] Besides advanced motor function disabilities, depressed stroke patients are more likely to be cognitively impaired.[24] Studies have shown that PSD increases the mortality rate at 1 year following a stroke.[25] Some trials observed that depression increases the risk of first and recurrent stroke by 45% to 80%.[26,27] In a systematic review and meta-analysis including 13 studies and more than 59,000 patients, the OR for mortality after stroke was 1.22 (95% CI: 1.02-1.47) in depressive stroke patients.[28] In studies with a follow-up shorter than 2 years, no significant association between death and depression after stroke was found. In studies with >5 years of follow-up a trend was detected. Studies with a duration between 2 and 5 years after stroke reached statistical significance. A multi-centre prospective cohort study in China including 2,306 patients with acute stroke showed a 49% increase in OR of recurrent stroke at 1 year in patients with PSD, compared to patients without PSD following a stroke (OR: 1.49, 95% CI: 1.03–2.15). There was no significant correlation between anti-depressant drugs and the risk of recurrent stroke at 1 year following a stroke (OR: 1.96, 95% CI: 0.95–4.04).[29,30]

SSRI in Stroke Patients

A systematic Cochrane review found that antidepressant medications are effective in treating PSD.[31] Today, SSRIs are the recommended pharmacotherapy of PSD due to their favourable tolerability profile. However, antidepressive medication in elderly stroke patients might increase the risk of haemorrhagic or ischaemic stroke due to an interaction with antiplatelet agents.[32-35] A recent meta-analysis found that the use of SSRI was associated with a 1.48-fold increased risk of ischaemic stroke and a 1.3-fold increased risk of haemorrhagic strokes.[36] Mortensen et al.[37] studied the association between post-stroke SSRI use and outcome in a nationwide prospective score-matched follow-up study. Patients treated with SSRI had a lower risk of myocardial infarction (MI) and recurrent stroke. For the combined endpoint stroke and MI, the difference in both groups was significant with a HR of 0.77 (95% CI: 0.62-0.96). SSRI use after stroke was associated with increased mortality, which might reflect a combination of uncontrolled confounding by interaction owing to the underlying depression and an increased bleeding risk.[37] According to the results of a large meta-analysis of 52 studies using SSRI in stroke, participants receiving SSRI were more likely to have gastrointestinal side-effects, seizures, and bleedings.[30]

Improvement of Motor Function with SSRI

A small study including eight stroke patients demonstrated that a single dose of fluoxetine is able to improve motor performance.[38] A few other small studies using SSRI in stroke patients suggested that this drug might have positive effects.[39-41] Functional magnetic resonance imaging (MRI) revealed an activation of the ipsilesional

Table 1: Overview of prospective placebo-controlled studies analysing the motor recovery in patients after ischaemic stroke using selective serotonin-reuptake inhibitors.

Drug and treatment	Number of patients	Time of inclusion after stroke	Main results
Fluoxetine 20 mg per day and maprotiline[47]	48	1-6 months	10.7% improvement in HSS score
Fluoxetine 20 mg per day[38]	8	15-30 days	20-30% finger tapping improvement
Citalopram 40 mg per day[40]	8	>6 months	11.4% improvement in nine-hole peg test
Citalopram 10 mg for 30 days[39]	20	Not reported	38.8% improvement of NIHSS score
Fluoxetine 20 mg per day for 90 days[42]	118	5-10 days after stroke	Improvement of FMMS scores

HSS: Hemispheric Stroke Scale; NIHSS: National Institutes of Health Stroke Scale; FMMS: Fugl-Meyer motor scale score.

Table 2: Standardised mean difference (SMD) and 95% confidence interval (CI) in the disability score after treatment with selective serotonin-reuptake inhibitors (SSRIs) in different randomised controlled trials including 1,343 stroke patients (according to Mead et al.[44]).

	Number of patients with SSRI	Number of patients in the control group	SMD and 95% CI
Fluoxetine	394	339	0.68 (0.31-1.06)
Sertraline	65	65	1.38 (0.99-1.76)
Citalopram	108	104	1.07 (-0.26-2.39)
Paroxetine	149	144	1.31 (0.67-1.95)
Total	691	652	0.91 (0.60-1.22)

insular and lateral motor cortex 5 hours after application of 20 mg fluoxetine.[38] According to these positive results, a double-blind placebo-controlled trial in patients with ischaemic stroke with haemiparesis or haemiplegia was initiated in nine stroke centres in France.[42] 118 patients were randomly assigned to 20 mg fluoxetine or placebo and the motor recovery in these patients was compared using the Fugl-Meyer motor scale score (FMMS). The FMMS improved significantly after 3 months in the fluoxetine group (mean: 34 points, 95% CI: 29.7-38.4) versus 24.3 points (95% CI: 19.9-28.7, p=0.003; Table 1). The main adverse events in the fluoxetine and placebo groups were hyponatraemia, transient digestive disorders including nausea, diarrhoea, and abdominal pain, hepatic enzyme disorders, psychiatric disorders, insomnia, and partial seizure.[42] In conclusion, fluoxetine significantly improves motor function in stroke patients without depression after 3 months, and occurrence of depression was lower in the fluoxetine group. Another multicentre, randomised, placebo-controlled trial found that 10 mg escitalopram per day prevents the development of PSD and was associated with improved short and long-term memory recovery.[16] Experimental studies described a neurogenic and neuroprotective effect of SSRI.[43] Recently, a meta-analysis of all published and non-published randomised controlled trials with SSRI (52 studies and 4,059 patients) given within the first year after stroke to determine the effect on dependency, disability, and other clinical outcomes was performed by Mead et al.[44] The age of the patients

ranged from 55-77 years. The effect of treatment with SSRI versus placebo was greater in trials recruiting people with depression compared to people without depression at randomisation. In this meta-analysis SSRIs were effective in treatment of stroke patients even without depression (Table 2).

CLINICAL IMPLICATIONS

The lifetime incidence of depression is about 16% in the general population.[45] For the treatment of depression, SSRIs were recommended as first-line treatment. However, the use of these drugs might increase the risk of ischaemic and haemorrhagic stroke. On the other hand, depression and psychosocial stress were independent predictors for ischaemic stroke. Moreover, about one-third of stroke patients developed a PSD, which implicates worse outcome and an increased risk for stroke recurrence. Therefore a systematic screening for depression after stroke should be performed after stroke onset. Due to the reduced length of hospital stay after stroke, the diagnosis of depression might be complicated. Man-van Ginkel et al.[46] established a PSD prediction scale, which could help to identify stroke patients with a high risk of PSD. Other predictors for PSD were extent of stroke-related disability, pre-stroke depression, cognitive impairment, stroke severity, and anxiety.

Recently, a large amount of studies described a better clinical and functional outcome after stoke using SSRIs even in non-depressed patients. However, the evidence available in different studies does not provide a clear picture regarding the treatment of PSD and the efficacy and safety of SSRIs. Therefore, more placebo-controlled studies, including SSRIs but also non-medical therapies for PSD and functional outcome, are necessary. Moreover, potential side-effects such as increased bleeding risk, cardiac complications, and an increased risk of seizures should be taken into account.

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IMAGING AND TREATMENT DECISIONS IN SEIZURES AND EPILEPSY

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ABSTRACT

It has been clearly shown that magnetic resonance imaging (MRI) is the preferred modality of structural imaging for both new onset seizures and established epilepsy. MRI imaging in epilepsy requires a dedicated MRI protocol in order to detect subtle epileptogenic lesions such as focal cortical dysplasia or hippocampal sclerosis. Thin-slice thickness and orientation in the longitudinal axis of the hippocampus and perpendicular to it are the main characteristics of dedicated epilepsy MRI. An expert experienced in epilepsy and imaging should interpret epilepsy MRI. The new generation of 3 Tesla (T) MRIs is more sensitive, particularly for focal cortical dysplasia.

Epilepsy-dedicated MRI is indicated particularly at the time of first seizure or new onset epilepsy, and when epilepsy becomes drug refractory. Results of a lesional MRI will assist in classifying the epilepsy syndrome and may well have an influence on treatment planning. Particularly in focal drug refractory epilepsies, a lesional MRI result may indicate a good hypothesis for presurgical assessment. If structural MRI is non-lesional, MRI post-processing may help to identify subtle epileptogenic lesions. CT scanning should only be performed in acute settings if MRI is not available or if the patient is too unwell for MRI scanning.

Keywords: Epilepsy, seizure, MRI, neuroimaging, epilepsy surgery, epilepsy treatment.

INTRODUCTION

Imaging is a standard diagnostic technique in the assessment of seizures and epilepsy. The following review will focus on indication for structural imaging in everyday clinical settings, the most appropriate structural imaging methods, and the impact of structural imaging on treatment decisions with regards to seizure disorders. It reports on imaging for epilepsy syndromes and not for other acute neurological illnesses which may precipitate acute seizures. There is a vast amount of literature on this topic. This review will focus mainly on the key publications.

In principal, there are two main points in time for imaging in seizure disorders: 1) with new onset seizure or seizures; 2) in established epilepsy, particularly at the time when the epilepsy is becoming drug refractory.

IMAGING FOR NEW ONSET SEIZURES

Imaging of new onset seizures is done with two different indications: 1) to identify an acute illness as the underline course for the seizure and possible neurological deficit; and 2) particularly in patients who are not acutely admitted with the first seizure, to establish the aetiology of the new onset seizure disorder.

Acute imaging is done in most settings with computed tomography (CT) of the head, which is usually easily available. CT is able to exclude acute neurological diseases such as stroke, intracranial haemorrhage, cerebral contusion, sinus thrombosis, and skull fractures. Furthermore, the patient is more easily accessible in a CT scan machine than in a magnetic resonance imaging (MRI) machine, which is particularly important if the patient is unwell. However, where MRI is easily available and

safe for the patient, it is also the preferred method for brain imaging in epilepsy.

From the clinical point of view every patient with a new onset seizure, except in some childhood and juvenile epilepsies, is required to have imaging. Patients who have prolonged recovery periods after the first seizure, who present postictally with neurological deficits or signs of infection, should be imaged immediately. Patients who recover quickly, have no neurological deficit, and no signs of infection may be referred for MRI imaging in the first instance, even though this may take a few days or a couple of weeks to be performed.

EPILEPSY SYNDROMES AND IMAGING

Most often clinical diagnoses of epilepsy alone will not lead to the classification of the underlying epilepsy syndrome. Hence, neuroimaging is indicated in most cases of newly presenting epilepsy. It has been shown early on that MRI imaging is superior to CT imaging in epilepsy.[1-3] Most often MRI findings in epilepsy are focal abnormalities such as hippocampal scleroses (HS), malformations of cortical development, and especially focal cortical dysplasia, vascular malformations, tumours, both gliomas and metastasis, as well as post-traumatic scars.[4-6] In generalised epilepsies there may be very complex malformations of brain development such as double cortex, extensive polymicrogyria, or pachygyria. By identifying a structural lesion in the brain, MRI is contributing to the correct classification of the epilepsy syndrome and sometimes even the seizure type.[7]

No imaging is required in clear cases of idiopathic generalised epilepsies such as childhood absence epilepsy (CAE) or juvenile myoclonic epilepsy (JME), if presenting with typical clinical and electroencephalography (EEG) features. However, if these patients are not seizure-free under antiepileptic medication, imaging may well be required to exclude other epilepsy syndromes mimicking idiopathic generalised epilepsy.

MRI in Epilepsy

With the introduction of MRI, many focal structural lesions in the brain, which were not visible in CT scan or other previously used imaging methods, became detectable. A classic example is HS, which MRI findings described early as atrophy and signal increase in the hippocampus.[8,9] In 1997 the International League Against Epilepsy (ILAE) published the recommendations for neuroimaging of patients with epilepsy.[10] Epilepsy patients should be scanned preferably with MRI, using longitudinal relaxation time (T1) and transverse relaxation time (T2) sequences, including, if possible, a 3-dimensional T1 weighted sequence. The sequences should be at least performed in two different orientations, covering the whole brain. Slice thickness should be minimal and an expert experienced in epilepsy should report the imaging. It has been shown that standard MRI imaging of the brain is missing particularly the diagnoses of HS.[11] Furthermore, the comparison of a standard MRI, reported by radiologists and neuroradiologists outside of epilepsy centres, re-reported by neuroradiologists experienced in epilepsy as well as epilepsy-dedicated MRI, reported by neuroradiologists experienced in epilepsy, showed a clear advantage of epilepsy-dedicated MRI.[5]

HS was detected in <10% of standard MRI scans performed and reported outside of epilepsy centres. In contrast, the pick-up rate of HS in epilepsy-dedicated MRI and reporting picked up 100% of histologically proven HS in this group of refractory epilepsy patients undergoing epilepsy surgery. The same study showed similar but not as dramatic differences for benign tumours as well as malformations of cortical development and vascular malformations. Whilst the scan quality improved over the 3-year period of that study, quality of reporting outside of epilepsy centres did not. In the meantime, 3 Tesla (3T) MRI is widely available and has definitely led to a higher pick-up rate in focal cortical dysplasias.[12,13] A head-to-head comparison study between 1.5T and 3T MRI in a large population of patients with epilepsy has not been performed to date.

Epilepsy-Dedicated MRI

As mentioned earlier, MRI imaging is most important to detect lesions in focal epilepsy. A large proportion of focal epilepsy is originating from the temporal lobe. Hence, it is important to focus with the imaging method on the temporal lobe. Axial imaging should be performed within the longitudinal axis of the hippocampus and the coronal slices perpendicular to the longitudinal axis of the hippocampus. In particular, hippocampal and temporomesial structures are much more visible in this way of imaging as in standard MRI brain scans. Standard MRI brain scans are usually orientated in the AC-PC orientation and the hippocampus is cut in an angle of approximately

45 degrees. Therefore atrophy as well as signal increases might be easily missed due to the effect of the angle. Furthermore, coronal images through the hippocampus in the temporal orientation should be acquired with thin-slice thicknesses of 2-3 mm.[14] As practical advice, the coronal temporal orientated sequence should be positioned rather early in the MRI protocol, as patients are more likely to move during sequences towards the end of the examination.

Expected Pick-Up Rate in First Fit MRI

Experiences from first fit clinics show that, depending on the imaging and referral modality, MRI is expected to show epileptogenic lesions in between 14 and 23%.[15-18] The most common epileptogenic lesion is gliosis, most often post-stroke. However, about 10% of the epileptogenic lesions are HS. Malformations of cortical development, vascular malformations, and tumours are around 15% each.[17] Figures may vary slightly as some of the studies performed in large patient cohorts scanned all patients presented to a first fit clinic. Other groups may have a doctor's consultation first and would only image those patients who very likely had a seizure on clinical grounds. Around one-third of patients in first fit clinics may actually have suffered syncope. Furthermore, non-epileptogenic lesions, such as cerebral small vessel disease, unspecific white matter lesions, or global atrophy, are detected in almost the same quantity as epileptogenic lesions. However, the majority of scans are normal at this stage.[16,17]

The likelihood of detecting an epileptogenic lesion in first fit MRI scans increases with age. In a recently published study about imaging in a large first fit clinic, cohort patients over the age of 65 years were more likely to have an epileptogenic lesion than people in younger age groups, although, this difference was not statistically significant. In fact, almost one-third of the elderly patients showed epileptogenic lesions with another one-third showing non-epileptogenic lesions in MRI epilepsy imaging.[17] Interestingly the same study correlated abnormal EEG results with epileptiform discharges and found that focal epileptic discharges are twice as likely to be correlated with an epileptogenic lesion than generalised or normal EEG. Non-epileptogenic lesions in MRI are slightly more likely to show epileptic discharges and generalised discharges compared to patients with normal MRI. 8% of patients with abnormal MRI scans had discordant results in EEG abnormalities.[17]

Expected Pick-Up Rate in Drug Refractory Epilepsy

The majority of studies on MRI lesions in drug refractory epilepsy are from epilepsy surgery programmes. Several studies show that around 80% of patients referred for epilepsy surgery show epileptogenic lesions.[5,6,19] The most frequent pathology is hippocampal or amygdala sclerosis. Furthermore, benign long-term epilepsy associated tumours (LEATs), with mixed cystic and solid components as well as with predominant solid components, malformation tumours, and other low-grade gliomas, are the second largest group with around 17%. Malformations of cortical development, particularly focal cortical dysplasias including balloon cells and tuberous sclerosis, are - with around 15% - the third largest group of epileptogenic lesions in this cohort of patients. Malformations of cortical development such as nodular heterotopia, subcortical band heterotopia, polymicrogyria, and complex brain malformations are included in this group as well. The fourth largest group - with around 13% of all epileptogenic lesions - includes scars of post-traumatic, post-ischaemic, post-haemorrhagic, post-infectious origin, and ulegyria. Rarer aetiologies are oligodendrogliomas, oligoastrocytomas, or high-grade gliomas or meningiomas. Encephalitis including limbic encephalitis and Rasmussen's encephalitis is accounting for <2% of all scans with epileptogenic lesions. Around 6% are down to vascular malformations, with almost 5% alone for cavernomas. However, associated DVAs, arteriovenous malformation, or pial angiomatosis are included in this category as well. Extremely rare cases are hemimegalencephaly, hypothalamic hamartoma, or epidermoid cyst.[19] It has to be emphasised that, particularly in 3T MRI imaging, the detection rate of focal cortical dysplasia has increased.[12,13] Hence the proportion of malformations of cortical development might increase if larger populations are imaged in 3T scans.[20] However, as with the 1.5T scans, it is crucial that epilepsy patients are investigated with the epilepsy-dedicated MRI protocols even in 3T MRI scanners, and that the scans are reported by neuroradiologists experienced in epilepsy or epileptologists.[5,12]

Implication on Structural Lesion and Treatment Decision

Epileptogenic lesions will be crucial in identifying the right epilepsy syndrome. Furthermore, detection of an epileptogenic lesion will have a significant impact on management of the epilepsy, particularly if the epilepsy is becoming drug refractory, i.e. has not responded to two appropriately chosen drugs in adequate dosages to control seizures.[21] In fact, if cavernoma is detected as the underlying epilepsy aetiology, the ILEA recommends exploring epilepsy surgery after the first antiepileptic drug failed.[22] This is down to the fact that cavernomas are responding very well to epilepsy surgery. The likelihood of becoming seizure-free with the second drug is low in this patient group, and cavernomas pose an additional bleeding risk.

Even in the first fit clinic where people may present with generalised seizures in the first instance, detection of a focal lesion may well guide the clinician to use antiepileptic drugs which are primarily used in focal epilepsies.[23] However, if the imaging fails to detect a focal lesion the clinician may well consider using an antiepileptic drug for generalised seizures in that patient. This might exclude the choice of drug, which would suit the patient best with regards to the side-effect profile.[24]

In patients with focal epilepsy becoming drug refractory, a normal MRI brain scan should not withhold referral for evaluation for epilepsy surgery.[5,25] It might be worth at this point of the epilepsy management to confirm the diagnoses of epilepsy in the first instance with video electroencephalogram monitoring as well as performing a further dedicated advanced-epilepsy MRI in order to look for very subtle changes. Even if the structural MRI shows no abnormalities, MRI post-processing may well show abnormalities which could be used as a hypothesis for the epileptogenic focus.[26] Particularly for detection of focal cortical dysplasias, several methods of MRI post-processing have been described in order to identify focal areas of thickened cortex or abnormal grey/white matter differentiation.[27-29]

If an epileptogenic lesion is detected in MRI, the aetiology may also guide towards the success rate of epilepsy surgery.[30] For example, focal cortical dysplasia with balloon cells will have a very high likelihood of seizure control if the cortical part of the lesion can be resected completely.[31-35] HS also shows a high likelihood of a very good outcome in epilepsy surgery, although a recent study has shown that there may be a risk of late relapses in a reasonable number of patients.[36] On the other hand, cortical scars or ulegyria, are less likely to show good surgical outcome.[6] However, there may well be situations where the decision for an epilepsy surgery procedure with this aetiology is still very reasonable.[25]

Recommendations for MRI Protocol

A recent study has focused on the best MRI protocol for epilepsy.[19] The authors analysed, in a very structured approach, the characteristics of different epileptogenic entities on various MRI sequences. They performed a rank analysis of MRI sequences afterwards, which showed that fluid-attenuated inversion-recovery (FLAIR) and T2/short T1 inversion recovery (STIR) sequences are the most important. The authors concluded that the ideal epilepsy MRI protocol should contain six sequences: a 3D-T1 sequence with isotropic voxel size of maximum 1 mm, an axial and coronal T2/STIR sequence, an axial and coronal FLAIR sequence, and a susceptibility sequence for detection of haemosiderin or calcifications in the axial orientation. All sequences should be orientated to the longitudinal access of the hippocampus or perpendicular to it except the 3D-T1 sequence. All axial and coronal sequences should have a slice thickness of 3 mm or less.

One could consider adding a contrast sequence, although the authors state that only pial angiomatosis may be missed, which is an extremely rare entity. Although this study reported a higher detection rate for mesial abnormalities on axial planes orientated along the hippocampal axis, a previous study showed the opposite effect with more mesial abnormalities detected in the conventional axial orientation.[37] Therefore, the orientation of the axial planes remains controversial. However, 3D FLAIR and T sequences, additionally to the 3D-T1 sequence, are used more frequently, and will allow the reconstruction of either axial orientation. An epilepsy-dedicated MRI protocol, like that stated above, should certainly be applied to patients who have drug refractory epilepsy. It might be too time consuming to scan every first fit patient with this MRI protocol, which takes roughly 40 minutes scan time. However, first fit protocols should certainly have all three orientations included as well as temporal orientated coronal FLAIR and T2 weighted sequences.

CONCLUSION

In summary, imaging in epilepsy needs a dedicated approach. Particularly coronal MRI sequences have to be acquired in temporal orientation and thin-slice thicknesses. The reporting radiologist, neuroradiologist, or neurologist should be experienced in epilepsy and reporting epilepsy MRI scans. Lesions can be extremely subtle and may only be detected after several times of studying the scans. At least 20% of all people with epilepsy will have epileptogenic lesions in MRI, the rate being up to four-times as high in people with focal epilepsy. Detecting an epileptogenic lesion in MRI may well guide the clinical classification of the epilepsy syndrome and seizure type and therefore, help to decide on the most appropriate antiepileptic drug treatment. Once two antiepileptic drugs have failed to control focal epilepsies, detection of epileptogenic lesions in epilepsy-dedicated MRI will help to identify if epilepsy surgery might be a good treatment alternative. With regards to cavernomas, ILEA recommendations suggest considering epilepsy surgery even after one antiepileptic drug failed to control the epilepsy. CT imaging in epilepsy is helpful in acute situations to exclude other underlying neurological conditions, which may trigger acute seizures such as stroke, intracranial haemorrhage, and encephalitis, among others. CT may help to detect calcifications as - for example in patients who suffer from cysticercosis - the underlying aetiology of epilepsy. However, in non-acute imaging of epilepsy, dedicated epilepsy MRI is first choice.

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A SCARLET ENEMY OF THE BRAIN – A PRACTICAL APPROACH TO DIAGNOSIS AND MANAGEMENT OF CEREBRAL AMYLOID ANGIOPATHY

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ABSTRACT

We present two cases of elderly patients admitted with neurological dysfunction due to isolated focal cortical subarachnoid bleeding and intracerebral lobar haemorrhage, respectively. We discuss the distinguishing features in their clinical and radiological presentations which led to their diagnosis of probable cerebral amyloid angiopathy (CAA). In the hope of encouraging thoughtful learning, we have designed a series of case-based questions with accompanying answers to explain the investigative pathways and management strategies in suspected cases of CAA.

Keywords: Cerebral amyloid angiopathy, non-aneurysmal subarachnoid haemorrhage, focal cortical subarachnoid haemorrhage, intracerebral haemorrhage.

CASE 1

A 76-year-old retired engineer presented with two episodes of tingling in the left arm accompanied by tonic posturing of his fingers, occurring several days apart. The first attack lasted 30 minutes and was heralded by a 3-hour prodrome of gradually progressive occipital headache. The second episode was shorter in duration, lasting 15 minutes, and occurring in the absence of a headache. His past medical history included asbestos-related pleural plaques and right total hip replacement. He took no regular medication, has never smoked, and has consumed no alcohol. Admission blood pressure was 120/70 mmHg. Neurological examination including fundoscopy was unremarkable. Computed tomography (CT) brain images showed a small acute subarachnoid haemorrhage over the right central sulcus (Figure 1).

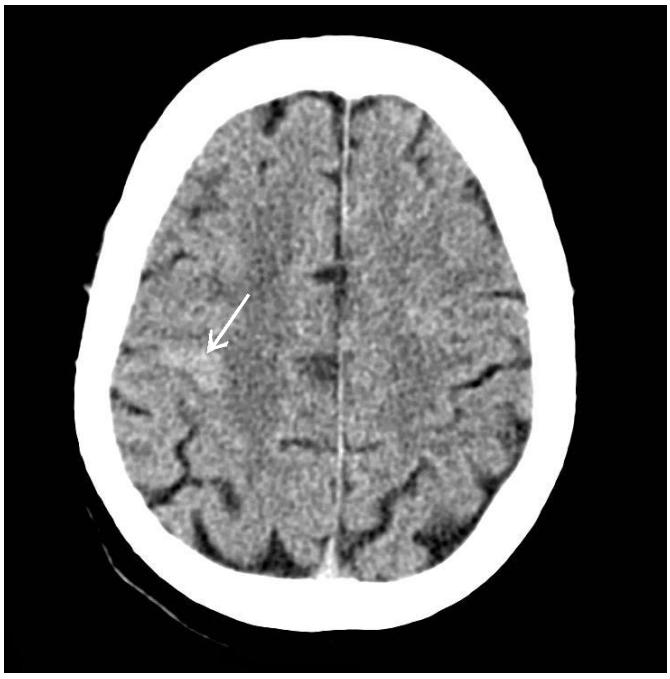

Figure 1: Non-contrast computed tomography scan showing hyperdensity in the right central sulcus (arrowed) consistent with acute subarachnoid haemorrhage.

Q1: What is the Differential Diagnosis of Subarachnoid Haemorrhage and How Would You Investigate Further?

The majority of subarachnoid haemorrhage is caused by an arterial aneurysmal rupture, with

Table 1: Causes of subarachnoid haemorrhage with no demonstrable aneurysm on cerebral angiography.[1,2,19]

Most common causes
Patients ≤60 years old
• Reversible cerebral vasoconstriction syndrome
• Posterior reversible encephalopathy syndrome
Patients ≥60 years old
• Cerebral amyloid angiopathy
Other causes
• Cortical/dural venous sinus thrombosis
• Pial arteriovenous malformation
• Dural arteriovenous fistulas
• Arterial dissection
• High-grade atherosclerotic carotid stenosis
• Vasculitides (Polyarteritis nodosa, Churg-Strauss syndrome, Wegener's granulomatosis, primary angiitis)
• Moya-moya disease
• Infectious/septic aneurysms
• Cavernomas
• Cerebral abscesses
• Coagulopathies, thrombocytopenia (e.g. idiopathic thrombocytopenic purpura)
• Primary and secondary brain neoplasms
• Drugs (cocaine, anticoagulants)

an associated mortality rate of up to 50%. Non-aneurysmal bleeding is much less frequent, accounting for 15%[1] of cases, and carries a varied prognosis depending on the underlying cause. Isolated convexity subarachnoid haemorrhage (as seen in case 1) refers to a distinctive pattern of non-aneurysmal bleeding where the extravasated blood is confined to the subarachnoid space over the surface of the cerebral hemisphere. A 5-year retrospective review of 389 cases of spontaneous subarachnoid haemorrhage by Kumar et al.[2] found localised bleeding restricted to the convexity sulci of the brain in 7.45% of patients, suggesting that it is an important subtype of subarachnoid haemorrhage. Cerebral amyloid angiopathy (CAA) appears to be a frequent cause in patients older than 60 years while reversible cerebral vasoconstriction syndrome may be the most prevalent cause in patients under the age of 60 years.[2] Other recognised aetiologies are listed in Table 1.

Our patient underwent cerebral magnetic resonance angiography (MRA) which did not identify any cerebral aneurysm. His T2*-weighted gradient-recalled echo (GRE) MRI brain images (Figure 2), however, revealed multiple cortico-subcortical microhaemorrhages. CAA is therefore postulated to be the probable cause of his subarachnoid bleed. Catheter angiography was not undertaken as the history and distribution of subarachnoid blood were not suggestive of a high pressure arterial bleeding event from an aneurysm.

Q2: What are the Pathological and Radiological Features of CAA-Related Haemorrhage?

CAA is characterised by the deposition of congophilic amyloid material in the media and adventitia of small-to-medium sized arteries, arterioles, and capillaries in the cerebral cortex and the overlying leptomeninges. Vessels infiltrated by amyloid are fragile and vulnerable to microaneurysm formation, extravasation, and haemorrhage.[3]

• Intracerebral haemorrhage and microbleeds

The lobar haemorrhages and microbleeds of CAA are characteristically cortical or cortico-subcortical in location, and are often multifocal or recurrent. All lobes can be affected, although the occipital cortex tends to be the most frequently and most severely involved.[4] CAA can also affect vessels in the cerebellar region, but in contrast to hypertensive vasculopathy (another common cause of intracerebral haemorrhage), it tends to spare the basal ganglia, thalami, and brainstem.[3]

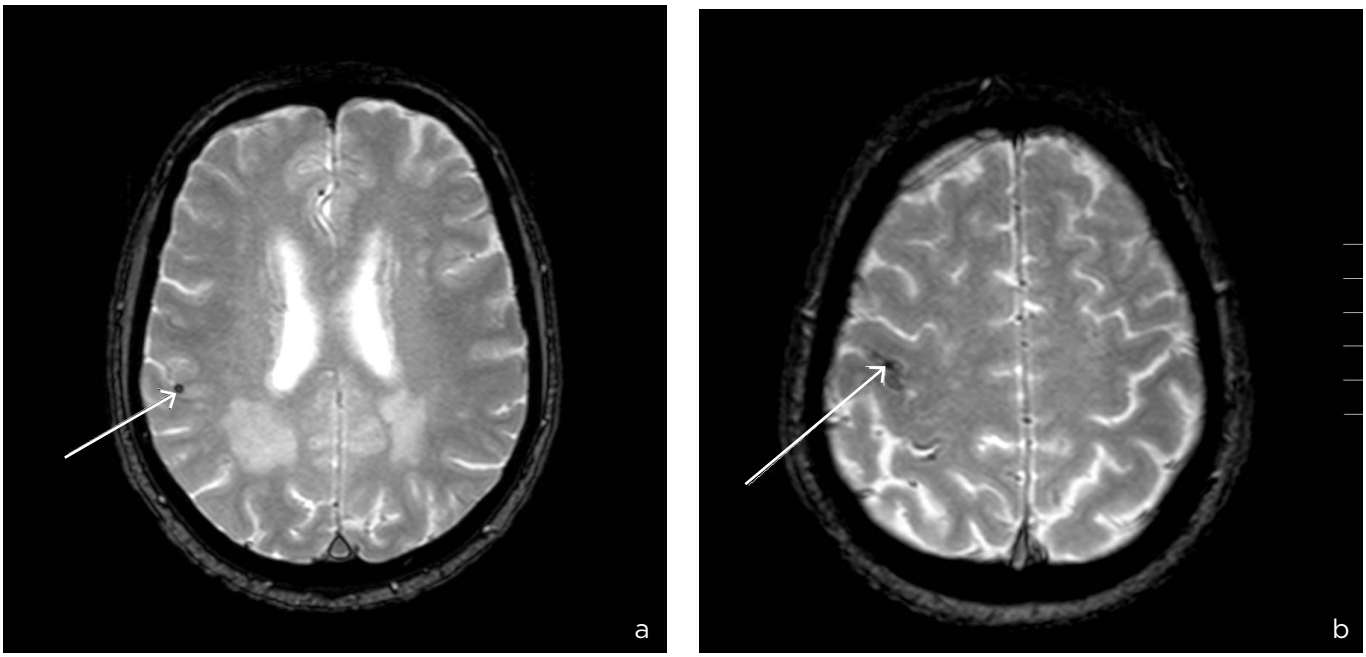

Figure 2: a) Gradient echo T2 scan (T2*) showing a subcortical area of low signal (arrowed) consistent with a small subcortical microhaemorrhage. This is one of several such lesions on the scan; b) another slide from the same study showing the right central sulcus subarachnoid haemorrhage.

• Convexal subarachnoid haemorrhage

It is recognised that the lobar haemorrhages of CAA often penetrate into the subarachnoid space causing secondary subarachnoid haemorrhage. Histopathological evidence from more recent autopsy cases have, however, indicated that - at least in some cases - haemorrhage in the cortical subarachnoid space (due to rupture of meningeal vessels) may in fact represent the primary site of bleeding, with or without secondary extension into the underlying brain parenchyma.[3]

• Cortical superficial siderosis

Focal or disseminated cortical superficial haemosiderosis (linear residues of blood in the superficial layers of the cortex) is another more recently recognised manifestation of CAA. Although it may, in some cases, represent extension of blood from a previous lobar haemorrhage, the primary mechanism may in fact be repeated leakage from brittle leptomeningeal vessels into the subarachnoid space with resultant haemosiderin deposition in the subpial layers of the brain.[5,6]

• Choice of imaging

Although acute intracerebral macrohaemorrhages and acute focal cortical subarachnoid bleeding can be revealed by a cranial CT scan, this imaging modality does not permit the detection of cerebral microbleeds or cortical superficial siderosis, both of which require T2*-weighted GRE MRI sequences for visualisation.[7] Indeed, cortical superficial siderosis and/or cortical-subcortical microbleeds may be the sole imaging indicators of CAA. Susceptibility weighted imaging (SWI) is a new MRI technique which has been reported to be more sensitive than GRE for microbleed detection, although its contribution to diagnostic accuracy and the clinical relevance of identifying different numbers of cerebral microbleeds have not yet been fully established.[4,8]

Q3: What are the Headache Characteristics in Patients with Isolated Convexal Non-Aneurysmal Subarachnoid Haemorrhage, in Comparison to Patients with Aneurysmal Subarachnoid Haemorrhage?

Thunderclap headache is the prototypical symptom of aneurysmal subarachnoid haemorrhage. In contrast, headache is typically absent in patients with isolated convexal non-aneurysmal subarachnoid haemorrhage due to CAA.[9] When headache is present, patients may report non-specific cephalalgia or complain of symptoms mimicking migraine with aura.

Some patients with convexal subarachnoid haemorrhage do present with an explosive onset severe headache akin to aneurysmal rupture, mostly in those with reversible cerebral vasoconstriction syndrome.[10]

Q4: What are the Recognised Clinical Manifestations of CAA?

• Amyloid spells

Transient focal neurological episodes in patients with CAA can be recurrent and stereotyped, sometimes termed 'amyloid spells'.[11] Both positive and negative symptoms may occur at equal rates. Positive symptoms may comprise of transient paraesthesia, limb-jerking episodes, and visual complaints such as photopsia or teichopsia. Negative symptoms include focal weakness, numbness, dysphasia, and visual loss. The spells are typically brief, usually lasting <10 minutes with up to 70% terminating under 30 minutes.[11]

Amyloid spells appear to be anatomically correlated with haemorrhagic lesions, i.e. the phenomenology of the spells corresponds to the cortical location of blood/haemosiderin.[11] The exact mechanism for these spells is not known. One postulated theory is focal seizure activity. Certainly, there are reports indicating either cessation or frequency reduction of amyloid spells following treatment with antiepileptic drugs. An alternative mechanism that has also been suggested is cortical spreading depression, triggered by the presence of blood/haemosiderin in the subarachnoid space and the superficial cortical layers.[12]

Of note, cortical superficial siderosis and/or focal cortical subarachnoid bleeds (which are thought to be primarily responsible for amyloid spells) may represent a warning sign for future intracranial haemorrhage. A study[13] of 51 patients with superficial siderosis found that almost half of these patients went on to develop new intracranial haemorrhagic events during a median follow-up period of 35 months. This is of important clinical significance as amyloid spells presenting with negative symptoms can masquerade as transient ischaemic attacks, prompting the initiation of antiplatelet agents which could further increase the risk of haemorrhage from CAA.

• Cognitive impairment and dementia

There are several mechanisms which may underlie intellectual impairment in patients with CAA. White matter leukoaraiosis is one such mechanism, giving rise to subcortical dementia over weeks to months.[3] A possible explanation for this leukoencephalopathy is chronic hypoperfusion of the periventricular white matter from diffuse amyloid-related narrowing or occlusion of cortical penetrating vessels. Other mechanisms that are likely to contribute include lobar macro and microhaemorrhages, as well as the cumulative effect of 'silent' ischaemic lesions. Two recent studies[14,15] have also found a notably greater prevalence of cortical superficial siderosis in cognitively impaired patients when compared to the general population, and its presence appears to be independently associated with lower cognitive scores, cerebral white matter hyperintensities, and microbleeds.

CAA is also found in association with Alzheimer's disease (AD), probably reflecting their closely related pathogenic processes. The vascular amyloid deposits in CAA are primarily composed of a 39-43-amino acid β-amyloid (Aβ) peptide, which is the same constituent of senile plaques in AD although the ratio of Aβ40/Aβ42 is higher in CAA.[3] Both sporadic CAA and AD share a common genetic risk factor – the apolipoprotein E ε4 allele. The apolipoprotein E ε2 allele is also associated with sporadic CAA, but not with AD.[7]

• CAA-related inflammation[7,16]

CAA-related vascular/perivascular inflammation is a rare but potentially reversible disease manifestation. It is thought to represent an immune-mediated inflammatory reaction to the presence of vascular amyloid deposits. The clinical picture consists of subacute, progressive cognitive and neurological dysfunction with a varying combination of focal neurological deficits, headache, seizures, and encephalopathy.

The typical neuroimaging appearance is that of asymmetric white matter lesions (often large and confluent, with or without mass effect) visualised on T2 or FLAIR-weighted MRI images, along with multiple microbleeds seen on gradient echo sequences. The white matter lesions may extend into the cortical grey matter and there may be meningeal or parenchymal enhancement following the administration of gadolinium. Mimics such as acute disseminated encephalomyelitis, progressive multifocal leukoencephalopathy, neurosarcoidosis, and malignancies need to be excluded. A brain biopsy may be necessary to secure the diagnosis.

It is important to recognise CAA-related inflammation as it may respond to immunosuppressive treatment. Responders may follow either a monophasic or relapsing course.

CASE 2:

A 69-year-old gentleman was admitted with a 10-day history of headache, vomiting, and some word-finding difficulties. Examination revealed a right haemianopic visual field defect. He was referred directly to the neurosurgical team following CT head findings of a left-sided irregular haemorrhagic mass lesion in the left occipital lobe (Figure 3). Brain MRI revealed the lesion as being predominantly haemorrhagic in nature with an additional soft tissue component suggestive, but not definitive, of an underlying tumour (Figure 4). CT chest, abdomen, and pelvis showed no radiological evidence of primary malignancy outside the central nervous system. He underwent uneventful surgical debulking of the left occipital mass. Histopathological examination of the excised tissue showed no evidence of tumour but instead identified amyloid deposition in many vessels.

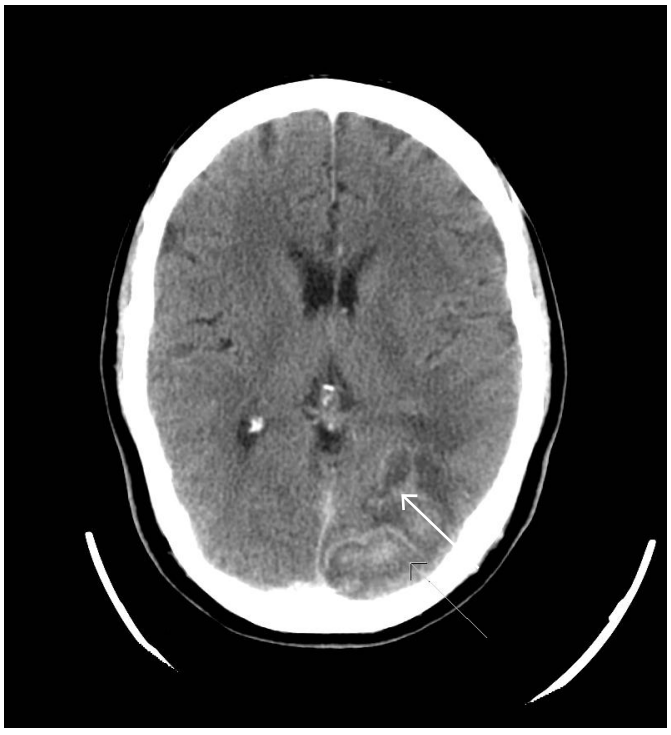

Figure 3: Non-contrast computed tomography scan showing area of irregular haemorrhage in the left occipital lobe (arrowed) with mass effect.

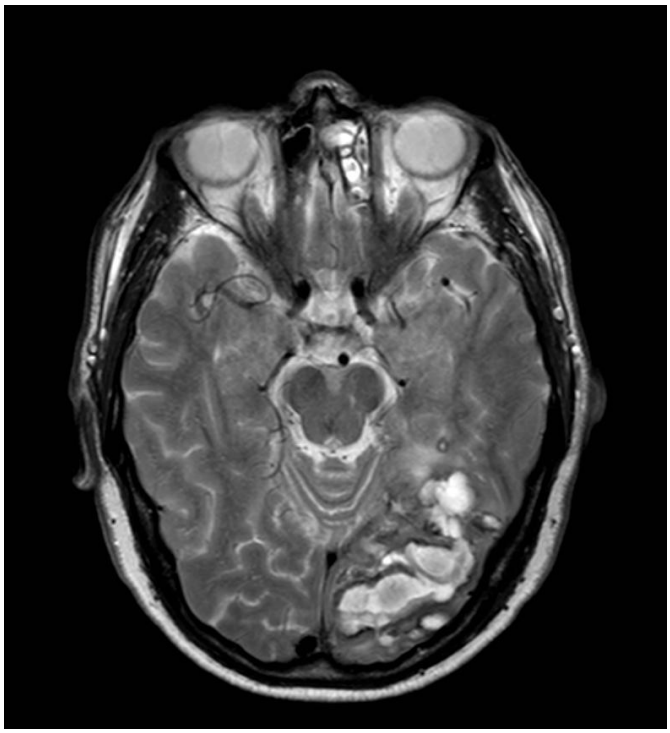

Figure 4: Axial T2 weighted MRI scan showing haemorrhage in the left occipital lobe. Superficial siderosis and distant microhaemorrhages were not seen on T2*-weighted sequences performed post-operatively.

Q5: In What Circumstances Should a Brain Biopsy/Surgical Intervention be Considered?

A brain biopsy in patients with possible or probable CAA will help to strengthen the diagnosis in accordance to the classic and modified Boston diagnostic criteria (Table 2). However, neuropathological examination seldom alters the clinical management, and the risk-benefit balance tends to be against a brain biopsy in the majority of cases.

An exception occurs when CAA-related inflammation is suspected or when neuroimaging and other investigations are unable to discriminate other potential causes of intracerebral haemorrhage such as an underlying tumour.

Some patients with a large haemorrhage require surgical evacuation due to further neurological deterioration. Previous assumptions that fragile amyloid-laden vessels within the intracerebral haematoma pose a particularly high risk of intra and post-operative bleeding appears to be unfounded.[7]

Table 2: Classic and modified Boston criteria for the diagnosis of cerebral amyloid angiopathy (CAA).[7]

Definite CAA
Full post-mortem histopathological examination demonstrating: - Lobar, cortical or cortical-subcortical haemorrhage - Severe CAA with vasculopathy - Absence of other diagnostic lesion
Probable CAA with supporting pathology
Clinical data and pathological tissue (evacuated haematoma or cortical biopsy) demonstrating: - Lobar, cortical or cortical-subcortical haemorrhage - Some degree of CAA in specimen - Absence of other diagnostic lesion
Probable CAA
Age ≥55 years Clinical data and MRI (or CT) demonstrating: - Multiple haemorrhages restricted to lobar, cortical or cortical-subcortical regions (cerebellar haemorrhage allowed) OR - Single lobar, cortical or cortical-subcortical haemorrhage, and focal or disseminated superficial siderosis - Absence of other cause of haemorrhage
Possible CAA
Age ≥55 years old Clinical data and MRI (or CT) demonstrating: - Single lobar, cortical or cortical-subcortical haemorrhage OR - Focal or disseminated superficial siderosis - Absence of other cause of haemorrhage

A study by Greenberg et al.[17] investigating the sensitivity and specificity of cortical biopsy for the diagnosis of CAA found that despite the patchy nature of the disease, the complete absence of vascular amyloid in an adequate tissue specimen would largely exclude a diagnosis of CAA.

Q6: How Should we Manage Patients with CAA-Related Intracerebral Haemorrhage?

Acute management with supportive measures to minimise secondary insults is important, as well as intensive blood pressure lowering to reduce haematoma expansion.[4] Surgical intervention needs to be considered if the patient continues to deteriorate.

Secondary preventive strategies aim to reduce the risk of recurrent CAA-related intracerebral haemorrhage:

1) Both anticoagulants and antiplatelet agents increase the risk of recurrent CAA-related haemorrhagic events and should therefore be avoided unless there is a compelling clinical indication to justify the use of these agents.[7]

2) Results from the PROGRESS trial found that blood pressure lowering (by a mean reduction of 9/4 mmHg) has a protective effect against further haemorrhagic events, irrespective of the presence of hypertension.[18]

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ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROID DISEASE

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ABSTRACT

Autoimmune thyroid diseases (ATDs) are immune-endocrine disorders affecting the thyroid gland and, eventually, also a number of other systemic targets, including the brain and the nervous system. Encephalopathy associated with autoimmune thyroid disease (EAATD) is a rare, heterogeneous condition arising from the background of an ATD. It is characterised by neurological and/or psychiatric symptoms with acute or sub-acute onset, and virtually any neurological or psychiatric symptom can appear. However, EAATD often presents with confusion, altered consciousness, seizures, or myoclonus. The majority of cases are associated with Hashimoto's thyroiditis, but a number of patients with Graves' disease have also been described. EAATD is likely an immune-mediated disorder. Its exact prevalence has not been precisely elucidated, with an increasing number of cases reported in the last few years. Most EAATD patients respond in a dramatic manner to corticosteroids. However, the immunosuppressive treatment may require a long course (up to 12 months). The increasing number of EAATD cases reported in the literature demonstrates a growing interest of the scientific community about this condition, which still requires a better definition of its pathophysiology, the diagnostic criteria, and the most appropriate management, including the long-term follow-up of patients. The current clinical evidence about EAATD is mostly based on the report of single cases or small cohort studies. In this review, we present the current knowledge about EAATD, with a dedicated focus to the clinical management of the patients from a diagnostic and therapeutic perspective.

Keywords: Encephalopathy, Hashimoto's thyroiditis, Graves' disease, thyroid.

INTRODUCTION

Autoimmune thyroid diseases (ATDs), namely Hashimoto's thyroiditis (HT) and Graves' disease (GD), are complex and multifaceted immune-endocrine disorders. Suboptimal or delayed diagnosis and management of ATDs can lead to a number of systemic complications, including global decline in brain function as well as organic brain damage. Encephalopathy associated with autoimmune thyroid disease (EAATD) was first described by Brain and colleagues[1] back in 1966. It is an uncommon condition which is characterised by neurological and/or psychiatric symptoms with acute or sub-acute onset. Though any neurological or psychiatric symptoms can appear, EAATD often presents with confusion, altered consciousness, seizures, or myoclonus.[1,2] The majority of EAATD cases are associated with HT; however, it has also been reported to occur in patients with GD.[3] EAATD is likely an immune-mediated disorder and its exact prevalence has not been precisely elucidated yet, with an increasing number of cases reported in the last few years. The mean age of onset of the neurological or psychiatric symptoms is during the patient's fourth decade of life, with women being more commonly affected than men.[4-9]

EAATD

Pathophysiology

The mechanism of EAATD is still not fully understood. An overactive autoimmune process

seems to be the underlying cause.[10,11] Several mechanisms such as cerebral vasculitis with endothelial inflammation or immune complex deposition, global cerebral hypoperfusion, cerebral tissue-specific autoimmunity, and thyrotropin-releasing hormone-related neuronal deficit have also been proposed as causal factors.[11-18] In addition, some antigens such as alpha-enolase and a 36-kDa protein detected in soluble fractions from the cerebral cortex are thought to play a role in the pathogenesis of EAATD.[19,20] Pathogenesis based on the presence of cerebral vasculitis is supported by a number of pathological and neurophysiological findings. Pathology examination at autopsy and brain biopsy have identified lymphocytic infiltration around small arterioles and venules in some cases.[6,14,21] A picture of cerebral hypoperfusion compatible with that observed in diffuse brain vasculitis has been reported in some EAATD patients using single photon emission computed tomography (SPECT).[13,16] Moreover, both focal and diffuse patterns of cerebral vasculitis may be present in EAATD and could variously influence the clinical presentation.[5,6,22] Focal involvement of the brain could determine stroke-like clinical manifestations. Very peculiar clinical pictures like cerebellar sub-acute syndrome,[23] sensory ganglionopathy,[24] or a selective involvement of the nucleus accumbens[25] have been described in EAATD patients. A condition of diffuse cerebral hypoperfusion could lead to progressively worsening manifestations, often characterised by sub-acute onset and psychiatric symptoms. Despite the findings supporting the labelling of EAATD as a vasculitis-like process, the inclusion of EAATD within non-vasculitic autoimmune inflammatory meningoencephalitis (NAIM) cannot be ruled out yet.[26]

Clinical Features

From single case reports and a few cohort studies, two patterns of presentation of EAATD have been described. A stroke-like pattern of multiple and recurrent episodes of focal neurologic deficits with a variable degree of cognitive dysfunction and alteration of the level of consciousness occurs in approximately 25% of patients.[6] However, also a diffuse progressive pattern characterised by gradual cognitive impairment with dementia, confusion, hallucinations, or somnolence has been described.[5,27] Some cases develop suddenly or have a more fulminant presentation, i.e. where rapid deterioration to coma occurs.[5,28] In addition to the above mentioned changes, other neurologic signs are common in EAATD patients regardless of the dynamic of the clinical presentation. More than half of EAATD patients experience focal or generalised tonic-clonic seizures.[6,8,29,30] Status epilepticus has also been described.[29,31] Myoclonus, either focal or multifocal, or tremor are seen in up to 38% of patients.[6,8] Hyper-reflexia and other pyramidal tract signs can often be seen.[5] Psychosis, predominantly visual hallucinations, have been reported in up to 36% of patients.[6,8] The clinical manifestation of EAATD seems not to be affected by the nature of the underlying ATD, and no differences between patients with HT and patients with GD have been described. Regardless of the type of ATD, the neurological or psychiatric symptoms appear to be very heterogeneous. Altered consciousness, involuntary movements such as tremor and myoclonus, seizures, and cognitive impairment are the most frequently reported symptoms.[6,11,32] In both groups of patients, sensory alterations, headache, focal symptoms, ataxia, language impairment, signs of encephalitis, and psychiatric symptoms have also been described.[32-34]

Laboratory Features

Patients suspected of having EAATD often undergo numerous biochemical and haematological analyses. The presence of elevated serum levels of anti-thyroid antibodies remains an essential characteristic for diagnosis, and suggests the presence of thyroid autoimmunity. Elevated serum levels of anti-thyroid peroxidase antibody (anti-TPOAb) and/or anti-thyroglobulin antibody (anti-TgAb) are a common laboratory feature in EAATD patients. However, there is no clear relationship between the severity and onset of the neurological symptoms and the type or serum concentration of anti-thyroid antibodies. In addition, antibody levels may or may not decrease following treatment. Therefore, this cannot be considered to be a specific finding for EAATD.[3,4,6,8,28] In addition to serology analysis, anti-thyroid antibodies can also be measured in the cerebrospinal fluid (CSF). The specificity and sensitivity of anti-thyroid antibodies in the CSF is unclear and they have been reported to be either elevated or not detected.[4,10,32] Measurements of thyroid hormone levels appear to be variable among EAATD patients. However, thyroid hormones should not be so abnormal to determine the occurrence of neurological or psychiatric symptoms. In EAATD patients with HT, thyroid hormone levels can range from a

picture of hypothyroidism to a certain degree of hyperthyroidism, with a number of cases reported to be in euthyroid status.[6,8,35] The majority of GD patients with EAATD present with mild hyperthyroidism at the time of EAATD onset or shortly before it.[32] In some patients with EAATD, inflammatory markers like C-reactive protein and erythrocyte sedimentation rate are elevated. In addition, mild elevation of liver enzymes was also reported.[36] Other CSF laboratory findings include elevated protein concentration,[5,32] lymphocytic pleocytosis,[5,8,32] and the possible presence of oligoclonal bands.[5] Elevated levels of 14-3-3 protein have also been occasionally reported but this is not a general finding.[8,37,38]

Electroencephalography and Neuroimaging

Electroencephalography (EEG) abnormalities are seen in patients with EAATD both at the time of presentation and then again after resolution of the symptoms and in the recovery phase. EEG studies often show non-specific slowing of the background electric activity.[5,28,35,39,40] Focal spikes or sharp waves and transient epileptic activity are less frequently observed.[5,39] Triphasic waves and frontal intermittent rhythmic delta activity have also been described. In some cases, EEG abnormalities recover rapidly with steroid treatment,[39] whereas others note that EEG improvement lags behind clinical improvement.[28,41] Again, no significant differences in the EEG pattern have been reported between HT and GD patients with EAATD, with the majority of the patients with abnormal EEG recordings often characterised by diffuse and non-specific slowing of the background EEG activity regardless of the type of ATD.[32,35] It appears that the EEG electric alterations are mainly localised in the temporal and/or frontotemporal region, and alternatively prevail on the two sides.[33]

The most appropriate set of radiological investigations and the advisable long-term follow-up studies in patients with EAATD have not yet been defined. Magnetic resonance imaging (MRI) and computed tomography (CT) of the brain could show a normal radiological pattern or intracranial changes that are either focal or diffuse. MRI is frequently normal; however, cerebral atrophy or non-specific tesla-2 (T2) signal abnormalities in the subcortical white matter area may be observed.[6,42,43] The latter findings have been described in approximately half of patients and are not shown to be associated with gadolinium enhancement.[5,6,28] This may be an incidental finding, although a number of reports have described regression or resolution of these findings after immunosuppressive treatment.[6] In some cases, diffuse or focal white matter changes at MRI suggest a process of primary demyelination.[6,36,42,44,45] Other findings noted in individual case reports include meningeal enhancement[36] and T2 signal abnormalities in the hippocampus region.[45] Follow-up imaging may help and inform on the radiological regression or resolution with treatment.[6]

Other radiological modalities, including CT, also reveal non-specific findings.[32,33,35] For example, cerebral angiography, when performed, appeared to be normal,[5] and SPECT may show focal, multifocal, or global hypoperfusion.[6,13,28,32] It is uncertain whether the perfusion defect on SPECT is attributable to vasculitis or is a secondary feature related to the autoantibody-mediated cerebral inflammation and oedema. Metabolic imaging such as 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) has been occasionally performed, suggesting the presence of a diffuse and multifocal cerebral hypometabolism.[32,43] The hypometabolic state appears to be transient and reversible following corticosteroid therapy, improvement of central nervous system symptoms, and the decrease of the anti-thyroid antibody titres. The underlying pathogenesis of the PET abnormalities is still unclear, but an autoimmune-mediated inflammation in multifocal brain structures could be the probable cause.[45]

Diagnosis

Considering the complexity of the clinical, laboratory, and radiological features of EAATD, the diagnostic criteria have not yet been clearly defined.[6,35] The diagnosis of EAATD often depends on a number of factors, including the neurological and psychiatric manifestations as well as the results of the laboratory and radiological investigations.[33] The finding of elevated anti-TPOAb or anti-TgAb in patients with a compatible clinical presentation is anyway essential for the diagnosis of EAATD. Thyroid hormones should also be measured, and clinically relevant abnormalities with an impact on the neurological or psychiatric functions should be ruled out with certainty. Essential hospital-based investigations to confirm EAATD and, conversely, to exclude other possible diagnoses should also include lumbar puncture and CSF analysis with routine biochemistry, cultures for microorganisms, cytology, and possibly target antibody screening. Brain CT and/or MRI with gadolinium administration

and EEG are also required for EAATD diagnosis and follow-up. Other laboratory and radiology testing for the most common causes of delirium, confusion, altered levels of consciousness, and stroke-like symptoms may be appropriate to exclude other diseases or abnormalities causing the symptoms.

The most common differential diagnoses to consider when EAATD is suspected include degenerative dementia (Alzheimer's disease, Lewy body dementia, or frontotemporal dementia), migraine (basilar or hemiplegic), cerebrovascular accidents (stroke or transient ischaemic attack), Creutzfeldt-Jakob's disease, and infective or neoplastic meningitis. In addition, acute disseminated encephalomyelitis, meningoencephalitis, paraneoplastic encephalitis, toxic metabolic encephalopathies, and, finally, psychiatric diseases such as depression, anxiety, or psychosis should also be considered. In acute and early medical management, most patients with a clinical presentation indicative of EAATD - or otherwise suggestive of a similar neurological disorder - should be investigated with various neuroradiology imaging, EEG, lumbar puncture, and targeted testing for appropriate biomarkers. The exclusion of paraneoplastic or non-paraneoplastic processes is critical for the differential diagnosis of an encephalopathy of unknown origin. Specific immunological testing, including the study of a number of antibodies to neuronal proteins, may be warranted to aid and avoid misdiagnosis.[46-48]

Treatment and Prognosis

The cornerstone of the treatment of EAATD is represented by the administration of corticosteroids or, as second line approach, other immunosuppressants. Once the medical treatment has been appropriately started, EAATD prognosis is usually satisfactory. Nonetheless, the persistence of neurological alterations and death cannot be excluded.[46,49] On the other hand, a spontaneous remission might also occur.[4,33,40] Given the rarity of the disorder and the lack of dedicated guidelines or an international expert consensus, an optimal corticosteroid dose and the subsequent treatment plan have not been defined. Oral prednisone doses ranging from 50-150 mg daily have been used.[5] High dosages of intravenous methylprednisolone have been administered in some patients, but its benefit compared with oral corticosteroids is unknown. From the literature, the majority of EAATD patients respond well to corticosteroids. Symptoms typically improve in a few days and resolve over a time ranging from days to a few weeks or, more rarely, months. The duration of the treatment and the rate of taper are generally titrated based on patient response and tolerance, though a 6-12-month treatment can be required. Other immunosuppressive medications for the treatment of EAATD include azathioprine and cyclophosphamide. These drugs are generally reserved for patients who do not respond to or cannot tolerate the corticosteroids. They are also given to patients with EAATD relapse after or during tapering of corticosteroid therapy.[10,28,50] Clinical improvement with intravenous immunoglobulin[51,52] or plasmapheresis[53-55] has been reported in individual cases. In addition, optimisation of the medical treatment for the underlying thyroid disease, and eventually the treatment of seizures with anticonvulsants, may be necessary.

The overall prognosis of EAATD is mostly good. Delay to diagnosis, and therefore treatment, might be associated with a less rapid or, potentially, incomplete recovery. Case series and reports suggest that patients can improve with treatment even after a few years from the onset of the EAATD symptoms. However, residual cognitive impairment occurs in about 25% of patients with long-standing untreated disease.[28,36,40] Rarely, spontaneous recovery can occur;[4,33,40] however, most reports of long-term follow-up are in treated patients.[5,6,32] Many of these patients remain disease-free after discontinuation of corticosteroids over several years of follow-up. Of course, reinitiating the corticosteroid treatment due to EAATD relapse or continuation of the same or other immunomodulatory/immunosuppressive treatment are possible options to take into account for maintaining remission.[36]

Alternative Denominations in Use for Defining EAATD

To date, there is still no consensus among researchers and clinicians with regards to adopting a univocal denomination of this condition.[56] EAATD was historically denominated by Hashimoto's encephalopathy, due to the fact that most patients have HT as background thyroid disease. However, such denomination may be misleading as it does not fit precisely to patients with GD and encephalopathy related to the same, and has never been universally used. Steroid responsiveness, for example, has been proposed as one of the possible criteria for making the diagnosis of EAATD. Hence, the term steroid-responsive encephalopathy associated with autoimmune

thyroiditis (SREAT) has been proposed as a possible definition alternative to EAATD.[36,44] This terminology, however, may not be conclusive again as some patients do not respond or are poorly responsive to corticosteroid treatment. Finally, it has also been suggested that such encephalopathy could be a variant of a non-vasculitic autoimmune inflammatory process, broadly termed NAIM.[26]

In our opinion, EAATD is the most precise denomination of this condition, as it takes into account the relationship of the encephalopathy with the ATD, regardless of the nature of the same (either HT or GD, which is not a thyroiditis), and it does not limit the definition to the patients who respond to corticosteroids.

SUMMARY AND AUTHORS' PERSPECTIVES

EAATD is a heterogeneous and complex condition arising from the background of an ATD. Such a condition may occur either in HT or GD patients. It may present either as a medical emergency or with a more gradual onset. Its course may be either progressive or relapsing with variable response to corticosteroids and other immunosuppressive therapies. Prompt investigations and treatment are warranted in patients with EAATD in order to achieve remission and minimise the risk of complications. The increasing number of EAATD cases in the literature demonstrates the growing interest of the scientific and medical community about this rare condition, which still requires a more thorough understanding of its pathophysiology, the definition of the criteria for the diagnosis, and the optimisation of the most advisable therapeutic approach.

The current clinical evidence about EAATD is based mainly on the report of single or small cohort studies. A universal and optimal diagnostic and therapeutic protocol has not yet been established. We wish to highlight the need for the development of an internationally acceptable and multidisciplinary characterisation of EAATD, with a particular regard to the definition, diagnosis, and management of such a condition.

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CURRENT CONCEPTS OF NEURODEGENERATIVE DISEASES

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ABSTRACT

Neurodegenerative diseases (NDDs) are described as disorders with selective loss of neurons and distinct involvement of functional systems defining clinical presentation. Extensive studies demonstrated that proteins with altered physicochemical properties are deposited in the human brain in NDDs. The present review focuses on predominantly sporadic disorders in adulthood. Major concepts of NDDs can be summarised as follows: 1) molecular pathologic classification of NDDs is protein-based; 2) the proteinopathy concept underpins the role of protein processing systems; 3) seeding of pathological proteins supports the theory of prion-like spreading; 4) the clinical symptoms are determined by the system affected and do not unequivocally reflect the molecular pathological background; 5) overlapping of NDDs may be more the rule than the exception. Accordingly, NDD-related proteins and their biochemical modifications can be used as biomarkers and may be targeted for therapy. However, due to the high number of combinations of different proteinopathies a personalised therapy strategy may be warranted.

Keywords: Biomarker, concomitant pathology, neurodegenerative disease, prion-like, proteinopathy.

INTRODUCTION

Neurodegenerative diseases (NDDs) are traditionally defined as disorders with selective loss of neurons and distinct involvement of functional systems defining clinical presentation. Comprehensive biochemical, genetic, and molecular pathological examinations have expanded this definition. During the last century, many studies have demonstrated that proteins with altered physicochemical properties are deposited in the human brain in NDDs. Furthermore, not only neurons but glial cells also accumulate these proteins. Involvement of proteins has led to the definition of the concept of conformational diseases.[1] According to this, the structural conformation of a physiological protein changes, which results in an altered function or potentially toxic intra or extra-cellular accumulation. Mutations in the encoding genes are linked to hereditary forms of disease. Molecular pathological, genetic, and biochemical studies have led to reclassification of several disorders, and opened completely new avenues for biomarker development or therapeutic strategies.[2] This review aims to summarise the major developments in this field with an emphasis mainly on sporadic disorders of adulthood. It must be noted that further neurological disorders are associated with neuronal degeneration, including mainly hereditary metabolic diseases and others such as multiple sclerosis or those with immune-mediated (autoimmune) aetiology; however, these are beyond the scope of the present review.

MAJOR CONCEPTS OF NDD AND THEIR IMPLICATIONS

1. Classification of NDDs is Protein-Based

A nosological classification of NDDs is based on clinical presentation, anatomical regions and cell types affected, conformationally altered proteins involved in the pathogenetic process, and aetiology if known (i.e. genetic variations or acquired pathways of prion diseases).[2]

In most cases, there is an overlap and convergence of the clinical symptoms in the course of the disease. Thus, clinical classification is helpful mostly when early clinical symptoms are evaluated. The major clinical features of NDDs correlate with the anatomical involvement as follows:

a) Cognitive decline, dementia, behavioural disturbances, and alterations in high-order brain functions. The most important anatomical regions involved are the hippocampus, entorhinal cortex, limbic system, and neocortical areas. In focal cortical symptoms, focal degeneration of the frontal, temporal, parietal, or the occipital lobe may be seen. A subtype of dementia is frontotemporal dementia (FTD), which is associated with degeneration of the frontal and temporal lobes (frontotemporal lobar degeneration [FTLD]). It is important to distinguish rapid (prion) diseases and slowly progressive forms of cognitive decline.

b) Movement disorders and other motor features. The most important anatomical regions involved are the basal ganglia, thalamus, brainstem nuclei, cerebellar cortex and nuclei, motor cortical areas, and lower motor neurons.

c) Combinations of these symptoms may be observed in some disease forms early during the clinical course and in many cases during the progression.

The neuropathological classification is based on the following:

a) Evaluation of the anatomical distribution of neuronal loss and reactive astrogliosis, and additional histological features such as spongiform change of the neuropil or vascular lesions.

b) Evaluation of protein deposits in the nervous system; these can be deposited intracellularly and extracellularly, and are analysed by immunohistochemistry and eventually by biochemistry.

The following proteins are associated with the majority of sporadic and genetic adult-onset NDDs:[2]

a) The microtubule-associated protein tau (MAPT) is important for the assembly and stabilisation of microtubules. The *Tau (MAPT)* gene maps to chromosome 17q21.2.

b) Amyloid-β (Aβ), which derives from the amyloid precursor protein (APP). The *APP* gene maps to chromosome 21q21.3. Among others, further genes with relevance to the pathogenesis of Alzheimer`s disease (AD) and familial disorders include presenilin-1 (*PSEN1*) (chromosome 14q24.3) and *PSEN2* (chromosome 1q31-42).

c) α-Synuclein is a 140-amino acid (aa) protein that belongs to a family of abundant brain proteins (α, β, and γ-synuclein). The α-synuclein gene locates to chromosome 4.

d) Prion protein (PrP) is a 253-aa protein central in the pathogenesis of prion diseases or transmissible spongiform encephalopathies. The encoding gene of PrP (*PRNP*) locates to chromosome 20.

e) Transactive response (TAR) DNA-binding protein 43 (TDP-43) is a highly conserved 414-aa nuclear protein. TDP-43 is encoded by the *TDP (TARDBP)* gene on chromosome 1p36.22. Among others, further most relevant genes for TDP-43 proteinopathy include progranulin (*GRN*; chromosome 17q21.32) and C9orf72 (chromosome 9p21).

f) FET proteins, which include the fused in sarcoma (FUS), Ewing's sarcoma RNA-binding protein 1 (EWSR1), and TATA-binding protein-associated factor 15 (TAF15).[3]

There are more forms of genetic NDDs with abnormal protein inclusions, comprising proteins encoded by genes linked to neurological trinucleotide repeat disorders such as Huntington`s disease, some forms of spinocerebellar ataxias, and spinal and bulbar muscular atrophy. Further rare, inherited disorders associated with proteins and genes include neuroserpin or ferritin-related NDDs where the molecular genetic defect resides in the ferritin light polypeptide gene. In familial British and Danish dementias, with deposition of amyloid proteins in the extracellular spaces of the brain and in blood vessels, the molecular genetic defect is a mutation in the BRI_2 gene. There are further, mostly hereditary, NDD forms, such as spinocereballar ataxias or degenerations of basal ganglia and brainstem, where protein deposits have not yet been discovered. These are mostly related to complex metabolic (e.g. mitochondrial, ion channel, etc) alterations requiring further characterisation.

From a diagnostic aspect, for the neuropathologists a further step is to evaluate the cell-specific subcellular localisations of the following:[4]

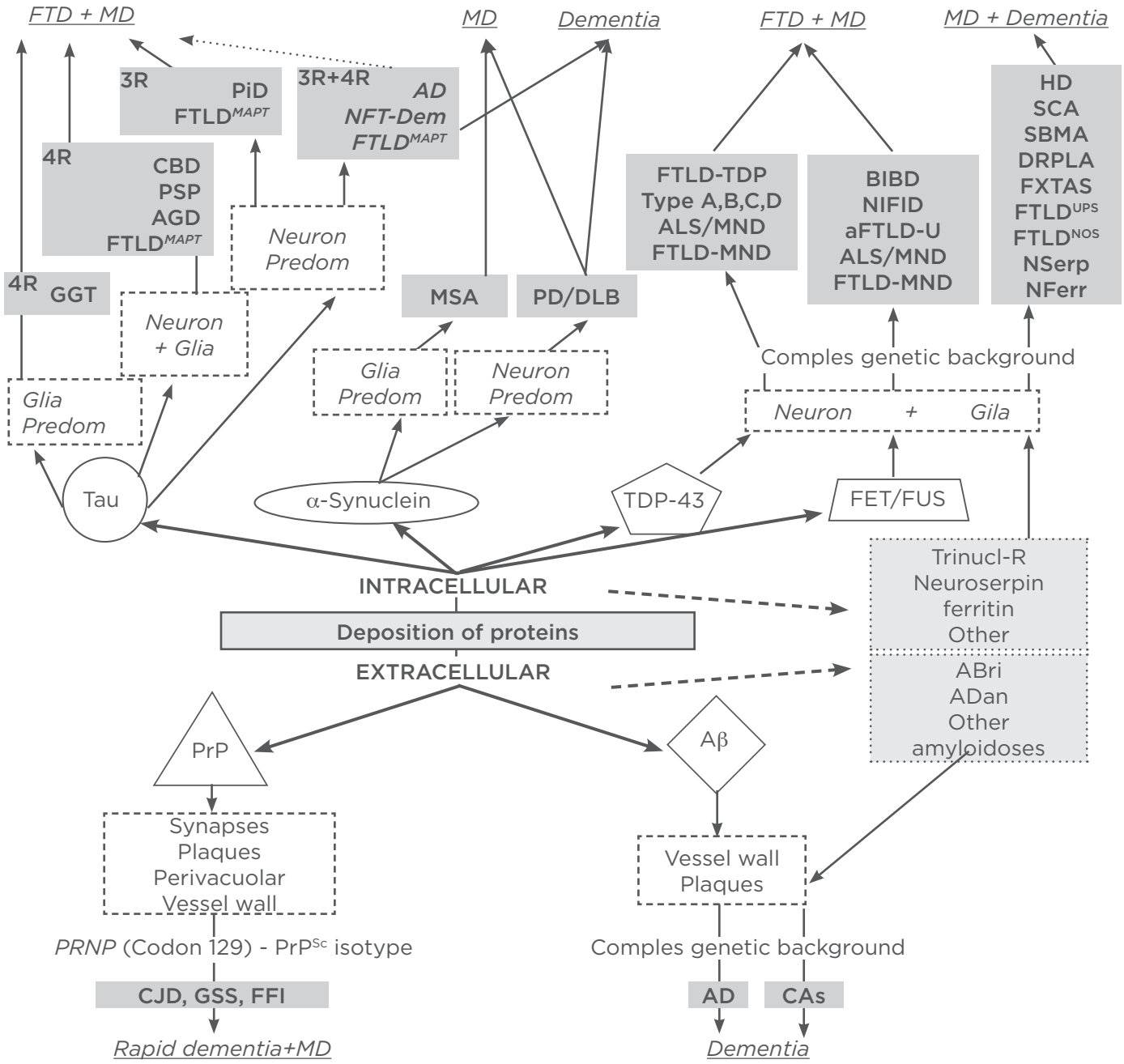

Figure 1: Algorithm for the classification of sporadic neurodegenerative disorders.

FTD: frontotemporal dementia; MD: movement disorder and other motor symptoms; PiD: Pick's disease; FTLD^{MAPT}: frontotemporal lobar degeneration, linked to chromosome 17 caused by mutations in the MAPT (tau) gene; AD: Alzheimer's disease; NFT-Dem: neurofibrillary tangle-dementia; HD: Huntington's disease; SCA: spinocerebellar ataxia; CBD: corticobasal degeneration; SBMA: spinal and bulbar muscular atrophy; PSP: progressive supranuclear palsy; TDP: TAR-DNA binding protein; BIBD: basophilic inclusion body disease; DRPLA: dentatorubropallidoluysian atrophy; AGD: argyrophilic grain disease; NIFID: neuronal intermediate filament inclusion body disease; FXTAS: fragile X-associated tremor/ataxia syndrome; FTLD^{UPS}: FTLD with inclusions immunoreactive for the ubiquitin-proteasome system; FTLD^{NOS}: FTLD not otherwise specified; NSerp: neuroserpinopathy; NFerr: hereditary ferritinopathy; ALS: amyotrophic lateral sclerosis; MND: motor neuron disease; aFTLD-U: atypical FTLD with ubiquitin inclusions; Glia predom: the inclusions are predominantly in glial cells; Neuron predom: the inclusions are predominantly in neurons GGT: globular glial tauopathies; MSA: multiple system atrophy; PD: Parkinson's disease; DLB: dementia with Lewy bodies; TDP-43: TAR-DNA binding protein-43; FUS: fused in sarcoma; PrP: Prion protein; CJD: Creutzfeldt-Jakob disease; GSS: Gerstmann-Sträussler-Scheinker disease; FFI: fatal familial insomnia; CA: cerebral amyloidosis.

Adapted from Kovacs et al.[2]

a) Extracellular deposits comprise deposits with immunoreactivity for Aβ or PrP. It is of diagnostic importance that disease-associated PrP deposits also in a synaptic pattern.

b) Major proteins that deposit intracellularly include tau, α-synuclein, TDP-43, and FET proteins; furthermore, those associated with trinucleotide repeat disorders or rare hereditary diseases.

Further stratification is needed to distinguish cell-types (neurons, astrocytes, or oligodendroglia) and subcellular localisations (cell-process, cytoplasm, nucleus). These are influenced by genetic variations and may associate with different biochemical signatures. Current molecular pathological classification is summarised in Figure 1, and the list of most important diseases is shown in Table 1.

2. The Proteinopathy Concept Underpins the Role of Protein Processing Systems

The two major elimination pathways, which control the quality of cellular components and maintain cell homeostasis, are the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway (ALP).[5] Chaperones and stress response proteins are in close relation to protein processing systems. Widespread molecular pathological and biochemical studies revealed that there are modifications of proteins intrinsic to disease (e.g. phosphorylated, nitrated, oligomers, proteinase-resistant, with or without amyloid characteristics; cleavage products).[2] The pathological conformers are also called misfolded proteins and are associated with the disruption of the homeostasis of the endoplasmic reticulum (ER). ER stress and upregulation of related pathways are called the unfolded protein response.[6] The common role of the protein processing systems in all NDDs renders these systems as general targets for therapeutic approaches. Further changes, which are out of the scope of this review, include pathways of energetic dysregulation (i.e. oxidative stress and mitochondrial instability), molecular damage (i.e. lipid peroxidation, DNA oxidation), metabolic changes (i.e. alterations of cholesterol metabolism), or dysregulation of ion homeostasis and adaptation, such as anti-inflammatory cytokines, microglial activation, anti-apoptotic, or antioxidant processes.[7] It needs to be clarified whether the altered proteins lead to neuronal damage (if yes, which modification like oligomer formation etc.) or whether their deposition is merely a reaction of the sick cells.

3. Seeding of Pathological Proteins: The Concept of Prion-Like Spreading

The proteinopathy concept serves as a basis for the theory of prion-like spreading of disease-associated proteins.[8] This stems from the observations that, in prion diseases, the disease-associated PrP spreads in the nervous system. Recent findings implicate disease-associated protein seeds as an essential element in the initiation and expansion of aggregated proteins in diverse NDDs.[9] Although human-to-human transmissibility has been proven only for prion diseases, several other NDDs were suggested to be associated with the prion-like spreading of the specific protein characterising it. It must be noted that in NDDs the spreading of disease alterations seems to be more selective than in prion diseases. There are no epidemiological evidences, which would suggest a similar transmissibility for Parkinson`s disease (PD) or AD. However, this issue needs great caution and attention in the near future to react adequately on the public health level should any further evidence arise.

The notion of prion-like spreading was supported by the neuropathological observations in human brains that protein deposition of α-synuclein in PD and tau in AD follows a hierarchical path defined as stages of disease.[10,11] Moreover, subjects with PD who had long-term survival of transplanted foetal mesencephalic dopaminergic neurons developed α-synuclein-positive Lewy bodies in grafted neurons, suggesting that the disease can propagate from host to graft cells.[12] Importantly, α-synuclein pathology is increasingly detected in peripheral tissue,[13] thus, spreading from the periphery could also be suggested. Analogously, five phases of Aβ deposition as AD-related pathology has been reported.[14] A similar concept of hierarchical spreading in the brain has been suggested for TDP-43 in amyotrophic lateral sclerosis (motor neuron disease) and FTLD with TDP-43 protein deposition.[15,16] Cell culture and animal experimental models have provided variable support for this prion-like theory.[8] It is also suggested that the considerable variability of NDDs is due to different 'strains'.[8]

These findings have implications for developing therapeutic strategies halting the spreading of protein deposits. It must be emphasised that vaccinations should aim to distinguish disease-associated from physiological forms of proteins to avoid unexpected complications by interacting with the normal forms of proteins.

Table 1: Overview of neurodegenerative diseases according to major proteins deposited.
1) In some forms of motor neuron disease (with/without FTLD) only FUS (and not FET) immunoreactive deposits are seen.
2) Globular glial tauopathies: recent studies have highlighted a group of 4-repeat (4R) tauopathies that are characterised neuropathologically by widespread, globular glial inclusions. Clinically these patients present with frontotemporal dementia with or without motor neuron disease and additionally extrapyramidal features.[30]
3) For spinocerebellar ataxias * indicates that only where inclusions were described are listed here.

Proteinopathy	Protein	Disease / Subtype
Alzheimer's Disease-related	Tau, Aβ	Alzheimer's disease
Tauopathy	Tau	Pick's disease Corticobasal degeneration Progressive supranuclear palsy Neurofibrillary tangle-dementia Argyrophilic grain disease FTLD^{MAPT} (FTDP-17T) Globular glial tauopathies
TDP-43 proteinopathy	TDP-43	FTLD-TDP: Type A-D MND FTLD-MND
FET(FUS)-proteinopathy	FET / FUS	FTLD-FET: aFTLD-U, NIFID, BIBD FUS: MND FTLD-MND
α-Synucleinopathy	α-Synuclein	Parkinson's disease Dementia with Lewy bodies Multiple system atrophy
Prion disease	Prion protein	Sporadic CJD Variably protease sensitive prionopathy Iatrogenic CJD (acquired) Variant CJD (acquired) Kuru (acquired) Genetic CJD, Gerstmann-Sträussler-Scheinker disease Fatal familial insomnia Prion protein-cerebral amyloid angiopathy
Trinucleotide repeat disorders	Huntington ataxin 1, 2, 3, 7, CACNA1A, TBP Frataxin Atrophin-1	Huntington's disease (SCA 1, 2, 3, 6, 7, 17)* Friedreich ataxia DRPLA
Other forms	Ferritin Tau, α-Synuclein Neuroserpin ABri, ADan	Hereditary ferritinopathy Neurodegeneration with brain iron accumulation Neuroserpinopathy Further hereditary amyloidoses

FTLD: frontotemporal lobar degeneration; FTLD^{MAPT}/FTDP-17T: frontotemporal dementia and parkinsonism linked to chromosome 17 caused by mutations in the *MAPT* (tau) gene; TDP-43: TAR-DNA binding protein-43; MND: motor neuron disease; FUS: fused in sarcoma; aFTLD-U: atypical FTLD with ubiquitin inclusions; NIFID: neuronal intermediate filament inclusion body disease; BIBD: basophilic inclusion body disease; CJD: Creutzfeldt-Jakob disease; TBP: TATA-binding protein; SCA: spinocerebellar ataxia; DRPLA: dentatorubropallidoluysian atrophy; FET: fluoro-ethyl-tyrosine.

4. Clinico-Neuropathological Correlations

Different disorders can affect the same anatomical regions. During the progression of disease, further anatomical regions will be affected, leading to complex constellations of symptoms, possibly hampering the correct diagnosis. The following examples can be mentioned:

a) Corticobasal syndrome. This can associate with corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP)-type tau pathology but also with TDP-43 proteinopathy and AD-related pathology.

b) PSP clinical syndrome (Steele-Richardson-Olszewski syndrome) can associate with CBD and PSP-type tau pathology but also with TDP-43 proteinopathy or even with prion disease.

c) CBD-type tau pathology can associate with FTD, moreover PSP-type tau pathology can associate with a spectrum of clinical syndromes apart from the classical Steele-Richardson-Olszewski syndrome, such as Dopa responsive Parkinsonism, pure akinaesia with freezing, or - mainly in the elderly - with cognitive decline and hypokinaesia.

d) FTD (including behavioural variant, or semantic dementia or progressive aphasia) with or without motor neuron disease can be associated with tau, TDP-43, or FET (FUS) proteinopathy or with the frontal variant of AD.

Thus, the clinical symptoms are determined by the system affected and do not unequivocally reflect the molecular pathologic background.

5. Concomitant Neuropathological Alterations

The term 'mixed or concomitant' pathologies in NDD means that in addition to the hallmark lesions of a NDD entity, further pathological alterations can be observed in the same brain. The term 'mixed pathology' has been earlier used when describing accompanying vascular pathology. Later, Lewy body pathology was also mentioned as concomitant pathology. However, deposition of multiple neurodegeneration-related proteins, in addition to co-occurrence of non-neurodegenerative pathology (vascular, metabolic, etc.), is a frequent event.[17] In fact, overlapping of NDDs may be more the rule than the exception, particularly in the elderly. Our recent community-based neuropathology study on 233 individuals is proof of this concept since we detected a large variety of proteinopathies with different combinations[18] reflecting the biological variability and arguing against simplified classifications. The high number of combinations reflects the different aetiologies showing overlapping pathogenetic pathways and is influenced also by the genetic background of patients and by other common diseases such as vascular or metabolic disorders. This suggests that in addition to therapeutic targeting of neurodegeneration, prevention and supplementary treatment of co-morbidities such as diabetes, alcohol consumption, hypertension, and previous stroke could be useful in a considerable fraction of patients.

These findings might have implications on: 1) therapy strategies aiming to target single pathological proteins in the brains of elderly individuals with dementia; 2) for the stratification of patients for a biomarker of genomic research.

This concept is supported by observations in genetic forms of NDDs where various proteins may show pathological deposits in the same brain.[19-21] Complex constellations of clinical symptoms (movement disorders and cognitive decline) may associate with the accompanying presence of diverse neurodegenerative disorders.

The term concomitant NDD indicates that the classical neuropathological features in an anatomical distribution defining a disease entity are seen in the brain together with the full features of another disease entity. The most frequent disease entities that overlap with others are AD and PD-related pathologies; these are reported as practically associated with all other types of NDD.

The term 'concomitant neurodegenerative pathologies restricted to certain anatomical regions' means that there are morphological features of a disorder fulfilling the criteria of its entity, but there are further neurodegenerative pathologies restricted to certain anatomical regions. Here TDP-43 and α-synuclein need to be mentioned, but deposition of Aβ and tau may also show different patterns when compared to the disease entity showing their deposition as a primary feature. Some important examples are as follows:

a) When appearing as a concomitant pathology, TDP-43 immunoreactivity usually involves the hippocampus, amygdala, and temporal cortex, and only rarely subcortical structures. This pattern can be seen in AD or in dementia with Lewy bodies

or argyrophilic grain disease (AGD) (up to 30-40%), rarely in PSP and CBD,[22,23] and is unusual in multiple system atrophy,[24] sporadic Creutzfeldt-Jakob disease,[25] or Pick`s disease.[26]

b) Presence of Lewy bodies, mostly restricted to the brainstem, may be observed in various disorders. A peculiar constellation is when the NDD is associated with α-synuclein deposition restricted to the amygdala and olfactory bulb. This is seen in up to 20-30% of AD patients.[27]

c) Coexistence of AD pathology and Aβ deposition is not infrequent in NDDs. One reason for unusual amounts of Aβ in another disease may be influenced by the apolipoprotein ε (apoE) genotype.[28] Deposition patterns of Aβ in PD, in particular in those showing dementia, seems to differ and may involve the striatum more than as expected only by aging.[29]

d) Among the sporadic tauopathies, PSP-type pathology and early stages of AGD-type pathology may be found in several other diseases restricted to certain anatomical regions.

For the clinical and neuropathological diagnostic practice, understanding the concept of 'lowering the threshold' for a clinical symptom is important. For example, the threshold of cognitive impairment, which shows inter-individual variability, could be reached by a prominent amount of AD-related changes (i.e. only plaques and tangles) but could not be reached by the concomitant presence of neuropathological alterations that, by themselves, are not sufficient to cause dementia (Figure 2).

SUMMARY AND CONCLUSIONS

Why is the Protein-Based Classification Important for Clinicians?

• These proteins and their biochemical modifications can be potentially detected in body fluids or potentially visualised in positron emission tomography imaging.

• The subcellular distribution of the pathological proteins can influence how these proteins reach the body fluids (i.e. different from an extracellular

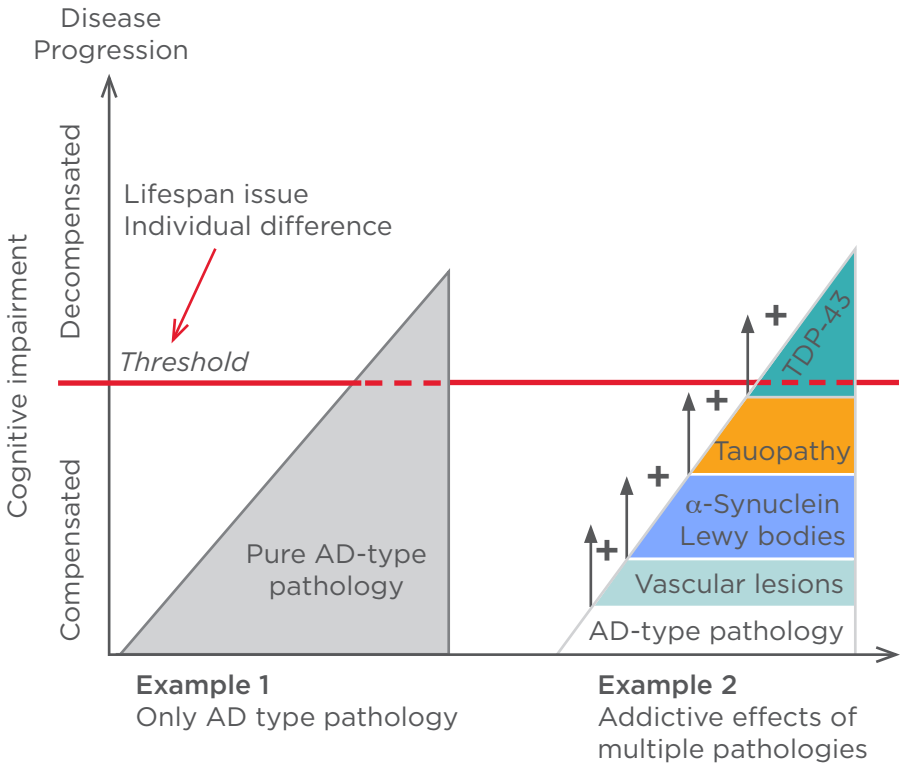

Figure 2: The concept of 'lowering the threshold' for a clinical symptom (i.e. cognitive impairment). The threshold shows inter-individual variability. This threshold can be reached by Alzheimer's disease (AD)-related neuropathological alterations (example 1), but can be reached by the concomitant presence of neuropathological alterations (example 2).

AD: Alzheimer's disease; TDP-43: TAR-DNA binding protein-43.

Adapted from Kovacs et al.[18]

protein deposit than from an intracellular inclusion including glia or neurons).

• These proteins may be targeted for therapy (elimination of diseased-forms) or halting prion-like spreading. It must be clarified which modifications of proteins have relevance to be targeted for therapy.

• Targeting the protein processing systems may help to maintain the healthy homeostasis of proteins.

What are the Perspectives for the Future?

Detection of a panel of neurodegeneration-related proteins and their modifications ('protein coding of NDDs') together with markers, which reflect the dynamics of disease (i.e. neuroinflammatory or signalling factors) in body fluids combined with neuroradiological approaches and genetic screening of disease-modifying gene variations, can lead to personalised diagnosis or better prediction of prognosis.[2] If these concepts are validated, accepted, and implemented into the daily practice, the patients with NDDs would most benefit from discussing the cases in a multidisciplinary setting, analogously to tumour boards in oncology: the clinician, the neuroradiologist together with the neurochemist, clinical neuropathologist, and neurogeneticist will try to provide an individualised interpretation of diagnostic markers. This makes more sense if there are therapies to offer, or at least to provide a better prediction of the prognosis. Finally, it should be emphasised that, without continuous neuropathological studies, this approach loses its sense due to the need for permanent quality feedback.

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A NOTE ON CHANGING APPROACH TO DIAGNOSIS OF ALZHEIMER'S DISEASE

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ABSTRACT

This short review summarises the conclusions of two different series of studies set out to revise the 1984 National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) criteria for the diagnosis of Alzheimer's disease (AD). The role of AD-pathology (AD-P), the characteristics of AD clinical expression, and the importance of positivity of biomarkers are concisely surveyed, and the diverging position of different research groups in reference to predementia AD are outlined. The importance of other factors such as age, inflammatory changes, and vascular pathology, which can variably interact with the main feature of AD, is signalled and some clinical questions are raised.

Keywords: Mild cognitive impairment, Alzheimer's disease, dementia, neurodegeneration, biomarkers.

INTRODUCTION

25 years after the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) position paper on Alzheimer's Disease (AD),[1] the vast amount of clinical and biological data available urged for a revision of the argument. The results were summarised in two series of recommendation papers, one from the International Working Group for New Research Criteria for the Diagnosis of AD (IWG),[2-4] the other, from the National Institute on Aging-Alzheimer's Association (NIA-AA).[5-7] Later, the Italian Society for the study of Dementias (SINDEM)[8] adhered to part of the IWG positions.

In December 2012, researchers from both groups convened to a symposium held in Stockholm to summarise the respective positions as recently reported.[9,10] This short review is intended to approach some aspects of the two positions, summarising the common starting points and revising their different conclusions in the light of old and new findings. Clinical syndromes outlined in the Key Symposium[9] are reported in Tables 1 and 2 which respectively refer to IWG and NIA-AA criteria.

As it can be seen, the Symposium proposes that the term 'symptomatic AD' be used to describe the entire clinical spectrum of AD, from the earliest symptomatic stages (mild cognitive impairment (MCI)/prodromal AD) to the most severe. The two positions, however, differ mainly with respect to the criteria adopted to define the predementia state. Therefore, our analysis will focus on this early phase of sporadic late-onset AD. Although recommendations are addressed to research, their relevance will be examined by the viewpoint of the clinician.

THE REFERENCE MODEL

NINCDS-ADRDA criteria for AD diagnosis required the initial identification of a specified type of dementia.[1] The absence of alternative pathologies, which decline might be referred to, completed the requirements. Thus, AD diagnosis implied that dementia was inescapably associated to AD-pathology (AD-P), and by converse, neuropathological lesions were excluded in absence of AD dementia.

Contrariwise, the new criteria maintain that AD-P can exist in the absence of dementia. Such a position shared by all the groups[4,5] is related to the progress in knowledge of AD markers and of the corresponding biology. Namely, biomarkers shown in neuropathologically-confirmed AD[11] can be found also in normal patients where they predict the future conversion to full-blown dementia with fair accuracy.[12] Their presence broadens the range of AD-clinical syndromes (AD-C), allowing identification of an early phase, which starts long before the appearance of AD dementia (Tables 1 and 2).

Two series of biomarkers have been identified,[3,5] one related to the AD-associated amyloid deposition, and the other, to neuronal dysfunction. The biomarkers of amyloidosis are: 1) increase in amyloid β (Aβ) burden as shown by positron emission tomography (PET) imaging with Pittsburgh Compound B (PiB-PET);[13,14] 2) reduction of amount of Aβ peptide in cerebrospinal fluid (CSF). The biomarkers of neuronal damage or dysfunction are: 1) elevated CSF tau protein; 2) hypometabolism in an AD-like pattern (i.e. in posterior cingulate, precuneus, and/or temporoparietal cortices) on fluorodeoxyglucose-PET (FDG-PET); and 3) hippocampal atrophy on volumetric magnetic resonance imaging (MRI) and cortical thinning in specific areas, as lateral and medial parietal, posterior cingulate, and lateral temporal cortices.

Relevance of biomarker changes is credited by both approaches as reported in Tables 1 and 2. According to IWG criteria biomarkers function as surrogates for pathophysiological lesions in AD and are incorporated to diagnosis.

Conversely, NIA-AA considers them simply a support for the diagnosis. Cautiously, indeed, NIA-AA reviewers observed that more work is needed to establish the optimal PET, MRI, biofluid techniques, their normal thresholds, and their reliability.[6] Furthermore, questions have been raised by the weak intra-individual correlations among amyloid accumulation at PET, reduction of CSF amyloid, and increase of CSF tau.[15] Finally, it has been shown that a positive PiB-PET scan does not necessarily imply the presence of AD-P neuropathology, as cerebral amyloid angiopathy[16] can lead to dementia with a typical AD distribution scan[17] even in absence of AD-P. Therefore, NIA-AA operates with 'core clinical criteria' - also for MCI - and suggests that biomarkers are only used for research purposes. IWG criteria do not sufficiently address this issue.

Overall the model refers to the amyloid cascade hypothesis whose core signs are represented by formation of amyloid plaques and aggregation of neurofibrillary tangles (NFT).[18] AD-P starts with the deposition of Aβ, which, once it reaches toxic concentration, is followed by changes of the properties of tau, a microtubule-associated protein and the major constituent of NFT. These first emerge during normal ageing in the basolateral cortical strip where cholinergic axons arising from the nucleus basalis of Meynert travel towards the mesial temporal cortex.

Table 1: International Working Group for new research criteria for the diagnosis of Alzheimer's disease (AD) (*Modified from Morris et al.*[9]).

		Presence of impairment on memory tests	Evidence of biomarkers *in vivo*	Additional requirements
Alzheimer's Disease	Prodromal AD	Required	Required	Absence of dementia
	AD dementia	Required	Required	Presence of dementia
Preclinical AD	Asymptomatic at risk for AD	Not present	Required	Absence of AD Symptoms
	Presymptomatic AD	Not present	Not required	Absence of AD Symptoms; presence of AD mutation
	Mild cognitive impairment	Not required	Not required	Absence of AD Symptoms or biomarkers

Table 2: National Institute of Aging and the Alzheimer's Association (NIA-AA) for new research criteria for the diagnosis of Alzheimer's disease (AD) (*Modified from Morris et al.[9] and Petersen et al.[31]*).

AD Dementia	Key criteria remain unchanged from the 1984 McKhann et al.[1] criteria for 'probable AD' except now allow nonamnestic presentations of AD dementia; Identify intra-individual decline in cognition and function as the salient clinical features AD biomarkers enhance confidence in clinical diagnosis
Preclinical AD	Refers to the pathophysiological stage when *in vivo* molecular biomarkers of AD are present, but symptoms are absent. Establish that AD has a long asymptomatic stage Can only be identified with *in vivo* AD biomarkers
Mild cognitive impairment	A diagnosis of MCI due to AD requires evidence of intra-individual decline, manifested by: Self or informant reported complain Objective cognitive impairment Preserved independence un functional abilities Increased diagnostic confidence may be suggested by positive Aβ biomarker and a positive degeneration biomarker

Here, in its component structures as piriform cortex, amygdala, hippocampus, and enthorinal cortex, NFT reach their maximum concentration in MCI and AD.[19,20] Once filamentous tau has been formed, it can be transmitted to other brain regions, likely along different network systems.[21,22]

NIA-AA criteria suggest a model for staging preclinical AD grounded on a hypothetical temporal ordering of different biomarkers. According to the model, biomarkers of Aβ deposition become abnormal early, before neurodegeneration and clinical symptoms occur. Biomarkers of neuronal injury, dysfunction, and neurodegeneration become abnormal later in the disease. Cognitive symptoms are directly related to biomarkers of neurodegeneration rather than biomarkers of Aβ deposition. Thus, hippocampal atrophy is followed by episodic memory impairment, grey matter atrophy, and finally, by changes in non-memory cognitive domains.[23,24]

Aβ deposition was estimated to start around 17 years before the onset of dementia, whereas hippocampal atrophy and memory impairment were considered to become abnormal about 3–6 years before the onset of dementia. Although this statement raises some doubt,[25] it evidences how lengthy the processes involved in AD may be.

ASYMPTOMATIC AT RISK OR PRECLINICAL STAGE?

According to the IWG criteria, this stage includes cognitively normal (CN) individuals presenting changes of one or both series of biomarkers (i.e. of amyloidosis and of neuronal damage).

Recommendations differentiate 'presymptomatic AD' from 'asymptomatic at risk state for AD'.[3,4] The first category refers to an individual who certainly will develop AD due to the presence of a fully genetic mutation. The second one includes patients who might develop AD as shown by autopsies of CN patients which document the occurrence of AD-P.[26,27]

Such a possibility is well known and many examples are offered of severe AD-P in ageing patients,[28] defined as 'healthy' for their normal levels of cognitive performances and their adequacy in functional abilities.[29] It has been observed that neuropathologic lesions can be associated with an incredible range of clinical manifestations from no symptoms to severe deficits.[30] No direct relationship exists between symptoms and the severity of lesions. Mostly lesions are mild or moderate but there can also be a very severe spread of AD-P[30] to the whole brain.

Conversion from prodromal at risk state to AD might depend on the degree of pathology present in the brain of the individual as well as the degree of resistance to the clinical expression of lesions related to individual susceptibility, including genetic factors (e.g. Apolipoprotein E ApoE genotype), risk or protective factors (e.g. vascular factors, diet, etc.), compensatory mechanisms (e.g. cognitive reserve), and comorbidities (e.g. diabetes).[3] These factors can modulate the risk of developing clinical symptoms, but from present data it is not possible to determine whether an individual is in a position to maintain a state of healthy ageing, remaining asymptomatic, and why. From the practical point of view, this category is profitable in so far as it offers the rationale for looking at factors able to influence the clinical picture, and for orienting the search for suitable treatments.

Opposite to this position, NIA-AA recommendations see biomarker changes in CN individuals as a starting point of the AD pathway so that, if they live long enough, they will progress to MCI and then to dementia. The syndrome is identified as a preclinical stage and – with the limitations already mentioned in the previous paragraph - its fate seems to be unavoidable along a continuum where AD-P modifications are the beginning of the path and dementia the end-stage of pathologic accumulation.[5]

Admittedly patients in the group might present subtle cognitive decline (SCD), namely a low cognitive performance,[6] which does not yet meet the standardised criteria for MCI.[7] The meaning of SCD and its relationship with MCI are not clear and they have been a matter of discussion.[31,32] Operationally, their cognitive performance has been conventionally set below a cutpoint corresponding to the 10th percentile of normal performance.[33-35] In keeping with the hypothesis of the ordered change of biomarkers, such a condition has been partitioned into three stages of growing severity.[6] Namely: 1) stage of asymptomatic cerebral amyloidosis with biomarker evidence of Aβ accumulation and normal cognitive and behavioural performances; 2) stage of amyloid positivity plus evidence of one or more markers of neuronal injury in absence of cognitive changes; 3) stage of amyloid positivity plus evidence of neurodegeneration and SCD. The attempt to validate the stage hypothesis revealed a more composite picture. Besides the three stages early predicted, a further condition had to be added, identified as suspected non-AD pathophysiology (s-NAP).[34,35] Individuals in this class, with or without signs of SCD, were characterised by pathological changes in biomarkers of neuronal damage in presence of normal biomarkers of amyloidosis. A Stage 0, characterised by normal biomarkers and an 'unclassified' category, completed the scheme.

Figure 1 presents the distribution of the preclinical subjects (green bars) as computed by averaging the data of frequency distributions reported by two studies[34,35] whose results coincided perfectly with each other, as noted,[31] despite the different techniques applied.

PRODROMAL AD OR MCI?

MCI definition is the point of maximal divergence between IWG and NIA-AA groups. On one side, the patient population is split into a Prodromal-AD (Prod-AD) group and a more generic MCI group. In the other, the classic definition holds true.[10,36-38]

Prod-AD refers to the patients who have AD both neuropathologically and clinically, before they meet the criteria for dementia, since AD signs are already present in these early stages, as reported.[3]

Prodromal AD neuropathology is characterised by a reduction of hippocampus volume,[39] whose atrophy has a predictive value.[40] These data fit well with pathological studies, which point at the mesial temporal lobe structures as the starting point of the degenerative process. Given the role of these structures in memory trace consolidation, such anatomic notion is in keeping with early and severe deficits of episodic memory presenting the characters of AD defect which regards encoding and retrieval of memorandum. Prod-AD patients present the same defect at a much lower degree. Tests asking for free and cued recall performances (e.g. the Grober-Buschke paradigm) seem to identify AD memory changes more effectively than traditional measures of free recall. Thus, a defective performance to such a paradigm can identify Prod-AD and predict incipient AD, differentiating its specific memory change from that of normal elders. According to IWG group, the Prod-AD category allows a more reliable estimate of incipient AD with respect to the common definition of MCI.

The relevance of this type of defect and the specificity of a particular test performance raised much interest and debate. Inconsistencies among

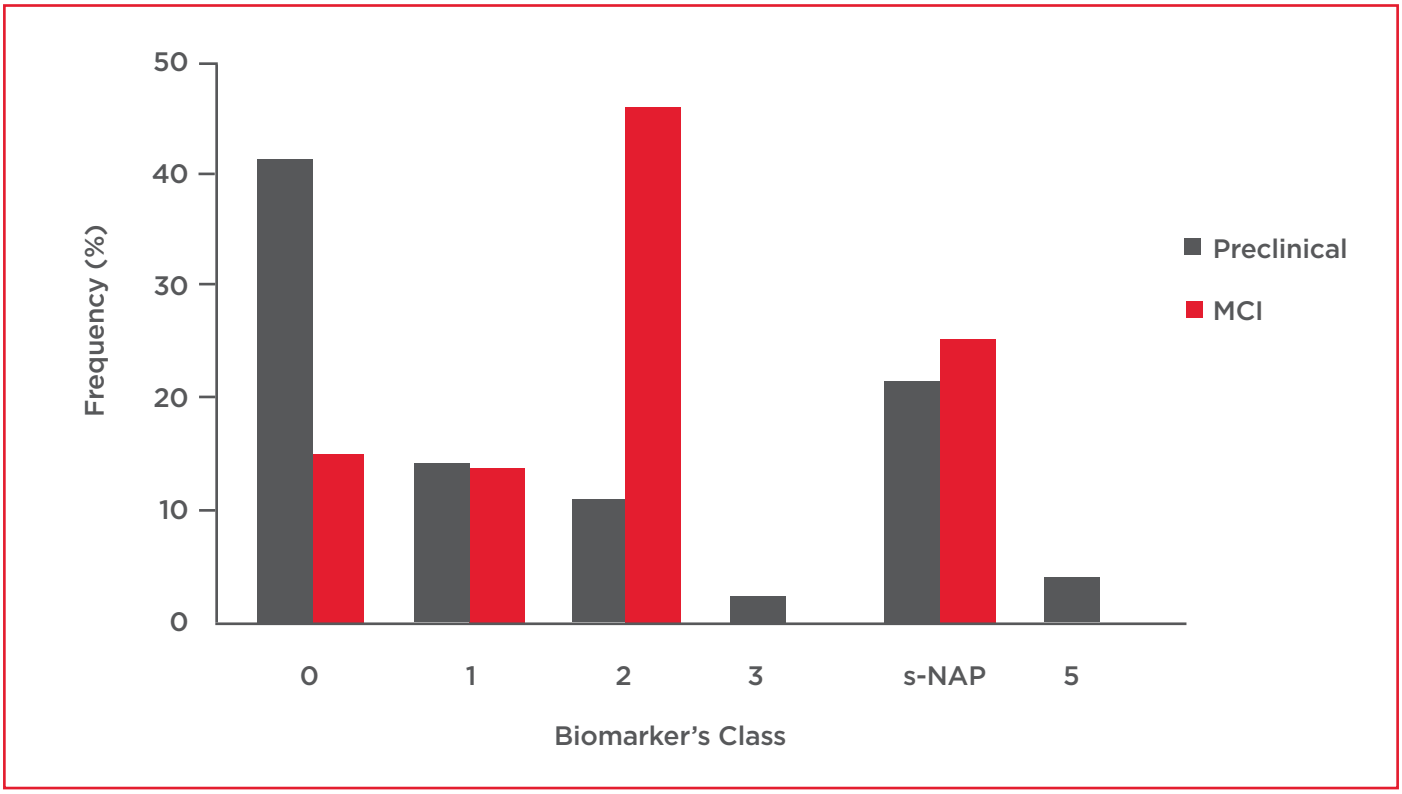

Figure 1: There is no apparent order in biomarker changes when passing from preclinical stage to mild cognitive impairment (MCI). Frequency distribution of biomarker classes in preclinical stage are obtained by averaging data from Jack et al.[34] and Vos et al.,[35] and those in MCI are drawn from Petersen et al.[44]
Biomarker class definition: 0 - Biomarkers negative; 1 - Amyloid only; 2 - Amyloid + neurodegeneration; 3 - Amyloid + Neurodegeneration + Subtle Cognitive Decline; 4 - suspected non-Alzheimer's disease pathophysiology- Neurodegeneration only; 5 - Unclassified.

results, however, suggest further studies before accepting the conclusion that AD conversion can be predicted by simply using a specific test paradigm.[41]

NIA-AA criteria still consider MCI a useful diagnostic category,[7] however difficult its definition might be. The diagnosis of MCI due to AD requires evidence of objective memory or cognitive impairment, adequacy in activities of daily living, and absence of dementia.[10] Patients in this group evolve toward dementia more frequently than CN individuals, though AD is not necessarily their final evolution.

Heterogeneity of MCI population, however, is great depending on many different factors. It is clear that MCI population varies within and among case series since the diagnosis applies to elderly individuals complaining of cognitive changes, irrespective of the aetiology or potential evolution of these changes. It includes, for example, physiological changes of ageing, functional disturbances of depression or drug-induced states, and pathological entities of brain degenerative processes or early AD. The same defect - lack of memory - may depend on the impairment of different functional processes (encoding, consolidation or retrieval) and may underlay distinct, non-overlapping, neuropathologic states.[3]

Furthermore, MCI variability mirrors the uncertain limits of normal ageing, whose definition may differ among studies. Lack of operational criteria for the identification of tests relevant to discriminate 'normal' versus 'pathological' performance may influence the individual diagnosis of MCI.[41] Stimulus modality, structure of the memorandum facilities to improve encoding and recall, the protocol itself (including one or more memory tests), and the level of normal cut-off (set at 1 or 1.5 standard deviation[42]) are influential. All these parameters can identify different sectors of the population and yield different predictions about their outcome.[41]

At the other extreme of the continuum, the definition of dementia can influence the prevalence of MCI patients. Dementia can vary from 13-31% depending on whether Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or International Classification of Diseases (ICD-10) criteria are applied.[43] Provided that the normal cut-off is held constant, the definition of dementia can influence the prevalence of MCI in a trade-off between the extension of the demented population and that of MCI. In the presence of a more demanding definition, e.g. ICD-10, the prevalence of MCI broadens to include patients who would be considered demented by the more lenient DSM-IV definition. Attention, therefore, is to be paid to all these parameters in order to reduce the heterogeneity of the group and to avoid bias in the analysis.

Increased diagnostic confidence may be suggested by positive Aβ biomarker, associated or not to an abnormal degeneration biomarker. As reported in Figure 1 (orange bars) the definition of MCI patients[44] includes patients who are in Stage 0 with normal biomarkers, or fall in the group of s-NAP where the lack of amyloidosis is associated with positive markers of neuronal damage.

FACTORS OF COMPLEXITY

The relationship between clinical picture and biomarkers, however, needs additional specifications. It has been shown that the within-subject levels of β-amyloidosis, measured by CSF Aβ, are minimally correlated with tau[45] and both correlate significantly with PiB-PET. This suggests that independent processes, one reflected by CSF Aβ and one by CSF tau, contribute to the preclinical development of fibrillar amyloid plaques.[45]

In a search[46] for differences in pathophysiological mechanisms at work in the normal elderly population, s-NAP subjects were compared to individuals with β-amyloidosis (i.e. in Stage 2 and 3; cfr Figure 1). Results showed that the two groups were similar in all the parameters investigated (PiB-PET, FDG-PET, hippocampal atrophy). The outcome confirms that β-amyloidosis is not the initial and causal AD event in CN elderly but that AD is to be considered as a multiparameter pathology subtended by several, partly independent, pathological processes.[45-47] The amyloid cascade hypothesis, indeed, does not take into account the role of other factors in modulating late changes of the brain; some of them will be listed below.

Age is an important risk factor, as implied by Perusini[48] when noting that neurofibrillary alterations very closely resembled 'the histo-pathological findings occurring in the involution of the brain during old age'. Since then, interpretation has been swinging from a position which sees AD as an exaggerated caricature of brain ageing, to the other, which views AD as a process that drops into age changes, mingling with its mechanisms.[49]

Actually, the relationship between AD-P and dementia changes as a function of age. The correlation between plaque and tangle burden versus cognitive status, which holds in younger AD patients, does not in older ones.[50]

Since elderly people without dementia may have pathological features of AD,[27,30] it has been possible to compare the neuropathological data of patients who have died with and without dementia. The results indicate that the prevalence of AD-P in patients who died from dementia remains constant or tends to decline with age, whereas the burden of Alzheimer's-type disease in patients dying without dementia increases with the age at death. There is a convergence of AD-P features in people with and without dementia at a very advanced age, so that the same burden of pathological features can be frequently found in age-related people who did not have dementia.[51]

In contrast, cortical atrophy, which reflects many other factors beyond plaque and tangle burden,[52] increases with age and continues to differentiate people with dementia from those without it in all age groups. Atrophy emerges as a robust marker of the accumulation of pathological lesions, not only plaques and tangles, and of the failure of compensatory mechanisms, both of which lead to dementia.[53]

Inflammation and activation of microglia, the predominant macrophage species within the brain, are the main features of AD. PET imaging of microglia and fibrillar amyloid, indeed, shows that levels of respective markers in the cortex of patients with AD are higher than those of non-demented controls. Microglial cells which accumulate around amyloid plaques in the brains of individuals with AD, may adopt a proinflammatory profile with deleterious effects on neurons, synapses, and cognition.[53,54]

Useful information comes from amyloid-β immunisation which, unsuccessful as therapy, significantly reduced microglial responses long after treatment finished. Tau pathology is downgraded as well, witnessing the role of inflammatory changes on AD and confirming the relevance of microglia in neurodegenerative disorders.[55]

Comorbidity due to vascular changes may interfere with the clinical picture as shown by a large body of data.[56] Although the Hachinski Ischaemic Score helps to identify the vascular component in diagnosis, the application of standard clinical and pathological criteria leads to the reclassification of many clinical diagnoses of AD as mixed dementia.[57,58] On the other hand, it is well known that the most severe AD cases present a significant vascular component.[29,59]

CONCLUSION

Summing up, the data so far outlined, which are simply fragments of an enormous body of knowledge, highlighted some aspects of progress in AD debate. Further studies are expected to hit the central heart of the disease where clinical signs, biological parameters, and neuropathological processes compound into a unifying model.

NOTE

While this review was still in press, the IWG group presented a new version[60] of the diagnostic framework, confirming the previously published lexicon. Thus diagnosis of typical AD was allowed long before the appearance of dementia, if a specific memory defect (i.e. low free recall not normalised by cueing) occurred in the presence of biomarker changes. Likewise, the asymptomatic at-risk state was confirmed when biomarker changes occurred in the absence of a clinical phenotype.

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NEUROPSYCHIATRIC FEATURES OF PARKINSON'S DISEASE WITH COGNITIVE IMPAIRMENT: AN OVERVIEW

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ABSTRACT

Parkinson's disease (PD) is known to cause neuropsychiatric symptoms (NPS). It has been established that the more advanced the motor stage of PD is, the more frequent and severe the NPS may be. However, the relationship between NPS and stage of cognitive decline is less well understood. This is important because the majority of people with PD will experience some degree of cognitive decline during the course of their disease, and there is a high risk of developing dementia (PDD). In non-PD populations there is a strong association between NPS and cognitive impairment and the same association may apply in PD. Consequently, the aim of this article is to provide a brief overview of NPS in PD from the perspective of stage of cognitive decline. We highlight studies that have demonstrated the increasing prevalence and severity of NPS with increasing cognitive impairment in PD. We point out the importance of apathy as a possible precursor to PDD. We also describe the negative impact of NPS and cognitive impairment on caregiver distress and quality of life. Finally, we have summarised findings from key studies of cognitive enhancers in PDD which have examined the effect of these treatments on NPS.

Keywords: Parkinson's disease, cognitive impairment, neuropsychiatric, mild cognitive impairment in PD (PD-MCI), dementia in PD (PDD), caregiver burden, quality of life.

INTRODUCTION

Idiopathic Parkinson's Disease (PD) has been known predominantly as a motor disorder; however, over recent years there has been an increasing focus on non-motor symptoms (NMS) of PD.[1] NMS occur in >90% of people across various stages of PD, and some of the most common manifestations of NMS include psychiatric symptoms, cognitive changes, autonomic instability, and sleep disturbance.[1] While psychiatric syndromes, including depression, anxiety, psychosis, and apathy, have been well characterised in PD in general, the specific relationship of these syndromes to the cognitive changes in PD has not been as extensively described. In this paper, our aim is to provide a general overview of the neuropsychiatric symptoms (NPS) of PD with regards to the stage of cognitive impairment and to highlight the negative impact of these symptoms on quality of life (QoL) and caregiver burden. Since this is not intended to be a systematic review but rather a synopsis to highlight a new perspective on NPS in PD in order to aid the clinician, we will conclude our discussion with a summary of the efficacy of cognitive enhancers on NPS derived from therapeutic trials in PD dementia (PDD).

NPS

Non-PD Cognitive Impairment

The spectrum of NPS is frequently encountered in a range of primary mental health disorders such as psychosis, anxiety, and mood disorders, as well as conditions affecting brain function such as neurodegenerative disorders, delirium, traumatic brain injury, and systemic conditions. Additionally,

NPS commonly exist in people with mild cognitive impairment (MCI) and dementia outside of the context of PD, and have been described in care home residents,[2] clinical dementia populations, and community-based epidemiological samples.[3,4] The Cache County Study,[3] one of the very few epidemiological studies examining NPS in dementia, found that >60% of a community sample of people over the age of 65 with dementia had at least one NPS. Of these, >50% had 'clinically significant' NPS, rated as 'moderate-to-severe' on the Neuropsychiatric Inventory (NPI).[3] The most prominent NPS observed included apathy, depression, and aggression. As for MCI in non-PD populations, another community-based study, the longitudinal Cardiovascular Health Study (CHS), which examined 824 people, found that the prevalence of these symptoms was as high as 43%, with 29% having 'clinically significant' symptoms,[5] which exceeds the prevalence of NPS in older people with intact cognition.[6] Data also demonstrated that 270 of the 362 participants (75%) with dementia had at least one NPS, with >60% having a NPI score ≥4, demonstrating a severity of clinical significance. This suggests that NPS may be a precursor to subsequent cognitive decline, rather than being within a constellation of symptoms that exist in memory impairment, and may therefore have a predictive role. Consequently, examining the profile of NPS in relation to cognitive stage in PD has merit, and probes whether a similar continuum of severity of NPS exists in PD populations.

PD

NPS manifesting at some point in the clinical course of PD is already well recognised and the significant negative impact of these symptoms on the QoL of those affected has previously been documented.[7,8] However, hitherto, there has been very little attempt to examine these symptoms in relation to the degree of PD-related motor and cognitive impairment. A 'stage-based' understanding of NPS and their impact in PD is important since the appearance of NPS may be a harbinger of cognitive decline or the onset of dementia, or vice versa. Specifically, once dementia has been diagnosed, the 'neuropsychiatric slippery slope'[9] may appear, heralding the onset of a more rapid global decline in health and QoL and a step-up in caregiver burden. Furthermore, the progression of underlying neurodegenerative pathophysiology through the Braak stages[10] supports the notion that brain stem nuclei related to both the neuropsychiatric (e.g. raphe nuclei and locus coeruleus) and the cognitive symptoms of PD may appear simultaneously or in close proximity to each other.

One of the most fruitful ways to examine NPS in PD is using the NPI (Cummings et al.[11]), which is the gold-standard rating scale for NPS in dementia. The NPI is a structured 12-item caregiver-rated screening tool designed to help assessment of behavioural disturbances in dementia by ascertaining the presence of a range of NPS 'domains' and rating them according to their frequency and severity. It is a valid instrument, with high inter-rater and test-retest reliability, but despite its strengths, NPI data are prone to recall bias as carers give their own account of observed behaviour. For example, one of the domains - apathy - is a loss of motivation; however, informants can struggle to differentiate between apathy and depression. This diagnostic challenge has been debated frequently and studies have demonstrated the ability to discriminate between the two using validated rating scales for both apathy and depression.[12,13] Nevertheless, in PD, several studies have utilised the NPI, although unlike the larger epidemiological studies in dementia, these have generally been confined to clinic samples or PD-specific cohorts as outlined below.[14-16]

NPS According to Cognitive Stage in PD

Intact cognition in PD

Aarsland et al.[17] conducted a large cohort study in order to describe the neuropsychiatric profile in untreated people with PD without dementia. By using the NPI, this study found that >50% of 175 people with PD had positive scores in at least one domain compared to a much smaller proportion of non-PD participants ($p<0.001$). Of these, nearly 35% of participants' carers endorsed two or more NPI items. The most prevalent NPS to emerge were apathy and depression. Ojagbemi et al. (2013),[18] compared people with PD (n=50) with a non-PD control group (n=50). The NPI showed that delusions, hallucination, and apathy were significantly higher in the PD group, and the mean total NPI magnitude scores for the PD and control groups were 9.4 (SD 10.6) and 3.5 (SD 7.7), respectively ($p=0.002$).

MCI IN PD

Until recently, there were no clearly defined operationalised criteria for cognitive impairment in PD. To address this, the Movement Disorder Society (MDS) established a task force to define specific criteria for two different cognitive states in PD: PD-MCI[19] and PDD.[20] These clinical consensus criteria have been based on clinical, cognitive, and functional parameters to clearly define the phenotype of each syndrome. It has been argued that the presence of PD-MCI increases the likelihood of developing PDD,[19] therefore, early recognition of cognitive decline in PD and its subsequent management is crucial. Since the criteria for PD-MCI have only recently been established, very few studies describing NPS in PD according to this cognitive classification exist in the literature.

One study using the new categorisation of PD-MCI and PDD is that of Leroi et al.[21] In this cross-sectional study, 127 PD participants with intact cognition (PD-NC; n=54), PD-MCI (n=48), and PDD (n=25) were examined using the NPI. Nearly 78% of all participants, regardless of cognitive stage, reported at least one NPS on the NPI. Interestingly, there was no significant difference in the frequency or severity of NPS between PD-NC and PD-MCI, other than in the domain of apathy. Apathy in the PD-MCI group had a frequency of 48% and a mean magnitude (frequency x severity) of 3.79 (SD 4.91), nearly three times more than the PD-NC group. The rate of apathy in PD-MCI was similar to the rate found in the PDD group (52%). This correlation of apathy between both groups suggests the possibility that the emergence of apathy in PD-MCI could presage the conversion to PDD. This argues for a closer scrutiny for the presence of apathy in the PD-MCI population. In another slightly larger study,[22] those with PD-MCI (n=246) had higher rates of four NPS domains compared to those with intact cognition (n=164). Specifically, in those with PD-MCI, rates of depression (65.5%), sleep disturbance (63.3%), anxiety (58.2%), and apathy (50.7%) were all prominent in PD-MCI but not statistically different in frequency from the PD-NC group. Irritability was found to be significantly higher in the PD-MCI group compared to the PD-NC group. In this study, PD-MCI was defined more loosely than in the previous study and included gradual cognitive decline, Mini-Mental State Exam (MMSE) score ≤23.8, absence of or minimal impairment in activities of daily living, and absence of dementia. Those with PD-MCI were further subdivided into amnesic and non-amnesic subtypes (PD-aMCI and PD-naMCI, respectively) according to Petersen's criteria.[23] This difference in the definition of PD-MCI may account for the differences observed in the two studies. Furthermore, this study also found that motor symptoms, demonstrated by the Unified Parkinson's Disease Rating Scale (UPDRS) were significantly higher in PD-MCI than PD-NC suggesting a relationship between motor symptoms and NPS, either secondary to a psychological reaction to disability or to the neuropathological progression seen in PD.

PDD

The mean duration of subtle cognitive symptoms in PD developing into a full dementia syndrome is around 10 years,[24] emphasising the importance of understanding different cognitive stages along this progression. Such an understanding will aid in the detection of associated complications and will enable further support and intervention. As the degree of cognition declines in PD, NPS become increasingly common. This is supported by a handful of studies examining NPS in PDD cohorts. For example, Lee et al.[25] found that 113 out of a cohort of 127 (89%) participants with PDD had at least one NPS, with anxiety (57.5%), sleep problems (53.5%), and apathy (52%) being the most common. Amongst these participants, hallucinations were most strongly linked to extent of cognitive impairment as demonstrated by MMSE score. Aarsland et al.[26] found that 64% of 527 participants with PDD endorsed at least one NPI item in the 'clinically significant' range (score ≥4). The rate of 'any NPS' regardless of severity was similar to that found by Lee et al.[25] at nearly 90%. It is notable that the rate of NPS in PDD is significantly higher than the rate of NPS found in those with Alzheimer's Disease (AD),[3] suggesting that those with both physical and cognitive difficulties, such as is the case in PDD, have a greater neuropsychiatric load. This greater degree of impairment suggests more cognitive involvement in PDD than AD and may, therefore, lead to greater caregiver burden.

Few other studies have compared neuropsychiatric differences between PDD and AD. Starkstein et al.[27] reported no significant differences between apathy, delusions, and irritability. However, major

depression was significantly more prevalent in PDD whereas disinhibiton was significantly more prevalent in AD. Interestingly, Aarsland et al.[28] reported hallucinations to be more commonly seen in PDD than AD, whereas other NPS of apathy, agitation, disinhibition, and irritability were more prominent in those with AD. These differences, yet not fully understood, suggest different regional and neurochemical pathways as mechanisms of cognitive impairment. A summary of NPS in PD-NC, PD-MCI, and PDD is summarised in Table 1, and the frequency of NPS is shown in Table 2.

THE NEGATIVE IMPACT OF NPS ASSOCIATED WITH COGNITIVE IMPAIRMENT IN PD

The majority of people with PD live in their own homes with family members who are integral in providing care for them. Caregivers assist with household chores and help with physical and personal needs. As PD progresses, caregivers take on more tasks, particularly related to changes in cognitive ability in the person with PD. Consequently, the burden of care increases significantly as cognition declines.[29]

Table 1: Summary of neuropsychiatric symptoms in Parkinson's disease with different stages of cognitive impairment (mean frequency x severity scores on the NPI).

	Parkinson's Disease without Cognitive Impairment				Parkinson's Disease with Mild Cognitive Impairment			Parkinson's Disease Dementia		
	Ojagbemi[18]	Aarsland[17]	Leroi[21]	Monastero[22]	Monastero[22]		Leroi[21]	Lee[25]	Aarsland[26]	Leroi[21]
					PD-aMCI	PD-naMCI				
	n=50	n=175	n=54	n=164	n=142	n=104	n=48	n=127	n=537	n=25
Mean NPI Item Score (frequency x severity) (Standard Deviation)										
Delusions	0.88 (2.02)	0.06 (n/a)	0.19 (0.99)	0.04 (0.4)	0.3 (1.5)	0.06 (0.5)	0.15 (0.88)	1.94 (3.3)	1.03 (2.29)	1.08 (1.93)
Hallucinations	0.36 (1.74)	0.04 (n/a)	0.21 (0.70)	0.1 (0.7)	0.7 (1.8)	0.3 (1.3)	0.40 (1.35)	1.96 (3.1)	1.48 (2.34)	1.00 (1.97)
Agitation	0.54 (1.91)	0.15 (n/a)	0.33 (1.25)	0.3 (1.2)	0.7 (2.1)	0.4 (1.2)	0.34 (1.78)	1.32 (2.2)	1.05 (2.07)	0.84 (1.67)
Depression	1.42 (2.24)	1.06 (n/a)	0.92 (1.67)	0.02 (0.3)	0.2 (1.4)	0.05 (0.6)	1.02 (1.91)	1.57 (2.6)	1.96 (2.57)	1.52 (1.80)
Anxiety	1.00 (2.12)	0.59 (n/a)	1.04 (1.41)	0.6 (1.5)	2.0 (3.1)	1.2 (2.3)	1.21 (2.07)	1.82 (2.7)	1.93 (2.72)	1.36 (2.81)
Euphoria	0.22 (0.98)	0	0.25 (0.96)	2.8 (3.2)	3.7 (3.3)	2.9 (3.1)	0.26 (1.75)	0.19 (0.6)	0.10 (0.67)	0.12 (0.60)
Apathy	1.64 (3.52)	1.06 (n/a)	1.01 (2.62)	2.9 (3.3)	3.4 (3.5)	2.7 (3.1)	3.79 (4.91)	2.50 (3.5)	2.95 (3.43)	2.8 (3.87)
Disinhibition	0.04 (0.28)	0.08 (n/a)	0.15 (0.87)	2.1 (2.5)	3.1 (3.4)	2.4 (2.9)	0.13 (0.88)	0.49 (1.3)	0.34 (1.20)	0.24 (0.72)
Irritability	0.76 (1.67)	0.22 (n/a)	0.71 (2.00)	0.05 (0.4)	0.1 (0.8)	0	0.70 (2.19)	1.41 (2.6)	1.04 (2.21)	1.52 (2.33)
Aberrant Motor Behaviour	0.28 (1.21)	0.14 (n/a)	0.25 (1.67)	0.1 (0.8)	0.5 (1.7)	0.2 (0.8)	0.13 (0.88)	1.35 (2.5)	1.05 (2.40)	1.20 (2.53)
Sleep Problems	1.02 (2.33)	0.69 (n/a)	3.29 (3.75)	3.8 (3.8)	3.9 (3.4)	3.4 (3.6)	3.91 (4.08)	2.49 (3.5)	n/a (n/a)	2.16 (3.39)
Appetite Problem	1.08 (2.40)	0.70 (n/a)	0.27 (1.03)	0.5 (1.6)	1.2 (2.9)	0.8 (1.7)	0.06 (0.44)	2.00 (3.1)	n/a (n/a)	1.28 (3.05)
Total NPI	9.36 (10.57)	n/a (n/a)	9.53 (13.03)	13.3 (11.0)	19.8 (15.8)	14.1 (11.2)	12.38 (12.55)	19.02 (20.4)	12.93 (12.0)	14.56 (10.5)

PD: Parkinson's disease; MCI: mild cognitive impairment; NPI: neuropsychiatric inventory; PD-aMCI: PD-amnesic MCI; PD-naMCI: PD-nonamnesic MCI.

Table 2: Most common NPS in Parkinson's disease with different stages of cognitive impairment (percentage on the NPI with any score greater than zero).

Parkinson's Disease without Cognitive Impairment				Parkinson's Disease with Mild Cognitive Impairment			Parkinson's Disease Dementia		
Ojagbemi[18]	Aarsland[17]	Leroi[21]	Monastero[22]	Monastero[22]		Leroi[21]	Lee[25]	Aarsland[26]	Leroi[21]
				PD-aMCI	PD-naMCI				
n=50	n=175	n=54	n=164	n=142	n=104	n=48	n=127	n=537	n=25
Most common NPS on NPI with any score (%)									
Depression (46)	Depression (34.3)	Sleep (55.6)	Sleep (57.3)	Depression (70.4)	Depression (60.6)	Sleep (58)	Anxiety (57.5)	Depression (57.5)	Depression (56)
Sleep (30)	Apathy (27.4)	Anxiety (42.6)	Anxiety (54.9)	Sleep (66.9)	Sleep (59.6)	Apathy (48)	Sleep (53.5)	Apathy (54.3)	Apathy (52)
Apathy (28)	Sleep (17.8)	Depression (33.3)	Depression (54.9)	Anxiety (60.6)	Anxiety (55.8)	Anxiety (36)	Apathy (52)	Anxiety (49)	Irritability (52)
Appetite (26)	Anxiety (16.4)	Irritability (22.2)	Apathy (45.1)	Apathy (54.2)	Apathy (47.1)	Depression (36)	Depression (50.4)	Hallucinations (43.9)	Anxiety (48)

PD: Parkinson's disease; MCI: mild cognitive impairment; NPI: Neuropsychiatric Inventory; NPS: neuropsychiatric symptoms; PD-aMCI: PD-amnesic MCI; PD-naMCI: PD-nonamnesic MCI.

The 'Parkinson's UK Members' Survey (2007; n=1,881) found that caregivers with an increasing number of tasks, financial strain, and with their own health problems have a greater burden of care.[30] Moreover, there is now evidence that one of the most important predictors of institutionalisation for people with PD is the presence of visual hallucinations and dementia.[31] Other NPS such as depression are also important predictors of caregiver distress, even outweighing the impact of other non-neuropsychiatric factors.[32] This underscores the importance of NPS in the emotional wellbeing of caregivers, which ultimately reflects on the wellbeing and QoL of the person with PD.

Just as depression in PD impacts negatively on caregiver distress, the negative impact of depression on health-related quality of life (Hr-QoL) is also significant.[33] Leroi et al.[29] examined the impact of cognitive stage in PD on QoL using the Parkinson's Disease Questionnaire (PDQ-8), which focuses on eight dimensions. This study found more impaired QoL in the group with PDD (n=25) compared to PD participants with intact cognition (n=54) and those with PD-MCI (n=48), although no specific association with frequency and severity of NPS was examined. These findings support the negative influences that exist between disease severity, degree of cognitive impairment, and caregiver distress. The negative trajectory of change suggests that those with PD-MCI need more intense interventions to curb the likelihood of dementia, institutionalisation, costs of care, and caregiver burden.

MANAGEMENT OF NPS WITH COGNITIVE IMPAIRMENT

In PD, the underlying neurodegenerative pathology is largely characterised by deterioration of dopaminergic pathways. However, cholinergic pathways may also be affected, which plays an important role in cognitive impairment, particularly PDD. Consequently, attempts at increasing the cholinergic load in PD to improve cognition is a reasonable therapeutic strategy. Several randomised controlled trials (RCTs) have demonstrated the efficacy of cholinesterase inhibitors (ChEI) in improving cognition in PDD. Most notably, the EXPRESS study (Emre et al.[34]) demonstrated a positive effect of rivastigmine over placebo. There have been very few RCTs of typical treatments of NPS, such as antipsychotics and antidepressants, which have specifically taken cognitive stage into account, therefore, we have not addressed them here. Instead, several of the studies investigating the effect of cognitive enhancers in PDD have included the NPI as a secondary outcome measure in order to evaluate the efficacy of these interventions

on NPS. We have therefore summarised some of these key findings below.

Donepezil was the first ChEI to be trialled in PDD. Recently, Ishikawa et al.[35] reported that, in an open-label study with nine participants on donepezil, an improvement of 8.3 total NPI points was observed at week 12 ($p<0.01$). Aarsland et al.[36] conducted a 10-week randomised double-blind crossover single centre study comparing donepezil to placebo in 14 participants with PDD. Although a significant effect of donepezil on MMSE score was demonstrated, no similar effect was noted on NPI scores. Leroi et al.[37] also conducted a double-blind placebo-controlled RCT of donepezil in PDD and showed greater reduction in NPI scores in those on donepezil compared to those on

Table 3: Response of neuropsychiatric symptoms to cognitive enhancers in key Parkinson's disease dementia trials.

Medication	Author	Study Design	Neuropsychiatric Symptoms
Donepezil	Ishikawa et al.[4]	Donepezil in PDD; prospective open-label exploratory study over 12 weeks; n=9	NPI (primary outcome) showed improvements in predominantly aberrant motor behaviour, anxiety and hallucinations by 1.7, 1.6, and 1.3 points, respectively
	Aarsland et al.[35]	Donepezil vs placebo in PD with cognitive impairment; randomised double-blind crossover study over 10 weeks; n=14	NPI (secondary outcome) highlighted depression being most common at baseline but no significant change was observed in the donepezil group
	Leroi et al.[36]	Donepezil vs placebo in PD with cognitive impairment; randomised double-blind study over 18 weeks in 2 centres; n=16	NPI (secondary outcome) total score dropped 40.9% in the donepezil group compared to 26.4% reduction in final visit in the placebo group
Galantamine	Aarsland et al.[38]	Galantamine in PDD; multi-centre open-label study over 8 weeks; n=13	NPI (primary outcome) used to assess hallucination; 7 out of 9 (78%) improved from baseline
	Grace et al.[37]	Galantamine vs placebo in PD without dementia; randomised double-blind study over 16 weeks; n=69	NPI (secondary outcome) showed improvements by 1.14 points but no significant difference between groups
Rivastigmine	Emre et al.[33]	Rivastigmine vs placebo in PD with cognitive impairment; randomised multi-centre double-blind study over 24 weeks; n=541	NPI (secondary outcome) showed significant improvement in treatment group ($p=0.02$), with over 40% having at least 30% improvement in NPI scores
Memantine	Leroi et al.[41]	Memantine vs placebo in PDD; randomised double-blind study over 22 weeks; n=25	NPI (secondary outcome) showed no significant difference between groups ($p=0.70$)
	Aarsland et al.[42]	Memantine vs placebo in PDD; randomised multi-centre study over 24 weeks; n=72	NPI (secondary outcome) showed no significant difference between groups
	Emre[43]	Memantine vs placebo in PDD and DLB; randomised double-blind multicentre study; n=199	NPI (secondary outcome) showed no significant difference between groups at any point in PDD contrary to LBD: delusions ($p=0.02$), hallucinations ($p=0.02$), and sleep behaviour ($p=0.04$)

PD: Parkinson's disease; PDD: Parkinson's disease Dementia; NPI: Neuropsychiatric Inventory; LBD: Lewy Body Dementia.

placebo, suggesting that such interventions may have a promising role in managing NPS associated with PDD.

Galantamine, another ChEI but with a stronger affinity to nicotinic receptors than donepezil, has also been examined in a placebo-controlled trial in PDD. However, in this study of 69 participants with 38 on active treatment, no significant improvement in NPS was seen in the active treatment group as compared to those on placebo.[38] In another study of galantamine in PDD using an open-label design, Aarsland et al.[39] found that 8 out of 13 (62%) participants with PDD had improved cognition. Importantly, of the nine participants who had hallucinations at baseline, seven had improved by week 8 on active treatment.

The largest RCT of a ChEI in PDD is the EXPRESS study (Emre et al.[34]), which compared rivastigmine, the third ChEI, to placebo in 541 participants with PDD. The NPI demonstrated significant improvement in NPS in those who received rivastigmine compared to those on placebo (p=0.02). A minimum of 30% improvement in NPI scores was found in a significantly greater proportion of those on rivastigmine than those on placebo (45.5% versus 34.6%, respectively). These findings were supported by another study which also demonstrated a greater efficacy of rivastigmine on apathy and anxiety, and a significant improvement in aspects of cognition compared to placebo in people with dementia with Lewy bodies (DLB) (McKeith et al.[40]). Rivastigmine now has a specific UK license for use in PDD to improve cognition and may also be used as first-line therapy to manage hallucinations and delusion associated with PDD. This strategy may obviate the need for poorly tolerated antipsychotic medication if used as first-line therapy.

Finally, a cognitive enhancer of a different class that has also been trialled in PDD is memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist. Memantine has been shown to have a role in improving NPS in non-PD dementias;[41] therefore, it was hypothesised to have a similar effect in PDD-related NPS. In the first reported RCT of memantine in PDD, no significant difference in NPI scores between memantine and placebo was noted (Leroi et al.[42]). Another randomised study (Aarsland et al.[43]), this time looking at both PDD and DLB, also found no significant difference in NPS outcomes between memantine and placebo over a 24-week period. A subsequent larger study, which also included participants with PDD and DLB, showed no improvement in NPI scores (p=0.52) in PDD at 24 weeks but a significant improvement in delusions, hallucinations, and sleep behaviour in DLB was seen.[44] A summary of the findings on NPS from the key studies on cognitive enhancers in PDD is outlined in Table 3.

CONCLUSION

In conclusion, we have provided a brief outline of studies which demonstrate the increasing prevalence of NPS with worsening cognitive function in PD. Examining NPS, particularly apathy and psychosis, in the context of the clinical entities, PD-MCI and PDD can be important in order to anticipate further cognitive deterioration and to guide clinical decision-making, particularly regarding the use of cognitive enhancers. The high prevalence of NPS in PD with cognitive impairment emphasises the need to more fully explore the underlying pathophysiology, impact, and management of these symptoms. Further work is needed to examine the relationship of NPS and cognitive decline with disease duration of PD.

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MOTOR SYSTEM PLASTICITY AND COMPENSATION IN MULTIPLE SCLEROSIS

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ABSTRACT

Multiple sclerosis (MS) affects the central nervous system (CNS) by inflammatory lesions, direct axonal injury, and by a rather diffuse and widespread neurodegeneration. For a long time, research has mainly focused on these destructive aspects of MS, while the compensatory effects of cellular repair and neural plasticity have received little consideration. However, as current effective immunomodulatory therapies may limit rather than preclude demyelination and axonal damage, additional therapeutic strategies promoting compensation of CNS damage might be of great use for preventing persistent impairment in MS. As a precondition for the development of such strategies, which may encompass pharmacological and behavioural interventions, but also non-invasive stimulation techniques, it seems fundamental to get deeper insights into the mechanisms of plasticity and adaptation at the systemic level. This review will provide a brief overview of what is known about plasticity of the motor system in patients with MS at present, with the main focus relying on evidence from functional imaging, neurophysiology, and motor learning. Overall, rapid-onset motor plasticity seems to be preserved even in advanced stages of the disease. Reorganisation processes, which can be shown early in the course of MS, are functionally relevant for motor compensation. In advanced MS, however, the brain´s adaptive reserve might be exhausted due to exceeding CNS injury. Future studies should address the question of how the later stages of central motor plasticity can be promoted best to preserve the patient´s autonomy for as long as possible.

Keywords: Multiple sclerosis, plasticity, motor system, adaptation, reorganisation, compensation, functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS).

CLINICAL EVIDENCE OF ADAPTATION IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an immune-mediated disease that is characterised by inflammation and neurodegeneration within the central nervous system (CNS).[1] While the most characteristic pathological change in MS is the formation of large confluent demyelinated plaques in the white matter of the brain, cortical lesions are also present in early stages of MS.[1] In the majority of patients, MS initially shows a relapsing-remitting course (RRMS) with episodes of neurological impairment that occur months or years apart and affect different functional systems. As revealed by longitudinal studies, these episodes should be viewed as the tip of the iceberg since, on average, only about 5-20% of new lesions detectable on brain magnetic resonance imaging (MRI) are associated with clinical symptoms or signs.[2] Accordingly, the so-called 'clinico-radiological paradox' of MS refers to the common discrepancy between pathological findings on brain MRI on the one hand and clinical symptoms on the other.[3] This discrepancy can be particularly impressive in a subgroup of patients suffering from a clinically 'benign' phenotype of RRMS with preserved functional capacity for years in spite of a high CNS lesion load.[4]

Altogether, since repair on the cellular level commonly remains incomplete,[5-7] there must be additional mechanisms accounting for recovery from or nonappearance of symptoms despite persistent structural damage. Commonly, these

kinds of adaptive changes are attributed to neural plasticity, which refers to the capacity of single neurons or neuronal systems to adapt dynamically in response to external stimuli, environmental changes, or lesions.[8] In this context, the term 'plasticity' summarises a number of mechanisms which may operate on a timescale from minutes to months (Figure 1) and which seem to occur partly in parallel, partly successively.[9] Unmasking of latent neuronal connections[10] or increasing neuronal membrane excitability by altering the expression of ion channels[11] can be quick ways of adaptation. At the synaptic level, synaptic efficacy can be modulated in terms of long-term potentiation (LTP) or long-term depression (LTD).[12,13] Moreover, metaplastic phenomena might promote efficient recovery.[14] In contrast to these rapid-onset mechanisms, the anatomical changes underlying chronic cortical reorganisation might require the formation of new synapses and sprouting of axons to form compensatory pathways[15] and hence take more time (Figure 1). But are the mechanisms underlying rapid-onset neural plasticity and chronic reorganisation available in MS in spite of the whole-brain pathology, especially in view of the cortical involvement which may critically interfere with those mechanisms? Are they functionally relevant for the compensation of MS-related CNS injury at all? These questions will be assessed below based on data from functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), and motor training studies.

RAPID-ONSET CENTRAL MOTOR PLASTICITY

Rapid-onset central motor plasticity may occur on a timescale of minutes to hours (Figure 1, left box). The question of whether this early type of motor plasticity is preserved in patients with RRMS is of great interest. If we suppose that rapid-onset processes represent initial steps of more slowly evolving mechanisms of motor plasticity,[16] they might be rate-limiting on the course to successful adaptive reorganisation (Figure 1). Rapid-onset plasticity can be induced exogenously by non-invasive stimulation techniques such as TMS or transcranial direct current stimulation (tDCS), or endogenously by motor training tasks.[17-19]

Stimulation-Induced Plasticity

We have previously studied rapid-onset central motor plasticity and its relationship to motor impairment and CNS injury in patients with stable MS (RRMS or secondary progressive MS [SPMS], no relapse, and no changes of disease modifying treatment [DMT] within 3 months).[20] Paired associative stimulation (PAS), a protocol combining electric nerve stimulation with TMS of the contralateral motor cortex, may induce Hebbian LTP of synaptic efficacy in the human motor cortex.[21,22] PAS-induced plasticity shares distinct physiologic properties with synaptic LTP,[20-22] which is tightly related to skill acquisition in a motor training task.[20,23]

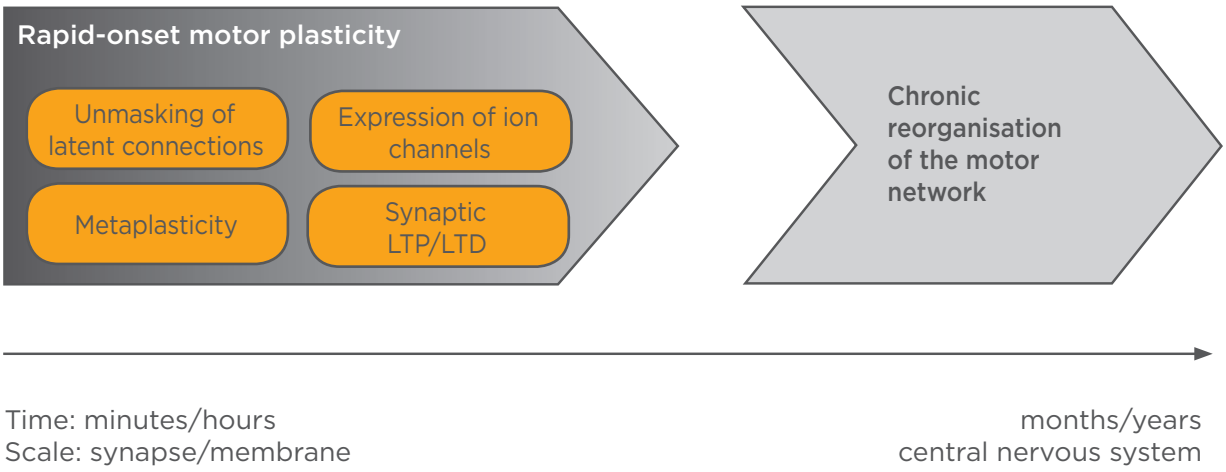

Figure 1: Depending on the spatial and temporal scales considered, a number of mechanisms may contribute to neural plasticity, reorganisation, and adaptation of the motor system. Rapid-onset processes (left box) are believed to represent initial steps of more slowly evolving mechanisms of motor plasticity and chronic reorganisation (right box).
LTD: long-term depression; LTP: long-term potentiation.

We found the PAS-induced enhancement of corticospinal excitability to be comparable between patients with moderately severe MS and matched controls.[20] There was no correlation between the changes of corticospinal excitability and the impairment of hand function or measures of CNS injury. PAS-induced plasticity in patients with high CNS injury and good motor performance was similar to the plasticity in patients with high CNS injury and poor motor performance. Thus, in spite of motor impairment and CNS injury, LTP-like rapid-onset motor plasticity in MS patients was comparable to that in healthy subjects.[20] As compensation of MS-related brain injury might also require excitability-decreasing mechanisms to focus on neuronal activity facilitating recovery of a specific motor function, we also assessed LTD-like rapid-onset motor plasticity in patients with RRMS (stable for ≥3 months). We applied an excitability-decreasing TMS protocol (continuous theta-burst stimulation [cTBS][24]), consisting of high-frequency, low-intensity bursts of three pulses, over the primary motor cortex (M1).[25] cTBS induces a depression of corticospinal excitability whose physiological properties are similar to those observed for LTD as studied in animal preparations.[24,26,27] Motor-evoked potential amplitudes were comparably reduced by cTBS in MS patients and matched controls. Altogether, LTP and LTD-like 'exogenous' motor plasticity remains largely intact in patients with mild-to-moderate MS. Therefore, compensation of MS-related CNS injury is unlikely to be constrained by insufficient rapid-onset neuroplasticity.

During a relapse of MS, PAS-induced LTP-like plasticity has been demonstrated to be normal in patients with complete recovery from the relapse 12 weeks after, but impaired in patients with incomplete or absent recovery.[28] This suggests that synaptic plasticity contributes to symptom recovery after a relapse, and that PAS effects may predict recovery from a relapse.[28]

Several pharmacological and biochemical factors have been shown to influence rapid-onset plasticity. For example, exposure of MS patients to a cannabis-based preparation used in the treatment of spasticity resulted in a shift in the polarity of synaptic plasticity induced by cTBS, pointing to metaplastic effects of cannabis ingredients on the motor cortex in MS patients.[29] Moreover, contents of amyloid-β_{1-42} in the cerebrospinal fluid (CSF) correlated with cortical plasticity deficits in MS, probably indicating that central inflammation due to MS is able to alter amyloid-β metabolism, leading to impairment of synaptic plasticity.[30] Platelet-derived growth factor in the CSF might play a role in favouring the brain plasticity reserve, which is believed to be crucial to contrast clinical deterioration in MS.[31] In addition, early application of disease modifying drugs may prove beneficial by reversing cognitive and cortical plasticity deficits in MS.[32] Finally, the subtype of MS was shown to influence the expression of stimulation-induced LTP-like motor plasticity in MS patients.[31]

Training-Induced Plasticity

Aside from exogenous stimulation protocols, motor plasticity can be induced by repeated performance of a motor task. Motor learning may challenge rapid-onset mechanisms of central motor plasticity and may result in a reorganisation of the output organisation of the motor cortex.[33,34] We tested motor learning in the course of repeated runs of a force production task and found comparable training-induced improvements of motor performance in MS patients without a relapse for at least 3 months and controls.[20] Motor learning performance did not correlate with motor impairment or measures of CNS injury, and was not different between patients with high CNS injury and good motor performance and those with high CNS injury and poor motor performance.[20] In line with these results, Tomassini et al.[35] reported comparable increments in short and long-term motor learning in MS patients (RRMS and SPMS) and matched controls. Even the patients with the most severe CNS damage showed a comparable success in the course of motor training.[35]

In a subsequent study[36] by the same group, behavioural and fMRI data were assessed during short-term (first practice session) and longer-term (after 2 weeks of daily practice) training of a visuomotor task. Again, MS patients and controls showed comparable performance improvements independent of MS-related brain pathology in MS patients.[36] However, brain regions relevant for improvements of the visuomotor performance differed between patients and controls: greater short-term improvements were associated with lower activation in the sensorimotor, posterior cingulate, and parahippocampal cortices for MS patients, whereas greater long-term improvements correlated with smaller activation reductions in the visual cortex of controls.[36] Hence, brain plasticity for visuomotor practice may be preserved in MS

patients, but partly based on systems different from those acting in healthy controls.[36]

CHRONIC REORGANISATION

Adaptive (and probably also maladaptive) reorganisation in response to MS-related CNS injury is described at the motor system level of the brain and may occur months to years after brain injury (see Figure 1, right box). It can be assessed by fMRI and by non-invasive stimulation methods. While fMRI provides a large-scale average of brain activity by detecting changes in local blood flow, stimulation techniques like TMS can probe the functional role of cortical reorganisation by inducing 'virtual lesions'.

fMRI

The majority of fMRI studies have investigated evidence for reorganisation of the motor system during the remitting (relapse-free) phase of MS. An important study by Reddy et al.[37] demonstrated that cortical adaptive responses contribute to the maintenance of normal motor function in MS patients with unimpaired hand function despite magnetic resonance (MR)-spectroscopic evidence of diffuse axonal injury. In MS patients, the activation of the ipsilateral sensorimotor cortex (SMC) with simple hand movements was increased as compared to controls, and the extent of this increase was strongly correlated with axonal injury as indicated by MR spectroscopy. These results point to an important role of cortical adaptive responses in compensating for axonal injury, even at the subclinical level of MS.[37] Taken together with subsequent studies based on fMRI during a motor task,[38,39] MS patients may need to activate more widespread sensorimotor networks to achieve a similar hand function as compared to healthy volunteers.[37-39] The association of additional activation with the extent of brain damage[37-40] suggests a compensatory function of such activation, which may develop over time in response to a functional demand.[39]

As fMRI changes can also occur due to disability, Reddy and colleagues[41] used an active as well as a passive finger movement task to test whether (at least part of) the fMRI changes were independent from voluntary recruitment and, thus, likely to reflect true functional reorganisation. MS patients were stratified according to diffuse brain injury (DBI) as assessed from MR spectroscopy (N-acetylaspartate concentration) and hand function.[41] Increased activity in ipsilateral sensorimotor networks correlated highly between active and passive finger movements. Patients matched for DBI, but differing in hand disability, showed greater bilateral primary and secondary somatosensory cortex activation with greater disability. Patients matched for hand disability, but differing in DBI, showed increased ipsilateral premotor cortex and bilateral supplementary motor area (SMA) activity with greater DBI. Changes of brain activation related to disability may, therefore, reflect responses to altered patterns of use, while those related to injury and disability - and even detectable with passive finger movements - may reflect true brain reorganisation.[41]

While longitudinal studies of plasticity in MS patients over the course of years are lacking, the temporal evolution of cortical reorganisation was studied by comparing patients with clinically isolated syndrome (CIS), RRMS, and SPMS.[42] During fMRI, MS patients performed a simple motor task with the unimpaired dominant hand. Early in the disease course (CIS) more areas typically devoted to motor tasks were recruited, then bilateral activation of these regions was seen, and late in the disease course (SPMS), areas that healthy people recruit to do novel or complex tasks were activated.[42] Hence, cortical reorganisation seems to vary across different stages of MS. However, there can be remarkable differences with respect to the disease course: a subgroup of patients presents with so-called benign MS (BMS), which is defined by an Expanded Disability Status Scale (EDSS) score ≤3.0 and a disease duration ≥15 years. Given a comparable lesion burden, patients with BMS differed from those with a SPMS phenotype with respect to movement-associated brain activations in fMRI: patients with SPMS showed increased activations of the occipital and left secondary SMC, inferior frontal gyrus, and right hippocampus, whereas they had reduced activations of the left SMA, putamen, and right cerebellum as compared to patients with BMS or healthy controls.[43] The rather selective and lateralised pattern found in patients with BMS largely resembled that of healthy controls.[43] Therefore, a functional adaptive reserve of the brain which is preserved over the long term is likely to contribute to a favourable clinical course of MS.[43]

In addition to sensorimotor cortical areas, the cerebellum is likely to contribute to motor compensation. Saini et al.[44] have assessed

neocortical–cerebellar functional connectivity by fMRI based on correlations between signal intensity changes in selected neocortical and cerebellar regions of interest. Subjects were asked to write '8' repeatedly on paper with a pencil in their right hand to complete one figure every second.[44] While healthy controls showed strong functional connectivity between the left motor cortex and the right cerebellar dentate nucleus, RRMS patients (EDSS ≤2.5, relapse-free for at least 3 months) had significant connectivity between the left premotor neocortex and the ipsilateral (left) cerebellar cortex, which was not found in the control group. Similar connectivity changes have been reported in the healthy brain during motor learning, suggesting that common mechanisms may contribute to normal motor learning and motor compensation after MS-related brain injury.[44]

Only a few studies have addressed brain reorganisation during an acute relapse of RRMS. In a case study of one patient, Reddy and colleagues[45] reported serial MR spectroscopy and functional MRI after new onset of hemiparesis from a relapse of MS. Clinical improvement was accompanied by recovery of neutron activation analysis (NAA), a MR-spectroscopic marker of neuronal integrity, and by a gradual reduction of abnormally large fMRI cortical activation with movement, demonstrating that dynamic reorganisation of the motor cortex may accompany remission from a relapse.[45] Following an acute relapse involving the motor system, Mezzapesa and colleagues[46] assessed cortical reorganisation over time by fMRI during performance of a simple motor task. At baseline, the primary SMC of the contralesional hemisphere was more active during task performance with the impaired as compared to the unimpaired hand. A recovery of function of the primary SMC of the affected hemisphere was associated with clinical improvement, while patients without clinical recovery persistently recruited the primary SMC of the unaffected hemisphere. Thus, the regain of function of motor areas of the affected hemisphere seems to be crucial for a favourable recovery from a relapse.[46]

TMS-Induced Virtual Lesions

We have previously studied the role of two ipsilateral motor areas during performance of a simple reaction time (RT) task in patients with stable MS in relation to their motor impairment and CNS injury.[47] Subjects responded to a Go signal as quickly as possible by performing isometric right-thumb abduction. To interfere transiently with neuronal processing, we used single pulses of TMS over contralateral ($M1_{contra}$) or ipsilateral ($M1_{ipsi}$) primary motor cortex or ipsilateral dorsal premotor cortex (PMd_{ipsi}). Motor impairment was evaluated by hand function tests. CNS injury was assessed by MR spectroscopy (relative NAA concentration), by the total cerebral tesla-2-weighted MRI hyperintense lesion load, and by the corticomuscular latency (CML) to the abductor pollicis brevis muscle. TMS over $M1_{contra}$ slowed RT in patients and controls, whereas stimulation of $M1_{ipsi}$ or PMd_{ipsi} increased RT only in MS patients.[47] Hence, recruitment of ipsilateral motor areas during a simple RT task may be functionally relevant in MS patients, but not in healthy subjects. Remarkably, there was a negative correlation between RT changes following TMS over $M1_{ipsi}$ and CML in MS patients. In other words, an increasing affection of the corticospinal tract to the dominant hand was associated with a less prolonged RT after TMS over the ipsilateral M1; importantly, this effect was not due to differences in baseline performance between MS patients. Taken together, these results may point to an important difference between MS and diseases with focal pathology: as the MS pathology also affects compensating brain regions, the capacity of the ipsilateral M1 to compensate dysfunction of the contralateral corticospinal tract may decrease (even though assumedly starting from variable levels) with higher regional injury.[47]

To probe the functional role of the contralateral M1 in force control in patients with stable RRMS as compared to matched controls, we assessed force production performance (FPP) in an isometric right thumb abduction task before and immediately after cTBS[24] over M1.[25] cTBS impaired FPP significantly in controls, but not in MS patients. However, FPP changes following cTBS correlated with CML in MS patients. Thus, increasing brain injury may render the neuronal networks less responsive toward lesion-induction by cTBS.[25]

CONCLUSION

Current evidence suggests that rapid-onset motor plasticity is preserved even in advanced stages of MS. Chronic reorganisation can be demonstrated early in the disease course and is functionally relevant to maintain motor function.

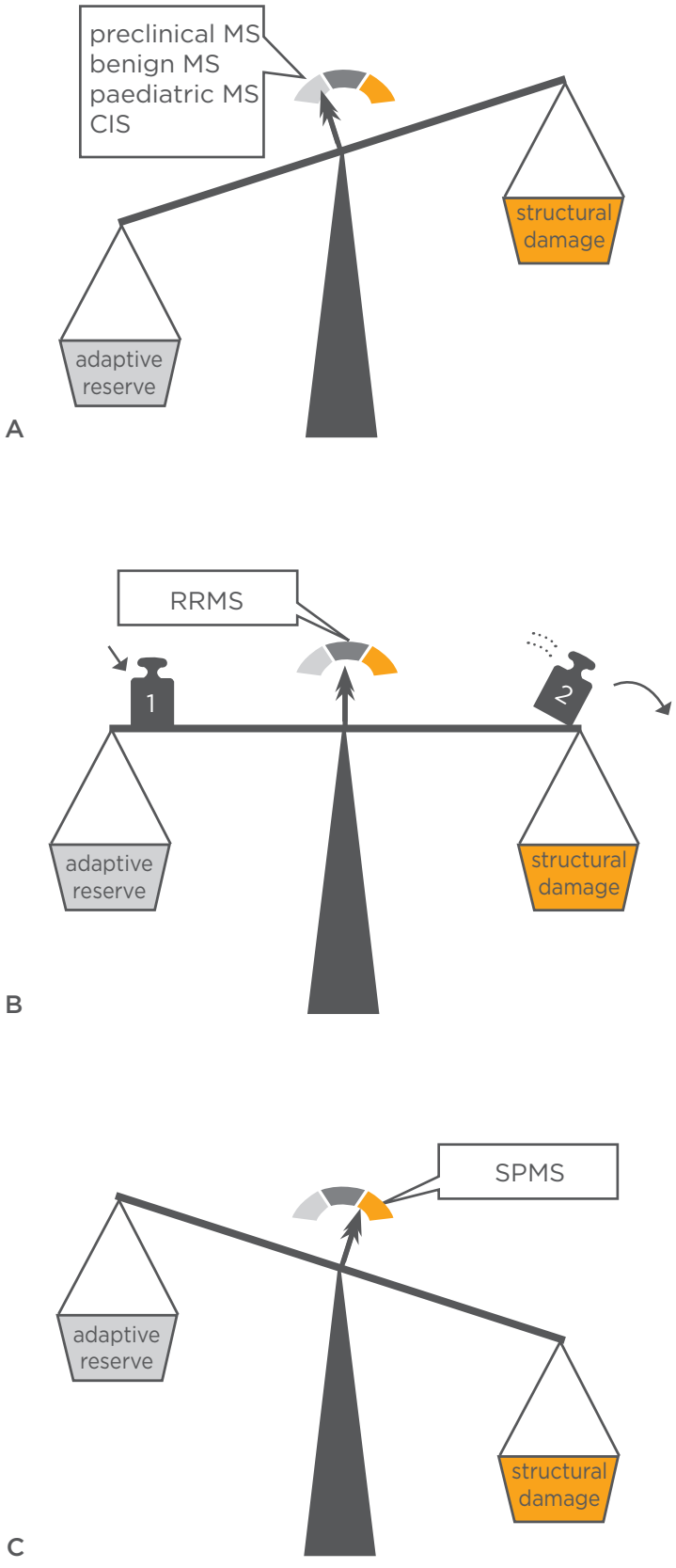

Figure 2: Schematic simplified illustration of the interaction between the adaptive reserve of the brain and MS-related structural CNS damage: A) early MS or benign courses of MS; B) relapsing-remitting phase with damage and compensation balancing each other (weights indicate therapeutic targets: 1) promotion of beneficial neural plasticity; 2) prevention of CNS damage); C) advanced MS.

CNS: central nervous system; CIS: clinically isolated syndrome; MS: multiple sclerosis; RRMS; relapsing-remitting MS; SPMS: secondary progressive MS.

Compared to healthy people, MS patients may need to activate more widespread sensorimotor networks to achieve a similar hand function. The extent of additional activation correlates with the extent of global and focal brain damage, suggesting a compensatory role of this adaptation. Accordingly, activation patterns close to normal can be found in early stages of MS, favourable clinical courses of MS, and during the remitting phase of MS. Therefore, the preservation of the brain´s functional adaptive reserve, which seems to be limited by high CNS injury in advanced stages of the disease, might constitute one of the main factors determining the clinical course of MS over the long term (Figure 2A-C).

In addition to established disease modifying and immunosuppressive treatments which are aimed at preventing CNS damage (Figure 2B, weight 2), future therapies might target the promotion of the brain´s innate ability to compensate for MS-related dysfunction (Figure 2B, weight 1). This may involve pharmacological and behavioural approaches as well as non-invasive stimulation techniques such as tDCS, which has already shown promising preliminary results in other neurological diseases (reviewed in[19]). In respect of rehabilitation, efforts may need to focus on mechanisms promoting the later stages of central motor plasticity, since short-term plasticity is largely preserved and, thus, may not represent a promising therapeutic target. To address the question of which rehabilitation approaches most efficiently induce endogenous plasticity, high-quality studies probing the effects of standardised training interventions on fMRI or TMS measures of plasticity in well-defined groups of MS patients are needed.

Acknowledgements

This article is partly based on a recently published review paper (Zeller and Classen[48]).

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Snail venom rivals morphine monopoly

MORPHINE may have met its match as five new pain relievers, based on snail venom, have proven to be a safe and effective oral medication for the treatment of chronic nerve pain.

The experimental substances, developed by scientists in Queensland, Australia, constitute oral alternatives to morphine and display greater strength, reduced side-effects, and a lower risk of abuse.

The venom of cone snails, marine creatures that paralyse their prey with a substance consisting of tiny peptide proteins called conotoxins, has given rise to these medicines. While deadly to the snail's waterborne prey, some of these conotoxins have been found to cause a drastic reduction in chronic nerve pain.

"This is an important incremental step that could serve as the blueprint for the development of a whole new class of drugs capable of relieving one of the most severe forms of chronic pain that is currently very difficult to treat," said Prof David Craik, senior principal research fellow, National Health and Medical Research Council (NHMRC), University of Queensland, Brisbane, Australia, who led the study.

Ziconotide is the only conotoxin-derived medicine currently in use, but must be administered into the lower spinal cord – a drastic process.

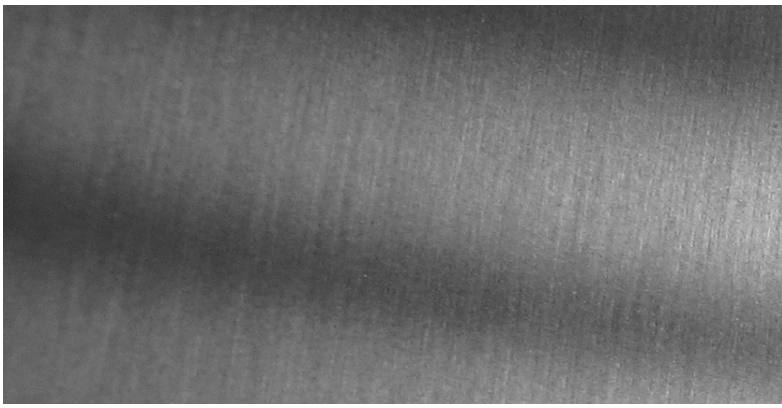
Prof Craik's team is currently developing an oral alternative, but the biggest challenge is enabling drug resistance to the body's enzymes. Past research has shown that manipulating the conotoxin peptides into circular chains of amino acids gives the drug a healthy chance of surviving the digestive system and reaching the nervous system.

In testing, the oral drug caused significant pain reduction in laboratory rats, leading the study team to confidently announce a 100-fold effectiveness over morphine or gabapentin, the current gold standard treatment for chronic nerve pain.

Testing in humans cannot begin for at least 2 years as the team has yet to acquire funding and approval, according to Prof Craik.

"This is an important incremental step that could serve as the blueprint for the development of a whole new class of drugs capable of relieving one of the most severe forms of chronic pain that is currently very difficult to treat."

Prof David Craik,
University of Queensland,
Brisbane, Australia



Autism: the battle of the sexes

GIRLS are more resistant to developing disorders of the brain compared to boys, leading scientists to have confidence in a 'female protective model'.

Geneticists from the USA and Switzerland have revealed that girls require a larger number of harmful genetic mutations to reach the diagnostic threshold of developmental disorders such as autism spectrum disorder (ASD), which means that boys may show symptoms of ASD while girls with identical genetic mutations may show none.

Nevertheless, while boys may be 5-times more likely to have autism, girls may experience more severe forms of the disease due to this higher female mutation threshold. 16,000 boys and girls with neurodevelopmental disorders had their DNA analysed, it was found that, on average, females diagnosed with ASD had 1.3 to 3-times more harmful genetic mutations than males with ASD.

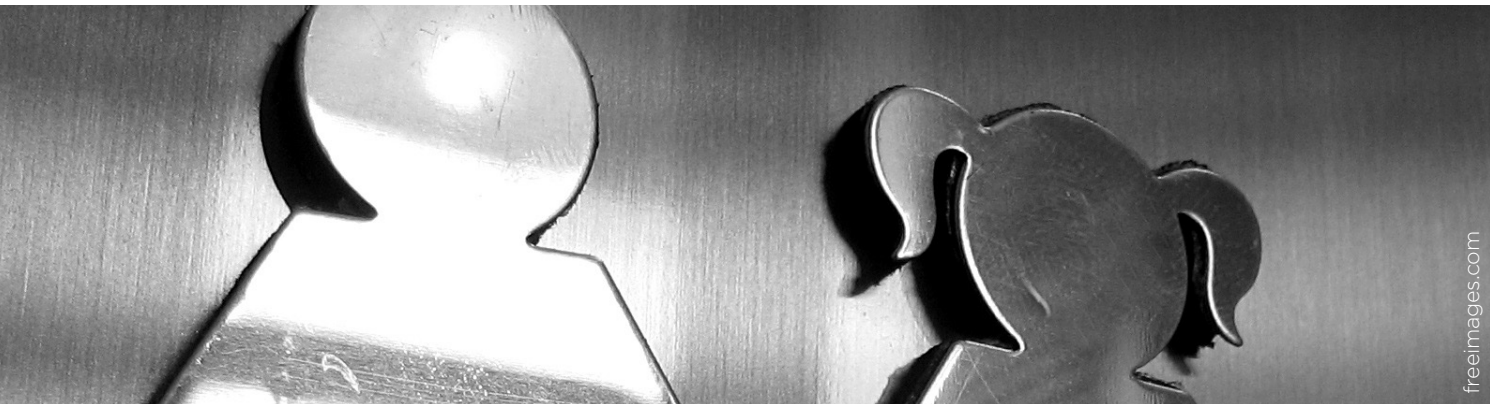
This shows that more complex and severe mutations in the developing brain are required to trigger ASD in females - who show worse symptoms - while only small, subtle mutations are required in males.

"There's no application in terms of treatment," said study author Mr Sébastien Jacquemont, University Hospital of Lausanne, Lausanne, Switzerland, but "it does help understand the inheritance dynamics in families."

However, there is still no answer as to why these disorders come about, and we still do not know if genetic glitches are passed down through generations. Some scientists still contest the role of genetics in neurodevelopmental disorders.

"Boys are swimming in measurably more testosterone than girls are. Some evidence suggests that social behaviours are, in part, determined by such early life exposures to sex steroids," said Dr Irva Hertz-Picciotto, Graduate Group in Epidemiology, Department of Public Health Science, University of California, Davis, California, USA.

> "Some evidence suggests that social behaviours are, in part, determined by such early life exposures to sex steroids."
>
> *Dr Irva Hertz-Picciotto, University of California, Davis, USA*



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Sleepers and dreamers differ in recalling dreams

"This may explain why high dream-recallers are more reactive to environmental stimuli, awaken more during sleep, and thus better encode dreams in memory than low dream-recallers. Indeed the sleeping brain is not capable of memorising new information; it needs to awaken to be able to do that."

Ms Perrine Ruby,
Lyon Neuroscience Research Center,
Lyon, France

DREAMS are more likely to be remembered by those who experience periods of wakefulness during sleep.

Spontaneous activity in the information processing hub of the brain was observed during sleep and wakefulness in those classified as high dream-recallers in a study led by Ms Perrine Ruby, Inserm Research Fellow, Lyon Neuroscience Research Center, Lyon, France.

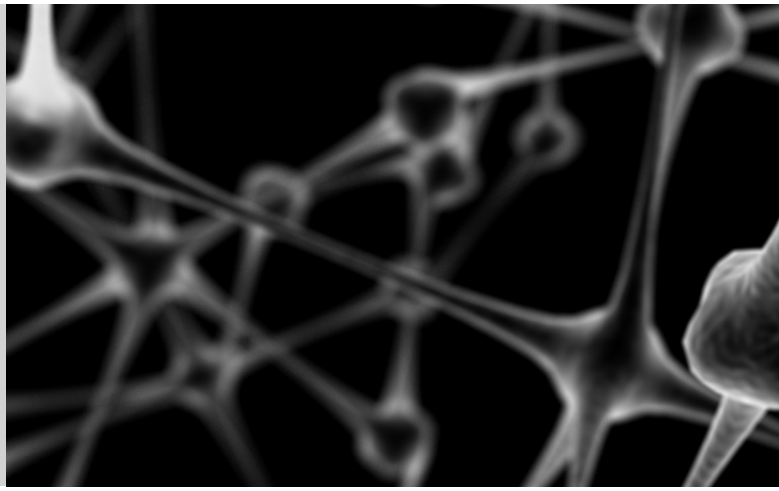
Participants labelled high dream-recallers remembered their dreams more than five mornings per week on average, compared to two per month for their deep-sleeper counterparts. Positron Emission Tomography (PET) scans measured both groups during sleep and during intrasleep wakefulness to reveal strong levels of activity in the medial prefrontal cortex and in the temporoparietal junction (TPJ) of the high recall group.

The TPJ is responsible for guiding attention to the external environment, and thus, increased brain reactivity might promote awakenings during the night, which would allow certain people to memorise their dreams during brief periods of wakefulness.

The study also found that high dream-recallers had twice as many periods of wakefulness during sleep and were more responsive to auditory stimuli.

"This may explain why high dream-recallers are more reactive to environmental stimuli, awaken more during sleep, and thus better encode dreams in memory than low dream-recallers. Indeed the sleeping brain is not capable of memorising new information; it needs to awaken to be able to do that," explains Ms Ruby.

The research exhibits that there are physical differences between those of us who remember our dreams and those who do not. It is supported by previous observations from Dr Mark Solms, Head of Psychology, University of Cape Town, Cape Town, South Africa, that lesions in these brain regions impeded the subject's ability to recall dreams.



Statins: the guardian of nerves

BRAIN shrinkage in sufferers of advanced stage multiple sclerosis (MS) can be slowed by taking statins, which may have anti-inflammatory and neuroprotective properties that guard the nerves from damage.

MS is an extremely debilitating disease that causes breakdown of muscle movement, balance, and vision by adversely affecting nerves in the brain and spinal cord. After about 10 years, half of MS-sufferers will go on to develop secondary progressive MS.

Early trial results observed by Dr Jeremy Chataway, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK, and colleagues, demonstrated that low-cost statins may be a solution to secondary progressive MS, a more advanced form of the disease.

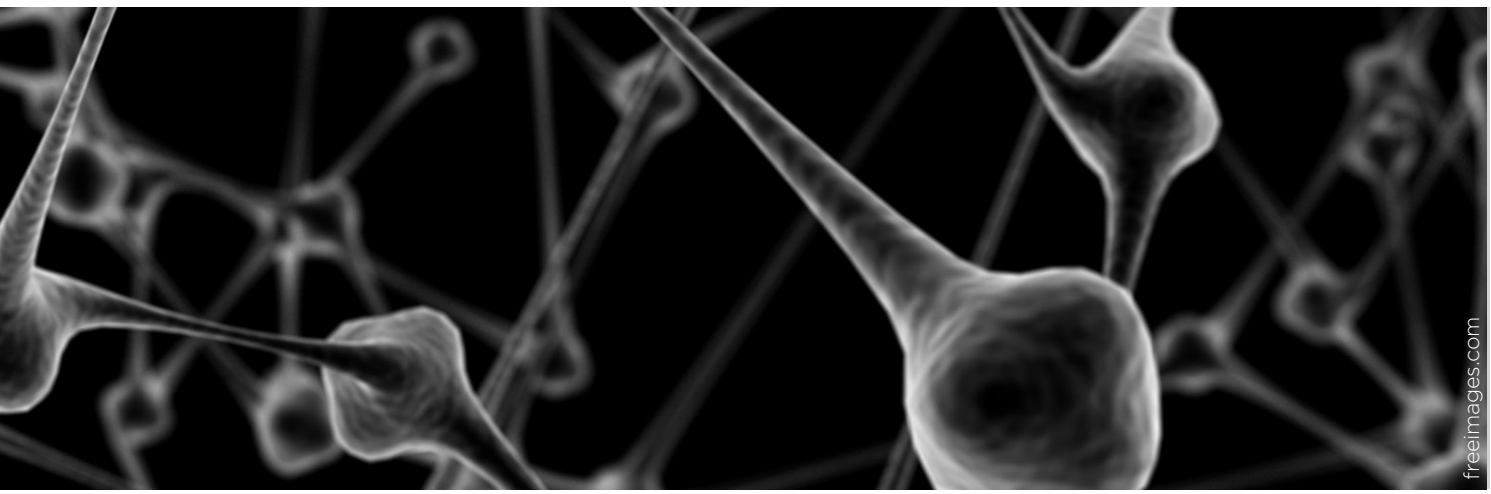
In this trial, 140 people with the later stage of the disease were randomly assigned either 80 mg of a statin called simvastatin or a placebo for 2 years. The group taking a high, daily dose of simvastatin displayed high tolerance to the statin, which caused a brain shrinkage slowdown of 43% compared with the placebo.

"Caution should be taken regarding over-interpretation of our brain imaging findings because these might not necessarily translate into clinical benefit. However, our promising results warrant further investigation in larger Phase III disability-driven trials," explained Dr Chataway.

> "Scientists have worked for years to find a potential treatment that could help people, and now, finally, one has been found that might. This is very exciting news."
>
> *Dr Susan Kohlhaas, Head of Biomedical Research, MS Society, London, UK*

Dr Susan Kohlhaas, Head of Biomedical Research at the MS Society, London, UK, said: "There are no treatments that can stop the condition from worsening in people with progressive MS. Scientists have worked for years to find a potential treatment that could help people, and now, finally, one has been found that might. This is very exciting news."

"Further, larger clinical trials are now absolutely crucial to confirm the safety and effectiveness of this treatment," Dr Kohlhaas added.



REST is all you need to protect from dementia

> "This raises the possibility that the structural pathology may not be sufficient to cause Alzheimer's disease."
>
> *Dr Bruce Yankner, Harvard Medical School, Boston, USA*

TANGLED proteins and plaque build-up do not cause neurodegeneration in older people with high levels of the neuroprotective protein, also known as REST.

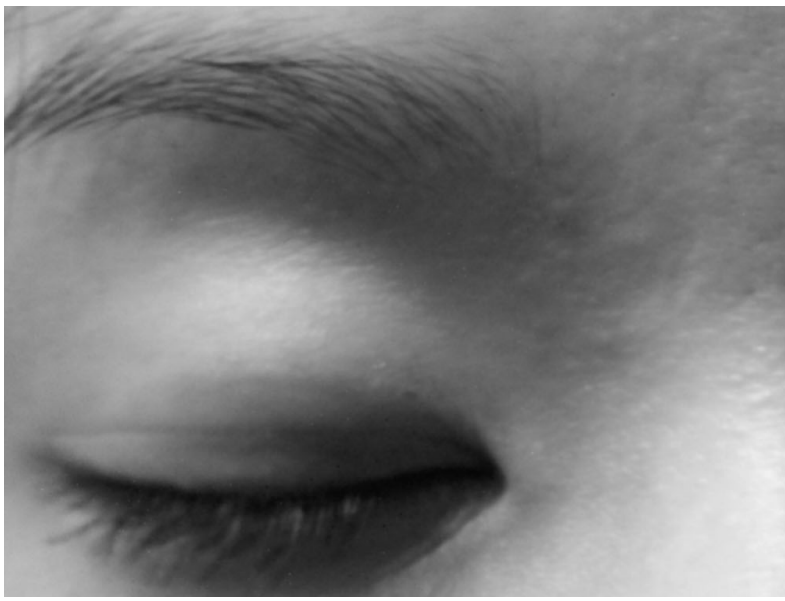
New research suggests that this is due to the transcription factor, REST, which is well characterised for its role in repressing neuron-specific genes during embryogenesis but has lately been identified from neural cell lines as one of the most active genes in the ageing brain.

Researchers have discovered that REST is switched on during middle-to-late adulthood where it protects the brain cortices by up-regulating the longevity transcription factor FOXO1. This blocks cell death related genes, and inhibits genes that contribute to the hyperphosphorylation of tau proteins, which causes amyloid plaques.

Elevated levels of REST were strongly correlated with cognition function in an analysis of 300 brain samples, which included deceased Alzheimer's sufferers who had previously undergone extensive neuropsychiatric assessment. Those with strong measures of cognitive ability at the end of life who also had brain plaques possessed 2-fold higher levels of REST compared to those with similar symptoms but who had dementia.

"This raises the possibility that the structural pathology may not be sufficient to cause Alzheimer's disease," said geneticist Dr Bruce Yankner, lead researcher, Harvard Medical School, Boston, Massachusetts, USA. "A failure of the brain stress response, which REST might mediate, may also be required."

Further research will include: 1) determining whether REST occurs as a general protective factor in cases of stress, such as trauma and stroke, as opposed to being specific to neurodegenerative disease; and 2) examining known signals such as the Wnt pathway, which may be responsible for up-regulating REST during late adulthood. This will be conducive to screening for REST as a target in drug development.



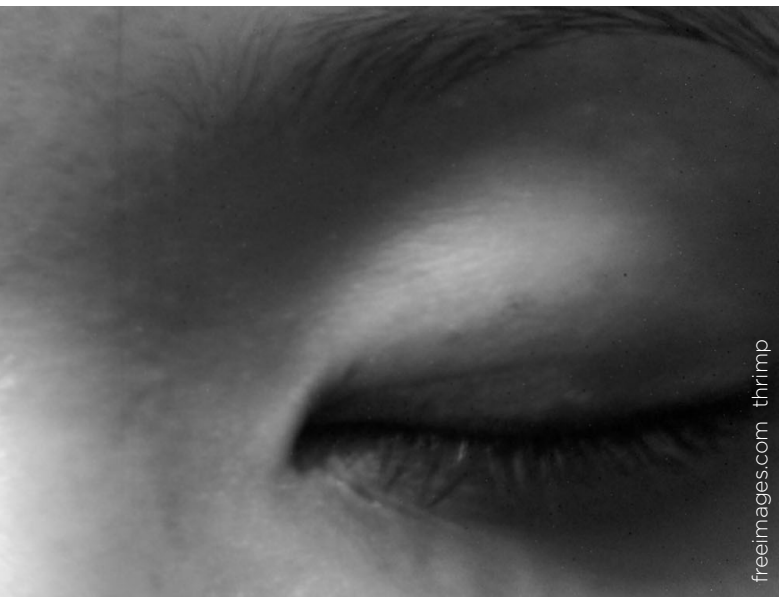
Headgear zapping headaches away

"This may help patients who cannot tolerate current migraine medications for preventing migraines or treating attacks."

Ms. Christy Foreman, FDA Center for Devices & Radiological Health, Silver Spring, USA

MIGRAINES can be averted by a state-of-the-art headband which shoots an electric current through the skin before any headache pain occurs.

The headband, Cefaly, would be available on prescription and operate as a small, self-adhesive, battery-powered device. Cefaly sends an electric current through the patient's skin, stimulating the branches of the trigeminal nerve - the area of the brain associated with migraine headaches.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"Cefaly provides an alternative to medication for migraine prevention," said Ms Christy Foreman, Director, Office of Device Evaluation, FDA's Center for Devices and Radiological Health, Silver Spring, Maryland, USA. "This may help patients who cannot tolerate current migraine medications for preventing migraines or treating attacks."

In a test of the Cefaly headband's effectiveness, 67 patients who suffered more than two migraine headache attacks each month and had not taken medication 3 months prior to the test were given either the headband or a similar placebo device. Those who wore the headband experienced a much-reduced number of migraines per month and needed less migraine-attack medication than those with the placebo.

However, the headaches did not disappear completely in either group, and struck with equal ferocity in both the Cefaly and non-Cefaly groups.

Adding to this was a parallel test examining satisfaction among 2,313 Cefaly users in France and Belgium. 53% of the pool said they would buy the headband, yet notable complaints were reported including a dislike of the sensation, drowsiness, and post-treatment headaches.

Dr Mark W. Green, Director, Center for Headache and Pain Medicine, Icahn School of Medicine at Mount Sinai, New York City, New York, USA, said that Cefaly shows "some promise" in treating migraines.

However, "since the device is not currently available, there is little practical experience, and we anticipate its release," Dr Green added.

Tunnelling for Alzheimer's cure

"We can observe proteins that we also know from human diseases like Alzheimer's to be toxic by measuring effects on neuromuscular function. This gives us insight into how Alzheimer's actually progresses on the molecular level."

Mr Martin Denzel, Max Planck Institute for Biology of Ageing, Cologne, Germany

WORMS may have revealed the answer to defeating Alzheimer's and other neurodegenerative diseases. The small round worm, *Caenorhabditis elegans*, is able to clear its body of toxic protein aggregates upon ingestion of a metabolite.

"It is a broad-spectrum effect that alleviates protein toxicity in Alzheimer's, Parkinson's, and Huntington's disease models in the worm, and it even extends their lifespan," said Mr Martin Denzel, Max Planck Institute for Biology of Ageing, Cologne, Germany.

Protein aggregation occurs in the human body during ageing, causing neuronal damage that can lead to onset of neurodegenerative diseases, a result of the aggregation becoming toxic and overloading the host cells.

Mr Denzel, Ms Nadia Storm, and the Director of the Max Planck Institute, Mr Adam Antebi, discovered that a metabolite called N-acetylglucosamine, which occurs naturally in the organism, stimulates the worm's defence mechanism against neurotoxicity. When the worm was fed an additional portion of the metabolite it was able to clear toxic levels of protein aggregation, including the prevention of toxic protein build-up and clearance of existing toxic aggregates.

"Although we cannot measure dementia in worms," explained Mr Denzel, "we can observe proteins that we also know from human diseases like Alzheimer's to be toxic by measuring effects on neuromuscular function. This gives us insight into how Alzheimer's actually progresses on the molecular level."

The mechanism of action by which N-acetylglucosamine prevents toxic aggregate build-up, thus causing a delay in onset of paralysis in models of neurodegeneration, remains a mystery. "And we still don't know whether it also works in higher animals and humans," said Mr Antebi. "But as we also have these metabolites in our cells, this gives good reason to suspect that similar mechanisms might work in humans."

Larger amygdalae shown to instil greater fear in children

"It is a bit surprising that alterations to the structure and connectivity of the amygdala were so significant in children with higher levels of anxiety, given both the young age of the children and the fact that their anxiety levels were too low to be observed clinically."

Dr Shaozheng Qin,
Stanford School of Medicine,
Stanford University,
Stanford, USA

RESEARCHERS at Stanford University of Medicine have found an interesting, correlative link between the size of a child's amygdala and anxiety.

The investigation involved 76 children aged 7-9-years-old, a period when anxiety-related traits and symptoms can first be reliably identified. To assess the child's level of anxiety, their parents were given assessments that would elucidate their anxiety level. The children then underwent non-invasive magnetic resonance imaging (MRI) scans of brain structure and function.

The study found that children with larger amygdalae (involved with emotions and the development of fear) had high levels of anxiety, and resulted in the formation of an equation that reliably predicted the children's anxiety level from the MRI measurements of amygdala volume and functional connectivity.

"It is a bit surprising that alterations to the structure and connectivity of the amygdala were so significant in children with higher levels of anxiety, given both the young age of the children and the fact that their anxiety levels were too low to be observed clinically," commented Dr Shaozheng Qin, Stanford School of Medicine, Stanford University, Stanford, California, USA.

Interestingly, the most affected region was the basolateral portion of the amygdala, a subregion of the amygdala implicated in fear learning and the process of emotion-related information.

"It is critical that we move from these interesting cross-sectional observations to longitudinal studies, so that we can separate the extent to which larger and better connected amygdalae are risk factors or consequences of increased childhood anxiety," said Dr John Krystal, Editor of *Biological Psychiatry*.

This study demonstrates the extensive nature of the neuroadaptations the brain undergoes after chronic exposure to alcohol.

New treatment for alcohol-obsessed brains

"These data provide important new support for the hypothesis that KOR blockers might play a role in the treatment of alcoholism."

Dr John Krystal, Professor of Psychiatry, Yale University, New Haven, USA

ALCOHOLISM has been extremely difficult to treat, with current methods mainly revolving around lifestyle changes. A study has suggested that kappa opioid receptors (KORs) could potentially be implicated in the mechanisms of alcoholism, and are, therefore, a promising target for developing new treatments.

Research in animals has shown that KORs do indeed play a role in alcoholism as they are stimulated during the intake of alcohol. Importantly, KORs are hypothesised to play a crucial role in alcohol dependence by promoting negative reinforcement processes; this occurs as KORs produce dysphoria and anhedonia, which are known to lead to further alcohol-seeking and escalation of alcohol intake that serves to self-medicate those negative symptoms.

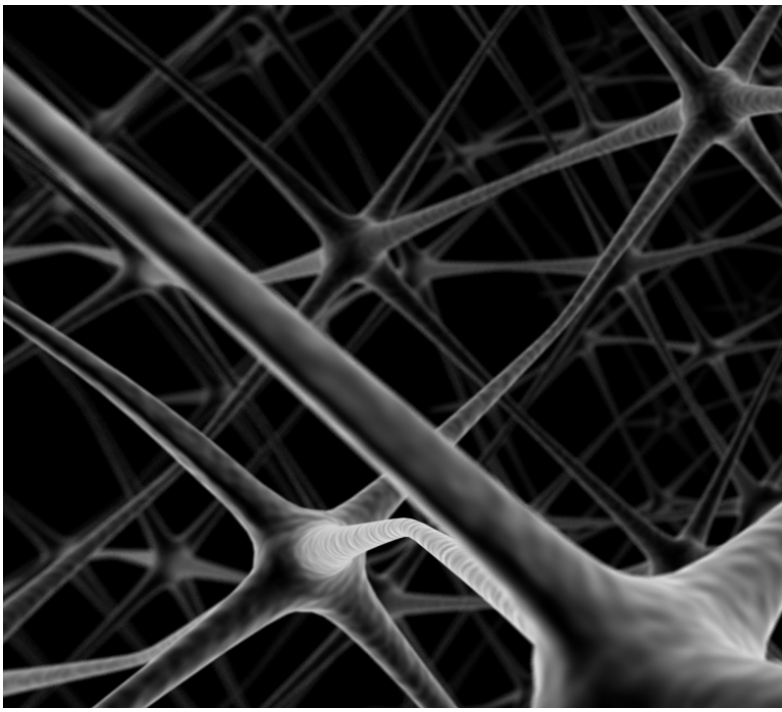
A study led by Dr Brendan Walker, Associate Professor, Washington State University, Pullman, Washington, USA, has used a rat model of alcohol dependence to directly investigate the KOR system following chronic alcohol exposure.

Their interesting results found that the KOR system is dysregulated in the amygdala of alcohol-dependent rats. This area of the brain is responsible for the regulation of emotional behaviour and decision-making.

When the rats were in acute alcohol withdrawal, the researchers administered different drugs directly into the amygdala which targeted the KOR system in precise ways. Using this site-specific antagonism, they observed that alcohol dependence-related KOR dysregulation directly contributes to the excessive alcohol consumption that occurs during withdrawal.

"These data provide important new support for the hypothesis that KOR blockers might play a role in the treatment of alcoholism," said Dr John Krystal, Professor of Psychiatry, Yale University, New Haven, Connecticut, USA.

Additional extensive research will be necessary to identify and test the effectiveness of specific drugs that act on the KOR system before they can be implemented into routine clinical practice.

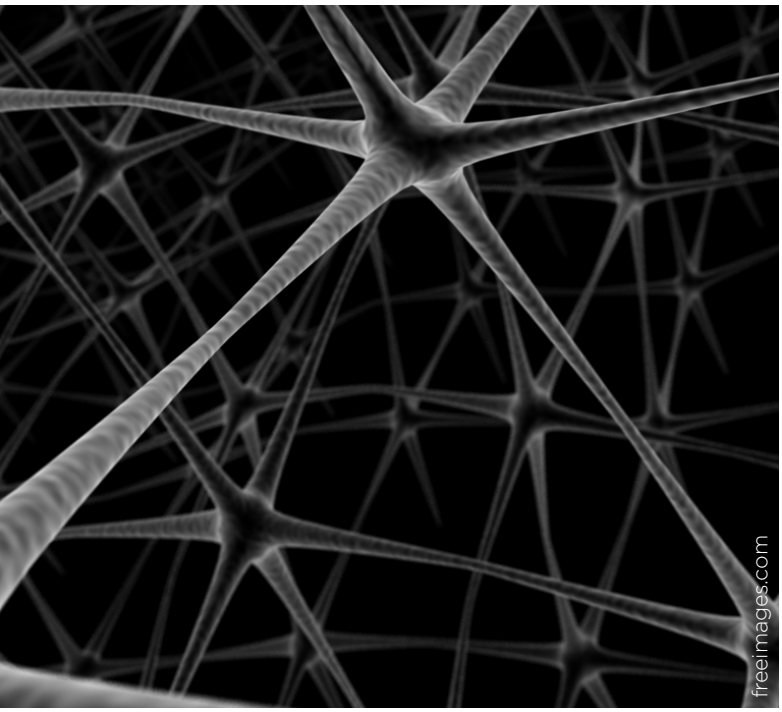


Astrocytes are more than plain old vanilla

STAR-SHAPED cells, also known as astrocytes, originally thought to be monofunctional, are now believed to be responsible for a plethora of roles across the central nervous system (CNS).

The development and maintenance of nerve circuits, as well as the proliferation of disorders including Lou Gehrig's disease (ALS) and possibly even developmental disorders such as autism and schizophrenia, have been linked to astrocytes, which in an abnormal state can be toxic to motor neurons.

"Our study shows roles for specialised astrocytes that function to support particular kinds of neurons in their neighbourhood," said Prof David Rowitch, research leader and Professor of Pediatrics and Neurosurgery, University of California, San Francisco, California, USA.



"To the extent that psychiatric or neurological disease is localised to a specific part of the brain, we should now be considering the potentially specialised type of astrocytes regulating nerve connections in that region and their contributions to disease."

Prof David Rowitch,
Professor of Pediatrics and Neurosurgery,
University of California,
San Francisco, USA

Upon examination of the spinal cord sensory motor circuit - the body's reflex control centre - researchers discovered unusually high levels of Sema3a, a protein secreted by astrocytes. The protein fuels the connection-forming function and survival of motor neurons, half of which die in its absence, and is the first demonstration that astrocytes underpin neurons around the CNS.

Astrocytes – which comprise the majority of the brain – vastly outnumber signal-conducting neurons, which have been the most implicated to date in the onset of brain diseases. Furthermore, there may be hundreds of types of astrocytes performing specific CNS functions.

Sema3a production is slashed in ALS and spinal muscular atrophy, causing the mass death of motor neurons and, in the latter case, the demise of newborn infants.

"To the extent that psychiatric or neurological disease is localised to a specific part of the brain, we should now be considering the potentially specialised type of astrocytes regulating nerve connections in that region and their contributions to disease," Prof Rowitch concluded.

Mind shock treatment zaps mentally ill

"This project offers hope because it is a totally new way of seeing how the parts of the brain interact in mental illness. It is as if we have been looking at still images of actors but will now be able to see the performance of a play."

Dr Vikaas Sohal,
Assistant Professor, UCSF,
San Fransisco, USA

MIND control could be the key to fixing abnormal brain activity during mental illness, with hopes high for a tiny implanted device that teaches the brain to alleviate disease symptoms.

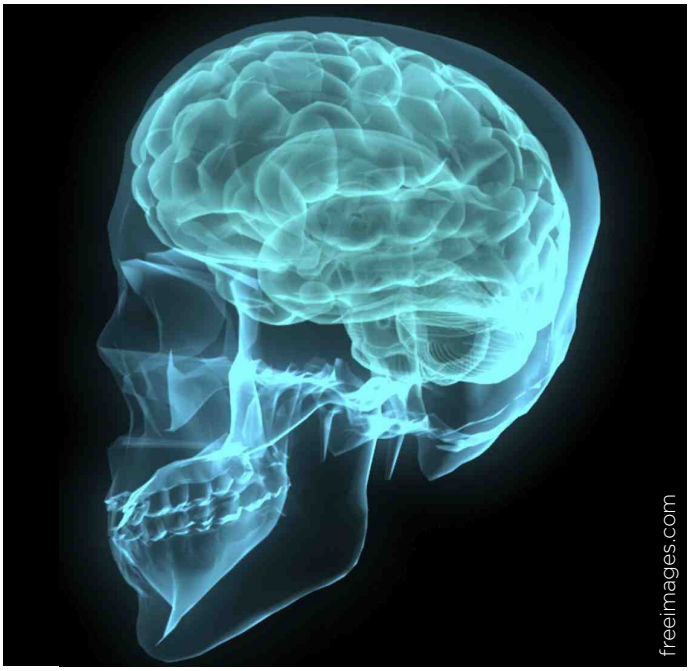
Scientists at the University of California, San Francisco (UCSF), USA, have embarked on a $12 million project as part of President Barack Obama's $100 million Brain Initiative. This will involve identifying brain signalling pathways linked to anxiety and depression, followed by device-initiated induction of a precise electric discharge to strengthen alternative circuits.

The device exploits the brain's capacity for neural remodelling and learning, and will potentially allow the reinforced circuits to bypass disease-associated impulses, thus eliminating symptoms and paving the way for treatment of anxiety disorders, depression, and addiction.

"There are millions of people for whom these disorders are not well treated. These patients are often not able to keep their jobs or to work at all, because they are constantly struggling with symptoms of their illnesses and the pain and suffering they cause," said team member Dr Vikaas Sohal, Assistant Professor, Psychiatry, UCSF. "This project offers hope because it is a totally new way of seeing how the parts of the brain interact in mental illness. It is as if we have been looking at still images of actors but will now be able to see the performance of a play."

For years the implanted device has been developed for patients with movement disorders such as Parkinson's disease, translating thoughts into control commands for a robotic arm or exoskeleton. However, the technology has been earmarked for use in psychiatric patients.

Adding the final touches to a grand theory, the brain could even 'unlearn' these abnormal signalling patterns due to its neural plasticity, thus, curing the patient.



Featured Suppliers

Neurology

Responsible for the development of some of the world's most important drug products in fields ranging from diabetes care to veterinary medicines, Bayer HealthCare is a key innovator in the manufacturing of pharmaceutical and medical products. The Bayer subdivision's aim is to create state-of-the-art, groundbreaking products to improve the lives of patients worldwide. It aims to accomplish this through its consumer care, medical care, and pharmaceutical divisions, addressing some of the great challenges in the modern era. The company has bases in 5 continents, with approximately 55,300 people working in over 100 countries.

Established in 1982, Britannia Pharmaceuticals Ltd. is a UK-based pharmaceutical company that specialises in neurology, particularly developing and marketing products for the treatment of Parkinson's disease. Active for over 30 years, the company recognised that apomorphine was essential in the treatment of Parkinson's sufferers, a revelation that has resulted in the drive in APO-go product development. In addition, Britannia has developed non-opiate-based therapeutics in order to assist in opiate detoxification and withdrawal. Further still, the company has made important advances in the areas of wound healing and respiratory disorders.

An established global player, GE Healthcare develops life-changing medical technologies and services designed to bring about a revolution in patient care. Based in the United Kingdom, GE Healthcare - a subdivision of the US-based General Electric Company - has operations extending to healthcare professionals and their patients in over 100 countries. It displays mastery of a plethora of therapeutic areas - including medical imaging and information technology, medical diagnostics, and patient monitoring systems - and enables state-of-the-art, affordable care. Key partnerships with healthcare leaders enable the company to pursue its goal of influencing drastic change in global policy with the aim of establishing sustainable healthcare systems.

Dedicated to unearthing and distributing game-changing therapies to patients with exceptional medical requirements, Genzyme has been fulfilling these targets for over 30 years to become one of the world's leading biotech companies, with more than 40 global locations serving patients in over 100 countries. The Boston-based firm was further boosted by the 2011 acquisition by global pharmaceutical giant Sanofi, adding clout to its reach and resources. Genzyme's main clinical investigative focus is rare genetic diseases, including lysosomal storage disorders, and has pushed the boundaries into other disease areas such as thyroid cancer and multiple sclerosis.

Novartis has one outstanding mission: to discover, design, and deliver state-of-the-art healthcare to patients worldwide. Founded in 1996 and based in Basel, Switzerland, this world-leading pharmaceutical company has consistently produced medical breakthroughs, developing innovative products for patients and consumers. A host of revolutionary pharmaceuticals, generics, vaccines, and consumer health products have provided pain relief and boosted patient quality of life since the company's inception. Operating in 140 countries, the seismic ambitions of Novartis have attracted a total of 135,000 associates, including top experts in research and development.

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- AMERICAN ACADEMY OF NEUROLOGY
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- EFNA - EUROPEAN FEDERATION OF NEUROLOGICAL ASSOCIATIONS
- EFNS - EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES
- ENS - EUROPEAN NEUROLOGICAL SOCIETY
- IBE - INTERNATIONAL BUREAU FOR EPILEPSY
- ILAE - INTERNATIONAL LEAGUE AGAINST EPILEPSY
- MDS - INTERNATIONAL PARKINSON AND MOVEMENT DISORDER SOCIETY
- SERONO SYMPOSIA INTERNATIONAL FOUNDATION
- UEMS - UNION OF EUROPÉENNE DES MÉDECINS SPÉCIALISTS
- YNT - EUROPEAN ASSOCIATION OF YOUNG NEUROLOGISTS AND TRAINEES

Mechanisms of Epilepsy and Neuronal Synchronization – Dissecting Epilepsy from Genes to Circuits

17th-22nd August 2014

West Dover, USA

This truly multidisciplinary conference will present state-of-the-art unpublished findings which are all related to basic mechanisms of epilepsy, current translational studies, and synchronisation of neuronal activity in cerebral networks. An important goal is addressing how basic scientific findings can one day be translated into therapies to treat those suffering with epilepsy.

Congress of the European Committee for Treatment and Research in Multiple Sclerosis 2014

10th-13th September 2014

Boston, USA

Partnered with the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), and Americas Committee for Treatment and Research in MS (ACTRIMS), this event will promote both basic and clinical research within the field. It will also aim to identify factors which determine MS susceptibility, disease course, and prognosis.

4th European Headache and Migraine Trust International Congress 2014

18th-21st September 2014

Copenhagen, Denmark

By covering the latest available research, therapies, and developments from internationally-recognised leaders in the field, this 4-day event aims to provide a better understanding of migraines, tension-type headaches and other headache disorders. Participants will gather new scientific evidence, and learn about improved diagnosis and treatments for patients.

World Stroke Congress 2014

22nd-25th October 2014

Istanbul, Turkey

This Congress provides cutting-edge educational and scientific experience, all of which will focus on the latest developments in stroke prevention, acute management, and restorative care after stroke. Throughout the Congress there will be a particular focus on challenges and strategies relevant to rapidly developing regions.

44th Annual Meeting of the Society for Neuroscience

15th-19th November 2014

Washington DC, USA

Acting as the premier venue for neuroscientists, attendees are able to learn from experts, present emerging science, forge collaborations with peers, advance careers, and explore new tools and technologies. This is one of the largest events where ideas and tools for global neuroscience can develop and prosper, with over 30,000 colleagues from more than 80 different countries attending this event.

10th International Congress on Non-Motor Dysfunctions in Parkinson's Disease and Related Disorders

4th-7th December 2014

Nice, France

This annual educational forum offers a unique opportunity to deliberate on brain diseases and how they contribute to cognitive decline. It also provides the chance to learn how to identify the specific psychological markers, biochemical and genetic factors of Parkinson's dementia. This event attracts leading neurologists and psychiatrists, as well as psychologists.

12th International Conference on Alzheimer's and Parkinson's Disease

18th-22nd March 2015

Nice, France

Attracting international medical and scientific professionals worldwide, this conference is at the forefront of unravelling the mechanisms and improving the treatment of Alzheimer's, Parkinson's, and other related neurodegenerative diseases. There will also be a strong focus on mechanisms of disease, prevention, and therapy.

5th International Congress on Neuropathic Pain

14th-17th May 2015

Nice, France

Recent advances in pathophysiology, epidemiology, diagnosis, assessment, prevention, and management of neuropathic pain will be addressed. There will also be a combination of plenary sessions, topical workshops, debates, and poster presentations. In addition, there will be training sessions for medical doctors, students, nurses, and physiotherapists.