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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

Royal Hospital for Neuro-disability

A national medical charity

Forthcoming events:

3 March 2016

An Interdisciplinary Team Approach to the Management of Patients in Prolonged Disorders of Consciousness

16 March 2016

A Multi-Disciplinary Approach to the Assessment and Management of Huntington's Disease

25-29 April 2016

SMART Course Five Day Assessor Training

5 May 2016

Managing Behaviours that Challenge in Brain Injured Individuals: The positive behaviour support approach

16-18 May 2016

An Introduction to Thermoplastic Splinting of the Upper Limb in Neurological Conditions

6-7 June 2016

An Introduction to Casting in Neurology

1 July 2016

National Brain Injury Symposium: Challenges for Nursing in the UK

19-20 September 2016

Introduction to Casting in Neurology

7 September 2016

Managing Behaviours That Challenge in Brain Injured Individuals

6 October 2016

An Introduction to Music Therapy Techniques in Neuro-disability

10 November 2016

An Introduction to the Assessment and Management of Communication in Complex Brain Injury

6 December 2016

Managing Behaviours that Challenge in Brain Injured Individuals: the Positive Behaviour Support Approach

All events will take place at the Royal Hospital for Neuro-disability, London

For more information on any event
contact: institute@rhn.org.uk
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ONLINE FIRST

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UKABIF Annual Conference;
MS Trust Annual Meeting

Front cover picture: painted by Nataly Martynyuk for the Brain Repair Spring School, Cambridge. Nataly is a 2nd year PhD student and is with Selwyn College. Nataly accepts orders for medical and scientific illustrations.

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Martin Turner receives Graham Bull Prize

Professor Jane Dacre and Professor Martin Turner

Professor Martin Turner has received the prestigious Graham Bull Prize for Clinical Science from the Royal College of Physicians. Professor Turner will deliver the prize's associated Goulstonian Lecture to the Royal College on 9 February 2016. His work focuses on identifying markers of disease activity across the different types of motor neuron disease. In particular, he heads up the Oxford Study for Biomarkers in MND (BioMOx). He is also a Consultant Neurologist.

Angela Vincent receives British Neuroscience Association Award

The British Neuroscience Association (BNA) has awarded Angela Vincent, FRS the 2016 Outstanding Contribution to British Neuroscience Award. The award recognises one individual each year who has made a significant impact in their field of work in neuroscience, neurology or mental health research; and who, in addition to international calibre research, has also influenced the advancement of neuroscience by participation on high-level committees and work groups in the UK and beyond.

Angela Vincent has created a step change in the diagnosis and treatment of autoimmune disorders, including myasthenia gravis and encephalitis. She is recognised as one of the pioneers in this area of neuroscience and her active translational research has led to the discovery of new brain and neuromuscular diseases. Her work has paved the way for new and improved therapy in some cases, where none was previously available.

Fondazione Gino Galletti Neuroscience Prize 2015

Dr Rita Guerreiro, an Alzheimer's Society Senior Research Fellow who works at the Department of Molecular Neuroscience at the UCL Institute of Neurology, London, has been awarded the prestigious Fondazione Gino Galletti Neuroscience Prize 2015. Her innovative work has led to the identification of a new genetic risk factor for Alzheimer's disease, the first discovery of such a gene for the condition in 15 years. Dr Guerreiro won the prize, which is given to an early-career researcher working in Europe in the field of 'Neurodegenerative pathologies' in recognition of her discovery of the association of the gene TREM2 with the development of Alzheimer's disease.

UCL launches free online dementia course

UCL Institute of Neurology has announced a free four-week online course "The Many Faces of Dementia" aiming to provide valuable insights into dementia through the stories, symptoms and science behind four less common diagnoses. The interactive MOOC (massive open online course) features interviews with world-leading experts, people with dementia and their families as well as articles and discussion. It is aimed at anyone who wants to learn more about dementia and may be of particular interest to those who interact with people living with dementia regularly such as family members, carers and health professionals. It will begin on 14 March 2016 and run for four weeks, with two to three hours of online learning each week.

Todd Hardy, Co-Editor.

Welcome to 2016 and the latest issue of ACNR. In this issue Emma Devenney and John Hodges from Sydney write an update on frontotemporal dementia (FTD), highlighting the major advances in the field which, over the last decade or so, have seen a greater understanding of how the different clinical FTD subtypes relate to their underlying pathology and genetics, and how the groundbreaking identification of the C9orf72 gene expansion has contributed to understanding the connection between FTD and motor neurone disease.

Viorica Chelban, Conceição Bettencourt, and Henry Houlden from London write a cogent update on multiple system atrophy including a neat summary of the underlying genetics and pathology, with a focus on treatment options and promising future therapeutic strategies and targets. The article is paired with a note from MSA Nurse Specialist, Samantha Pavey from the UK MSA trust raising awareness of the role of this organisation in delivering care to MSA patients throughout the UK and Ireland.

Craig Pearson and Keith Martin from Cambridge write a fascinating article about the current state of play with regard to cell-based therapies for glaucoma. Areas of active research include inducing endogenous pluripotent stem cells to repair trabecular meshwork function in the eye damaged by glaucoma, transplantation of mesenchymal stem cells which can release neurotrophic factors into the retina, and transplantation and graft integration of differentiated cells into damaged retina.

Killian Welch from Edinburgh has written an invaluable approach to the commonly encountered, but often dreaded, scenario of assessing and managing the agitated ward patient.

Claire McCarthy from Cambridge provides a summary of the recent report on the burden of hospitalisation of MS patients in England; part of a collaboration between the MS trust and the NHiS Commissioning Excellence group. The document is an important one for highlighting areas where anticipatory care might prevent admissions in MS patients.

The issue also contains the latest conference reports on the AAIC conference in Washington, the Wessex Dementia Collaboration Conference in Southampton and a report on Meningitis and Septicaemia in Children and Adults. On the website we have a report on the UKABIF conference in London and the MS Trust Annual Meeting in Windsor. There is also a book review from Ronan O'Malley and a journal review from Luca Nart.

Todd Hardy, Co-Editor.
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Editorial board and contributors

Mike Zandi is Co-Editor of ACNR, Senior Clinical Research Associate in the Department of Clinical Neurosciences, University of Cambridge, and Honorary Consultant Neurologist at Addenbrooke's Hospital and Cambridgeshire and Peterborough NHS Foundation Trust. He is working on psychiatric presentations of autoimmune encephalitis, and the development of clinical trials and biomarkers for NMDAR and other antibody-associated neuropsychiatric disorders.

Todd Hardy is Co-Editor of ACNR. He is a Neurologist at Concord Hospital and Clinical Senior Lecturer in Neurology at the University of Sydney, Australia. He is interested in multiple sclerosis and other neuroinflammatory disorders.

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Gemma Cummins is ACNR's Journal Reviews editor. Gemma is a Specialist registrar in Neurology at Addenbrooke's Hospital, Cambridge and is currently completing a PhD on movement disorders and cognition at the Van Geest Centre for Brain Repair, Cambridge.

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Boyd Ghosh is the Editor of our Conference News section. He is currently a Consultant Neurologist in Southampton having completed a PhD in Cambridge in cognitive neuroscience. His special interests are cognition and movement disorders, with a particular interest in progressive supranuclear palsy.

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Valerie Voon, MD PhD is a Wellcome Trust Intermediate Fellow in Clinical Neurosciences and an Honorary Consultant Neuropsychiatrist at the University of Cambridge. She subspecialises in neuropsychiatric aspects of movement disorders. She is on the Board of Directors of the British Neuropsychiatric Association and the Chair of the Research Committee for the American Neuropsychiatric Association.

Roger Barker is Consulting Editor of ACNR, Professor of Clinical Neuroscience at the University of Cambridge and an Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. His main area of research is into neurodegenerative and movement disorders, in particular Parkinson's and Huntington's disease.

Alasdair Coles is Consulting Editor of ACNR. He is a Professor in Neuroimmunology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.

Recent Advances in Frontotemporal Dementia

Dr Emma Devenney
MB BCh BAO, MRCP, is a medical graduate from Queen's University, Belfast. She completed three years of her neurology training at the Royal Victoria Hospital in Belfast before coming to NeuRA as a visiting fellow in November 2012. She has since been awarded a PhD scholarship from UNSW to investigate the genetic link between FTD and MND. She has published 13 papers.

Professor John R Hodges
MD FRCP, trained in medicine and psychiatry in London, Southampton and Oxford before gravitating to neurology and becoming enamoured by neuropsychology. In 1990, he was appointed a University Lecturer in Cambridge and in 1997 became MRC Professor of Behaviour Neurology. A sabbatical in Sydney in 2002 culminated in a move in 2007 where he built a multidisciplinary research group focusing on FTD. He has written over 400 papers on aspects of neuropsychology (especially memory and languages) and dementia, plus six books.

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There have been major advances in the characterisation of frontotemporal dementia (FTD) over the past two decades culminating in the development of internationally accepted diagnostic criteria for each of the clinical subtypes. The behavioural variant of FTD (bvFTD) is characterised by changes in personality and behaviour which have now been clearly defined with levels of diagnostic certainty: possible, probable and definite (Table 1). For cases presenting with progressive aphasia, three variants are now recognised: the semantic variant (semantic dementia) characterised by fluent speech with anomia and impaired single word knowledge in association with anterior temporal lobe atrophy; the non-fluent variant with apraxia of speech and/or agrammatism associated with inferior frontal atrophy; and the logopenic variant in which word finding difficulties and impaired verbal span predominate, and atrophy is centred around the angular gyrus (Table 2). The distinction is not purely academic since underlying neuropathology is highly predictable. Those with semantic variant have TDP-43 type C and are rarely genetic. Those with the nonfluent form mostly have tau based FTD pathology, which may be genetic, and the logopenic form is associated predominantly with Alzheimer's pathology,[1,2] the pathology remains heterogeneous with an approximate 50-50 split between FTD-tau and FTD-TDP43 (Figure 1).

Table 1: Diagnostic criteria for bvFTD

1. Possible bvFTD – at least three of the following features must be present
a. Disinhibition
b. Apathy
c. Lack of sympathy/empathy
d. Stereotypic/ritualistic behaviours
e. Change in dietary preferences
f. Frontal dysexecutive cognitive profile
2. Probable bvFTD – all of the following features must be present
a. Meet criteria for possible (as above)
b. Show functional disability/decline
c. Frontal and or temporal abnormalities on neuroimaging (MRI or PET)
3. Definite bvFTD - either a or b must be present
a. FTLD pathology at autopsy
b. Known pathogenic genetic mutation

Developments in neuroimaging, notably functional MRI (fMRI), have heralded the concept of dysfunction within neural networks as the anatomical basis for abnormal behaviours and cognitive dysfunction in FTD. The salience network,

Figure 1 below represents the clinical and pathological subtypes of Frontotemporal Dementia. Weighted lines represent the approximate frequency of pathology for each variant.

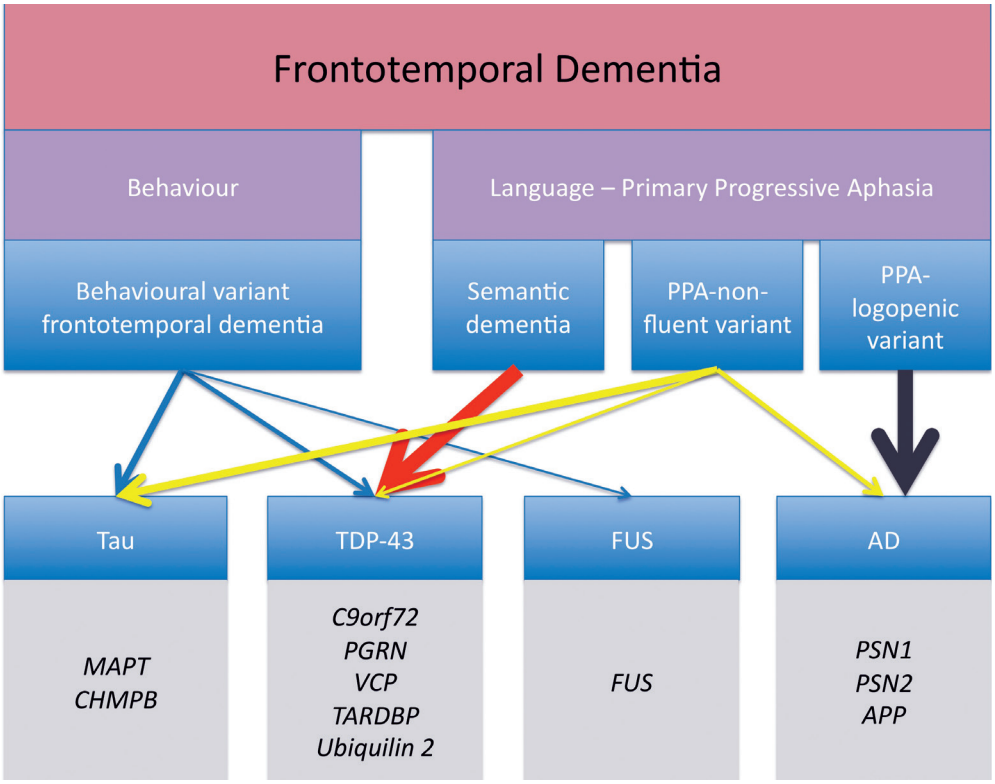

Table 2: Diagnostic criteria for PPA
1. PPA – all of the following must be met (a-d)
a. Language disturbance is the most prominent clinical feature
b. Language impairment is the cause of impairment in activities of daily living
c. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease
d. No other condition should better account for the presentation
2. PPA–sv (semantic variant) – Both of the following must be met
a. Poor confrontation naming (pictures/objects) particularly for low familiarity items
b. Impaired single word comprehension
Plus at least three of the following must be met
a. Poor object and/or person knowledge, particularly for low frequency or low familiarity objects
b. Surface dyslexia
c. Spared single word repetition
d. Spared motor speech, melody and phrase length
Plus neuroimaging abnormality – Predominant anterior temporal lobe
3. PPA-nfv (agrammatic/non-fluent variant) – At least one of the following must be met
a. Grammatical errors and simplification in language production
b. Effortful, halting speech with speech sound errors consistent with apraxia of speech
Plus at least three of the following must be met
a. Impaired naming, particularly of action verbs
b. Impaired comprehension of syntactically complex sentences
c. Spared content word comprehension
d. Spared object knowledge
Plus neuroimaging abnormality – Predominant left posterior fronto-insular
4. PPA-lv (logopenic variant) – Both of the following must be met
a. Impaired single word retrieval in spontaneous speech & confrontational naming
b. Impaired repetition of sentences and phrases
At least three of the following must be met
a. Phonological errors in spontaneous speech and naming
b. Spared motor speech
c. Spared single word comprehension
d. Spared object knowledge
Plus neuroimaging abnormality – Predominant left posterior perisylvian or parietal

comprising the insula, anterior cingulate cortex, amygdala, and a network of thalamic and subcortical structures, is involved early in the course of bvFTD and is implicated in the generation of social and emotional dysfunction.[3] The link between FTD, deranged metabolism and abnormal eating behaviour is becoming clearer and seems likely to be linked to a complex neural network centred on the hypothalamus.[4] Together these findings have encouraged FTD researchers to consider the contribution made by brain regions outside of the frontal and temporal cortices. The cerebellum, previously considered to be concerned primarily with motor function, has been implicated in a range of cognitive dysfunctions, and the thalamus, a key relay station for the signaling of sensory information and integration throughout the cortex, may also be involved.

Until recently MRI and Fluorine-18-Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) have been the imaging modalities of choice for the diagnostic work-up of patients with FTD. In more recent years, amyloid Pittsburgh compound B (PIB)-PET imaging has been useful to tease apart atypical cases when distinction from AD is clinically difficult. Following the success of amyloid PET imaging, researchers turned towards finding suitable tracers for tau protein and a number have been developed.[5] Tau imaging has the potential to improve diagnostic accuracy in FTD through the identification of tauopathies during life, whereas currently the underlying pathology can be identified post-mortem only. This may allow more accurate case selection for clinical trials and subsequent pharmacological therapies. Tau PET imaging could also improve disease staging, as tau burden is closely linked with cognitive impairment, and determine the role of tau deposition in the preclinical stages of neurodegeneration. Although the potential benefits of tau imaging for clinicians, researchers and patients are clear there are issues to be resolved before the ideal ligand is identified and introduced to clinical practice.

It seems likely that future research will focus on *in-vivo* identification of other pathological proteins notably trans-activating responsive (Tar) sequence DNA binding protein (TDP-43). The discovery of TDP-43 consolidated the overlap between FTD and MND given that this protein is found in a proportion of those with FTD and the vast majority of familial and sporadic MND cases.[6] Clinical overlap between these conditions has long been recognised but only fairly recently has the concept of an FTD-MND disease continuum become widely accepted.[7] Cognitive/behavioural deficits may develop in parallel with motor deficits although either can occur initially. Cognitive and behavioural abnormalities are reported to occur in 50-75% of MND cases while approximately 15-25% of patients meet criteria for FTD.[7] Of all the cognitive functions, executive function has received the most attention in MND that may have consequences for financial, medical and end of life decisions. Language deficits may be as common as executive dysfunction and adds another level of complexity to communication issues for MND patients. Similarly, social and emotional cognition domains are affected and behaviour is impaired, specifically a degree of apathy is found in up to 80% of patients, and disinhibition, lack of empathy and rigidity are also present.[8] Conversely around 10% of FTD cases develop frank MND but subclinical motor features can be found in a much higher proportion of cases. Patients with the FTD-MND overlap syndrome tend to have the shortest survival of all FTD syndromes with death occurring within two to three years.

In 2011 the concept of the FTD-MND continuum was cemented, with identification of the *C9orf72* genetic expansion on chromosome 9p21.1.[9] This genetic expansion, a hexanucleotide GGGGCC repeat found on the non-coding region of chromosome 9, is pathogenic at greater than 30 repeats with most patients having repeat lengths in the thousands. Studies of affected carriers, asymptomatic carriers and their family members will provide further insight into this gene defect which, may have features in common with other repeat disorders. The exact penetrance is still unknown but it is believed that it is not fully penetrant, as unaffected elderly carriers have been identified. Three pathological mechanisms have been proposed to cause disease in *C9orf72* carriers: loss of function of the protein encoded by the gene, toxic effects of RNA products which aggregate in the cell and toxicity caused by dipeptide repeat proteins. The *C9orf72* expansion has been identified with mutations in other well-known causative genes in FTD including *GRN* and *MAPT*,[10,11] which has led researchers to hypothesise that these genes and others may play a modifying role in *C9orf72* expression. This expansion accounts for approximately one-third of familial FTD and up to 75% of familial FTD-MND cases. Notably, a significant minority (5-20%) of patients with apparently sporadic bvFTD also have the expansion.[12] Collectively the three major genes, *C9orf72*, *GRN* and *MAPT* account for over 50% of familial FTD cases indicating there are clearly gene mutations yet to be discovered.

There is marked geographical variation in prevalence of the *C9orf72* expansion with high rates of the expansion found in northern European countries, while remaining rare in Asian populations. Across the clinical spectrum of FTD, the predominant phenotype associated with the *C9orf72* expansion is bvFTD, often occurring with features of MND, although non-fluent variant PPA cases have been reported. *C9orf72* positive patients can be distinguished from negative cases based on a family history of MND, Parkinsonism and prominent psychosis at presentation.[12] Delusions and hallucinations are generally rare in FTD but are a frequent presenting feature of the *C9orf72* expansion some of

who have a long history of psychiatric illness. A distinctive neuroanatomical signature has also emerged, with generally mild atrophy involving the thalamus and cerebellum in addition to the typical orbitomedial frontal and anterior temporal atrophy seen in bvFTD.[13] A proportion of patients labelled as 'slow-progressors' or 'phenocopy' cases habour the *C9orf72* expansion and in a study from our centre the proportion of possible bvFTD cases with the mutation was higher than found in cases with probable bvFTD.[14]

With regard to therapies for FTD, disease-modifying treatments have so far focused on tau pathology. Recent attempts to inhibit tau phosphorylation using lithium and tideglusib have failed, however a methylene blue derivative, leucomethylthioninium, shows promise as an inhibitor of tau aggregation and phase III clinical trials are currently underway. The discovery of the *C9orf72* expansion has led to the theory that antisense oligonucleotide therapy, which show activity against toxic RNA effects as seen in the *C9orf72* expansion, may be effective in the treatment of MND-FTD.[15]

In summary, the last few decades have seen rapid advances in our understanding of FTD encompassing clinical, neuroimaging, genetic and pathological fields with hopefully even more exciting discoveries on the horizon. Better awareness of FTD, together with the development of diagnostic criteria, has facilitated earlier diagnosis to ensure that these patients have timely access to necessary care and support although FTD is still poorly recognised in non-specialist settings. The identification of the *C9orf72* expansion has challenged the concept of MND and FTD as single disease entities by explaining the genetic link between the conditions, and provides a platform to study the complex underlying molecular pathogenesis of these diseases.

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Pooled Phase III data presented at the American Epilepsy Society Annual Meeting on the use of Fycompa® (Perampanel) in the treatment of primary and secondary generalised tonic clonic seizures

Abstracts provide a wealth of data to support the use of perampanel in patients with primary and secondary generalised tonic clonic seizures

Data presented at the American Epilepsy Society (AES) 69th Annual Meeting Philadelphia, show that Fycompa® (perampanel) treatment reduces primary and secondary generalised tonic clonic seizures and is well tolerated versus placebo. Results from a post-hoc analysis demonstrate treatment with perampanel was associated with a greater 50% responder rate versus placebo (61.8% vs 37.8%; p<0.0001) and conferred a median 65.5% reduction in primary and secondary generalised seizure frequency over 28 days versus placebo (-24.6; p<0.0001).

The analysis evaluated the efficacy and tolerability of 8mg/day perampanel on 492 people with primary or secondary generalised tonic clonic seizures, across four phase III studies. 26.9% of participants achieved seizure-free status with perampanel compared to 12.6% of people with placebo. Treatment with perampanel was well tolerated.

"Findings from this pooled analysis of Phase III data provide an important look into the efficacy and tolerability of perampanel in people with primary and secondary generalised tonic clonic seizures. It is encouraging that this examination of perampanel has shown it to offer a median 65.5% reduction in primary and secondary generalised seizures against placebo," comments Professor Eugen Trinka, Professor and Chair of the Department of Neurology, Paracelsus Medical University, Salzburg, Austria.

Perampanel is indicated for the adjunctive treatment for partial onset seizures, with or without secondarily generalised seizures, in patients with epilepsy aged 12 years and older and for adjunctive treatment of primary generalised tonic-clonic seizures, in patients with idiopathic generalised epilepsy.

Analysis of real world data on use of Zebinix to manage partial onset seizures

Real-world data at The American Epilepsy Society report that when Zebinix® (eslicarbazepine acetate) was used as add-on to antiepileptic monotherapy in 45 people with partial-onset seizures, who had a documented non-response to carbamazepine, after 6 months, the retention rate was 88.9% (95%CI 75.9 – 96.3%, n=45).

The AES represented a significant milestone for eslicarbazepine acetate, with 19 abstracts presented over four days with two important sub analyses from a European real-world study. This was the largest number of abstracts for eslicarbazepine acetate at a single congress which demonstrates its strong scientific presence in epilepsy.

The post hoc subgroup analysis examined data from the EPOS (Eslicarbazepine acetate in Partial-Onset Seizure) study programme, a multicentre evaluation of 247 people with partial-onset seizures across eight European countries over six months. Responder rates and seizure freedom rates in the eslicarbazepine acetate arm were 95.1% (95% CI 83.5–99.4%; n=41) and 33.3% (95% CI 19.6-49.5%, n=42) respectively. Mean QOLIE-10 score decreased from 2.8 (n=21) at baseline to 2.2 (-13.0%; n=18) after 6 months.1 A decreasing QOLIE-10 score is a measure of improvement in quality of life.

"People with partial-onset seizures may try several therapies before they find one they respond to. This data shows that a good proportion of people with partial-onset seizures, who have not responded when treated with carbamazepine, may respond to eslicarbazepine acetate. The results of the study further highlight the importance of trying different treatment options, "commented Professor Martin Holtkamp from the University Hospital Charité, Germany.

Updates on potential therapeutic targets in MSA

Dr Viorica Chelban, MD MSc MRCP
is a Research Fellow doing her PhD at the UCL Institute of Neurology. Viorica is working on genetics of MSA and creating a MSA biobank. Previously she has trained in France and Moldova. Viorica has a clinical and research interest in genetics of movement disorders.

Conceição Bettencourt, PhD
is a Postdoctoral Research Associate at UCL Institute of Neurology, London. She is interested in a deeper understanding of the molecular pathways underlying neurological and neuromuscular diseases by studying genetic factors influencing these diseases.

Henry Houlden, is a Professor of Neurology and Neurogenetics and Head of the Neurogenetics Laboratory at the National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology. He has a clinical and research interest in neurogenetics and movement disorders, genetics risks in MSA and defining disease pathways. Henry runs the MSA specialist clinic together with the MSA Trust nurses.

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Key take home messages:

- Research into the genetic and molecular mechanisms underlying MSA has grown significantly in recent years.
- No neurorestorative treatments for MSA are available to date but there are many ongoing trials targeting α-syn pathways.
- Currently the standard of care in this condition remains symptom control.
- Levodopa is widely used, but while a small number of patients have some response to it, its benefit is short lasting and can worsen MSA symptoms, including OH and dyskinesia. First line treatment of OH remains midodrine, but new drugs such as atomoxetine have shown greater improvement in OH compared to midodrine in randomised trials.

Multiple System Atrophy (MSA) is a neurodegenerative condition characterised by late onset, progressive, atypical Parkinsonism and/or cerebellar syndrome with autonomic failure. It has a prevalence of 4.4 in 100,000 individuals[1] and affects males and females equally. Despite extensive research, the prognosis remains poor with average survival of eight years, although with careful management we are seeing patients live for 20 years after disease onset.[2] Clinically, MSA usually presents either parkinsonian (MSA-P) or cerebellar ataxia (MSA-C) predominant features but in the later years combined clinical features are often found.

At present, management strategies are focused on symptom control with medication for parkinsonism, autonomic liability, bladder and bowel dysfunction and mood problems. The role of specialised MSA clinics and working closely with the MSA Trust nurses is most important in symptom management as discussed on page 12. Disease modifying treatments that can stop or reverse the disease have yet to be identified. In order to develop new neurorestorative drugs and attempt to halt or reverse the pathology we need to advance our understanding of the mechanisms underlying MSA. Cell and animal models, and genetic studies have provided interesting results, yet no treatments have been demonstrated to slow or reverse the disease in humans. This article provides an update into recent drug trials and potential therapeutic targets linked to advances in the molecular and genetic aspects of MSA.

MSA pathways and therapeutic targets

The neuropathological characterisation of MSA has led to significant advances in research revealing the accumulation of abnormally misfolded α-synuclein (α-syn) and the pathognomonic formation of glial cytoplasmic inclusions (GCIs).[3] Native α-syn is a soluble protein present in normal brain tissue, usually in neurons, and believed to be involved in the pre-synapse and neurotransmission via the SNARE complex.[4,5] Although the conformational states of α-syn in different cell compartments are not well known, the existence of a balanced combination of monomers and tetramers resistant to aggregation has been proposed.[6] The mechanisms by which α-syn, a neuronal protein ends up in the oligodendroglia and propagates from cell-to-cell and between cell types remains unclear. How this leads to neuronal degeneration is key to finding therapeutic targets in MSA. There is growing evidence that oligodendroglial pathology is the primary event in MSA leading to neurodegeneration and is involved in multiple pathways such as microtubule stabilisation and myelination.[7] In MSA patients, P25 accumulates early in the oligodendrocytes' body, rather than in the myelin where it would normally be located. It has been shown to promote oligomerisation and aggregation of α-syn.[8,9]

Another protein found to be involved early in α-syn aggregation is β-III tubulin. β-III -tubulin is identified in GCIs in MSA patients and furthermore, α-syn binds directly to β-III tubulin via an α-syn binding site forming insoluble α-syn aggregates. Mouse model and mouse derived cell cultures show evidence that α-syn binding to β-III tubulin could be the initial event leading to α-syn self-aggregation.[10] Inhibition of this binding site was shown to prevent α-syn accumulation.[11] These results suggest that β-III tubulin is an important candidate for therapeutic targets with the potential to halt neurodegenerative changes in MSA.

The α-syn oligomerisation ultimately leads to oligodendrocytes' apoptosis. The apoptosis itself is mediated by several proteins such as sirtuin 2 (SIRT2), a tubulin deacetylase exclusively found in oligodendroglia with a promoting role in neurodegeneration.[12] Ultimately, targeting the proteins involved in apoptosis could prove a good therapeutic strategy. It appears that disease-modifying treatments should target one or a combination of the following: α-syn aggregation and propagation, neuronal demyelination, inflammation, apoptosis and eventually halt neurodegeneration.

Genetic targets in MSA

Although a few familial cases with Mendelian inheritance have been reported[13,14] MSA is usually a sporadic disorder. Extensive work has been undertaken studying the genetics of MSA in recent years. As abnormal α-syn deposited as GCI's is the hallmark of MSA, several studies

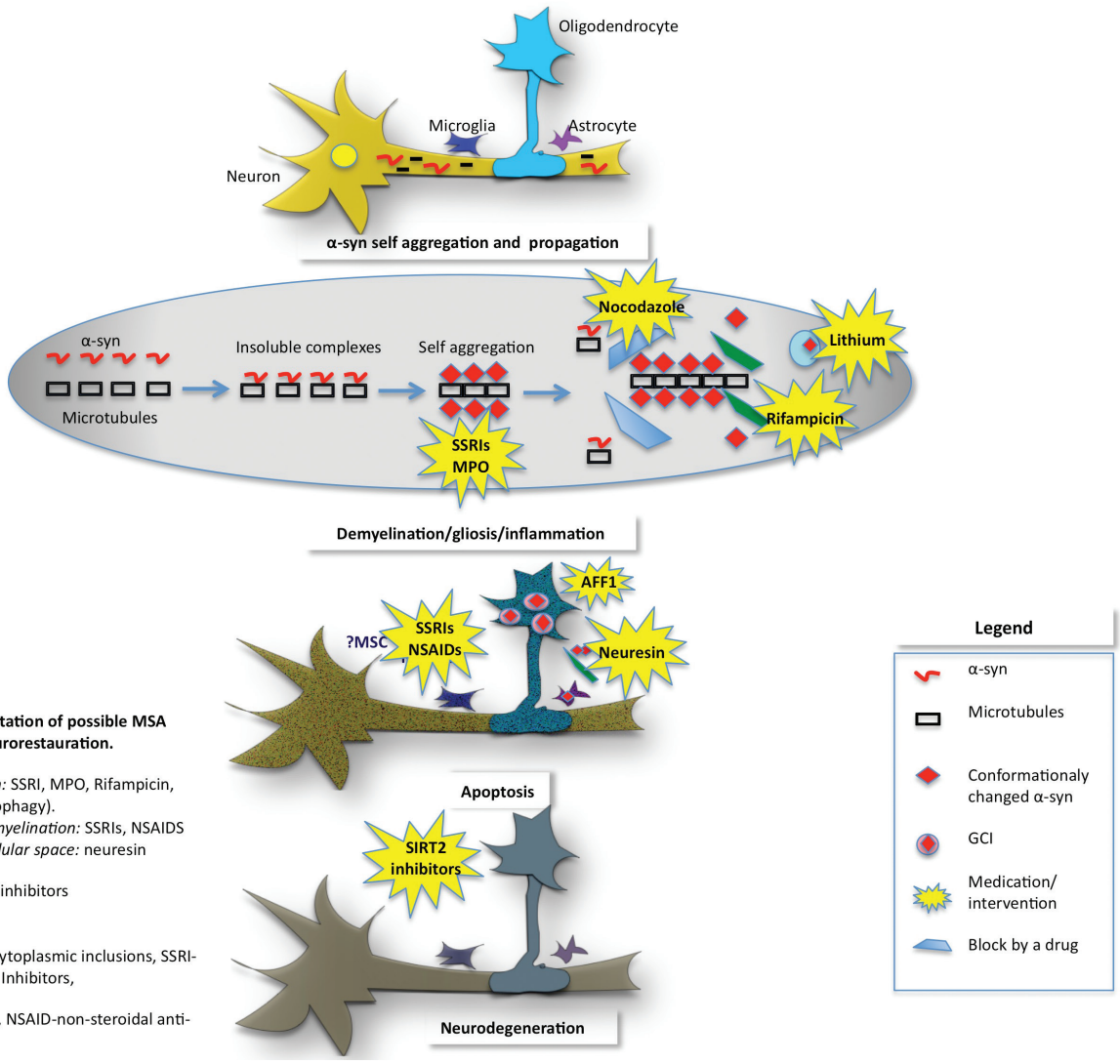

Figure 1. Schematic representation of possible MSA targets and pathways for neurorestauration.

Aggregation and propagation: SSRI, MPO, Rifampicin, Nocodazole, Lithium (via autophagy).
Inflammation, gliosis and demyelination: SSRIs, NSAIDS
Cleavage of α-syn in extracellular space: neuresin
α-syn antibodies: AFF1
Inhibition of apoptosis: SIRT2 inhibitors
Unclear mechanism: MSC

α-syn -α-synuclein, GCI-glial cytoplasmic inclusions, SSRI-Selective Serotonin Reuptake Inhibitors, MPO-myeloperoxidase, MSC- mesenchymal stem cell, NSAID-non-steroidal anti-inflammatory drugs.

have looked at *SNCA* mutations (gene encoding for α-syn) as a cause of disease. Despite *SNCA* mutations (A30P, H50Q, G51D, A53T, A53E,) being associated with familial Parkinson's disease (PD) leading to α-syn aggregation and cell toxicity, no *SNCA* mutations have been identified in true sporadic MSA. However, several families with *SNCA* mutations (e.g. G51D, *SNCA* triplications) presented with clinical and/or neuropathological similarities of autosomal dominant PD and MSA,[15,16,17] suggesting a possible link between the two conditions. A subsequent study targeting multiplications in *SNCA* in pathologically confirmed MSA cases did not identify any *SNCA* duplication or triplication.[18] Nevertheless, a study looking at single nucleotide polymorphism (SNP) identified SNPs in *SNCA* associated with increased risk of MSA in the Caucasian population[19] and replicated in other European studies,[20] but not replicated in Chinese or Korean populations.[21] Screening for other PD causal genes (*MAPT, LRRK2, PINK1*) has not yet revealed any association with MSA.[22-24]

Other genes believed to increase predisposition to MSA included *COQ2* mutations. A study combining linkage analysis and whole-genome sequencing found the mutations M128V-V393A/M128V-V393A (homozygous) and R337X/ V393A (compound heterozygous state) in two Japanese MSA families.[25] Also, the V393A variant was found over-represented in a cohort of Japanese MSA patients, suggesting it as a risk factor for MSA. However, several other studies were not able to replicate these results.[26,27]

Several recent reports have focused on prion-like mechanisms in synucleinopathies, but no variants in the prion protein gene (*PRNP*) were found to be associated with increased risk of MSA,[28] although no large scale study has been carried out looking at the *PRNP* gene in MSA. Finally, other genes have been screened for their association with MSA including several Spinocerebellar Ataxia (SCA) genes. There is no strong evidence to suggest an association with SCA and MSA at present, but larger studies in pathologically confirmed MSA cases are needed.

Therapies targeting α-synuclein

Several therapeutic strategies targeting α-syn aggregation and propagation have been attempted, but most were equivocal or failed. The only trial to date that reduced disease progression (based on UMSARS score) was a small-randomised mesenchymal stem cell (MSC) treatment. This suggests that MSC could be a potential treatment in MSA but there are limitations to the study due to the small number of patients involved,[29] the associated ischaemic side effects with the drug delivery and uncertainty over how the MSC targets α-syn.

Although in transgenic MSA mouse α-syn aggregation was significantly reduced after administration of rifampicin,[30] the trials with rifampicin in humans did not show any significant benefit. One hundred patients with possible or probable MSA were randomly assigned to either rifampicine (50 patients) or placebo (50 patients). The primary outcome measured was a change in the UMSARS score. This study showed that rifampicin did not slow progression of MSA.[31]

Lithium showed promising results in α-syn aggregation in mouse models by inducing autophagy and α-syn clearance. However, in a placebo-controlled double blind trial it did not pass the safety and tolerability in MSA and further lithium studies for this condition are not encouraged.[32] Selective serotonin reuptake inhibitors (SSRI) have been shown

Table 1. Symptom control trials in MSA published in 2014-2015

Drug Name	Mechanism of action	Study design and patients	Outcome measured	Results and Reference
Atomoxetine	Norepinephrine transporter (NET) blocker.	Atomoxetine vs placebo vs midodrine. 21 MSA patients (65 in total: MSA, PD, PAF).	*Primary:* improvement in standing BP at 1 min *Secondary:* sitting SBP and DBP, HR and symptoms scores.	Greater improvement in standing BP and orthostatic symptoms compared to midodrine.[46]
Droxidopa	α - adreno receptor agonist.	Randomised, withdrawal phase 3 study. 30 MSA patients (101 total: MSA, PAF, PD).	*Primary:* improvement in OHSA. *Secondary:* OHSA ratings, Clinical Global Impression (CGI).	No difference in OHSA between groups. Positive secondary outcomes.[47]
Nebivolol	Beta-blocker.	Randomised, placebo-controlled, double- blinded, crossover. 6 MSA patients with supine HTN (20 total: MSA, PAF, PD).	*Primary:* decrease in supine BP.	Reduced supine HTN with no worsening in OH.[48]
Rasagiline	MAO-B inhibitor.	Phase 2, Randomised, double-blinded, placebo-controlled trial. 174 MSA-P.	*Primary:* improvement in UMSARS I and II.	No significant benefit as per UMSARS between groups.[49]
Deep Brain Stimulation	Bilateral SNT stimulation.	5 MSA–P patients.	*Primary:* reduction in dyskinesia and postural instability.	No benefit. The UPDRSIII worsened at 1 year follow up.[50]
Cord blood mononuclear cells transplantation	Umbilical cord blood stem cells.	3 MSA patients received transplant in subarachnoid space and cisterna magna.	*Primary:* improvement in UMSARS.	Improvement in urinary symptoms and walking.[51]

OH-orthostatic hypotension, BP-blood pressure, SBP/DBP- systolic/diastolic blood pressure, PAF-Pure autonomic failure, OHSA-orthostatic hypotension symptom assessment, HTN-hypertension, UMSARS-Unified MSA Rating Scale, UPDRS- Unified PD Rating Scale

to prevent α-syn aggregation and propagation to oligodendroglia. Sertraline, Paroxetine and Fluoxetine are the most studied examples. In *in-vivo* transgenic mice models, fluoxetine reduced α-syn aggregation, gliosis and demyelination together with an increase in glial and brain derived neurotrophic factors. Clinically, the mouse showed improved motor and behavioural deficits.[33] Sertraline was shown to inhibit the propagation of α-syn to oligodendroglia in cell culture models.[34] Paroxetine is the only SSRI tested in MSA patients. A double-blind placebo-controlled randomised trial showed that the paroxetine treated group had improved motor and speech symptoms compared to placebo.[35] A new study currently at recruitment stage will assess Fluoxetine in MSA patients. All these studies show that SSRIs could represent promising therapeutic targets in MSA.

Interesting results were obtained using non-steroidal anti-inflammatory drugs (NSAIDs) to inhibit the formation of α-syn fibrils and even destabilisation of preformed α-syn fibrils in a dose-dependent manner.[36] NSAIDs have been extensively used in other conditions, have a well-known side effects profile and are inexpensive. All these aspects make them a potential therapeutic option and further studies are needed. As microglia activation plays an important role in MSA, a trial assessing the role of minocycline was conducted. Minocycline did not show any improvement in patients' motor symptoms or UMSARS. However, the group treated with minocycline showed a reduction in [11C] (R)-PK11195 PET activity suggesting that minocycline has an effect on microglial activation and requiring further research.[37]

Another study used nocodazole (microtubule depolymerisation drug) to stop α-syn accumulation on the basis that β-III tubulin was shown to be involved early in the disease by binding to α-syn forming insoluble complexes leading to MSA pathology. It was shown that in cultured cells nocodazole prevented the accumulation of insoluble α-syn when the drug was given before the formation of α-syn aggregates, but had no effect when given at later stages.[10] No P25 targeting treatment has been tried yet.

On the premise that SIRT2 is involved in oligodendroglial apoptosis and promotes neurodegeneration one study assessed the role of a SIRT2 inhibitor. They showed that the SIRT2 inhibitor partially prevented cellular apoptosis in a cell culture model, but the exact mechanism is still unclear.[12]

Recently, it has been shown that neurosin (human kalikrein6 -KLK6), a serine protease present in many human tissues including the astrocytes, is able to cleave α-syn aggregates. Furthermore, the down-regulation of neurosin leads to accumulation of α-syn. In the MSA mouse brain model the genetically stabilised form of neurosin allowed it to be delivered systemically and led to the reduction of α-syn aggregation and propagation, together with improvement in clinical features such as demyelination and behaviour.[38]

Several studies have or are looking at active vaccination in an attempt to stop α-syn aggregation and propagation. Mandler et al used short peptides AFF1 in a MSA transgenic mouse model and showed that active vaccination with AFF1 resulted in the production of anti- α-syn antibodies capable of identifying α-syn in oligodendroglia. In their animal model, this process led to a reduction of α-syn accumulation, demyelination and neurodegeneration.[39] A new European project (The SYMPATH project) is currently assessing a vaccine targeting α-syn (AFFITOPE) in PD and MSA in humans.

Therapies targeting symptom control in MSA

Symptomatic treatment remains the current standard of care in MSA. Trials targeting improvement in symptom control published in the last two years are summarised in Table 1. The symptom control efforts are focused on dopamine replacement in the parkinsonian type MSA, management of the autonomic dysfunction, bladder and bowel care, sleep, breathing and mood problems.

Part of the diagnostic criteria for MSA is the poor response to levodopa. However, in a recent USA study, about half of the patients, particularly with probable MSA-P type reported benefit from Levodopa.[40] The European MSA Study Group demonstrated a three years sustained Levodopa response in 31% of patients.[2] A retrospective review of pathologically confirmed MSA cases showed benefit from Levodopa in about 30% though this was not long lasting.[41] Levodopa is known to cause fewer hallucinations in MSA than PD but it can worsen orthostatic hypotension[42] and induce dyskinesia.[43] So far, there has been no randomised controlled trial assessing the efficacy of levodopa or dopamine agonists in MSA but it appears that levodopa provides short lasting, modest benefit, in a small number of patients.

Orthostatic hypotension (OH) represents

one of the major diagnostic criteria for MSA and is a very disabling symptom for patients. So far, midrodrine (α1-adrenoceptor agonist) is the only medication that showed improvement in neurogenic OH in randomised, double blinded placebo studies at doses up to 30 mg per day.[44] Patients on midodrine should have regular blood pressure monitoring as it can induce supine hypertension. Also, non-pharmacological measures, such as higher salt and fluid intake, smaller but more frequent meals together with head raising to 30° in bed, wearing elastic stockings and a special set of exercises, improve symptoms and should be recommended.

Symptomatic interventions tackling neurogenic bladder include intermittent self-catheterisation if post-void residual volume is >100 ml. Anticholinergics and α-adrenergic antagonists are indicated if post voidal residue is <100 ml. Side effects include urinary retention and worsening OH. In severe cases, Botox injections can be administered to the detrusor muscle or urethral sphincter. Botox injections are also indicated for the management of dystonia, camptocormia and excessive salivation.

For patients experiencing breathing problems continuous positive air pressure (CPAP) is beneficial or tracheostomy in advanced stages. First line treatment for REM sleep disorders is clonazepam[45] but other medication such as zopiclone, melatonin and temazepam can be used as second line. Selective Serotonin Reuptake Inhibitors (SSRIs) are recommended for the management of depression together with psychological support for the patient and the family. Levodopa can also have a beneficial effect on depression.

Conclusion

Research into the genetic and molecular mechanisms underlying MSA has grown significantly in recent years. However, thus far we have failed to find a successful neurorestorative treatment for MSA. Consequently the standard of care in this condition remains symptom control. Levodopa is widely used in MSA, but while its effect is short lasting it can also worsen MSA symptoms including OH. First line treatment of OH remains midodrine with close monitoring of supine BP. The recent randomised trials will hopefully provide alternative options for the management of MSA. Without trial proof of efficacy, those drugs that improve *in-vitro* pathology should be favoured. Further research into the molecular, histological and genetic aspects is needed in order to create accurate animal/cell models, to identify disease specific biomarkers and eventually, a breakthrough disease-modifying treatment.

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The MSA Trust

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The Multiple System Atrophy Trust (previously the Sarah Matheson Trust), was created after the founder Sarah Matheson was diagnosed with MSA in 1993 and became aware there was little support for people living with MSA in the UK. The Trust became a registered charity in 1997 and was renamed in 2010. It is run today by a group of trustees, many of whom had a personal connection to Sarah, or who have experienced MSA with a family member. Sir Roger Bannister CBE and Professor Christopher Mathias are the Trust's Patrons.

The vision of the MSA Trust is a world free of MSA – in the hope that one day there will be a cure for this devastating disease. The Trust is committed to supporting people whose lives are affected by MSA, their carers, family and friends. Support is provided in many ways, including:

- Three Nurse Specialists working within the MSA community.
- A telephone and email support service supplemented by our website.
- A network of 35 volunteer-led support groups located around the UK.
- An online local hub to harness community knowledge and to offer support at local level.
- An online forum where members can connect with others with similar issues.
- Education and support for health and social care professionals to help them provide the best possible care and treatment for people with this rare and complex disease.
- A sense of community for people isolated by the challenges of MSA.

The MSA Trust has a five-year strategic plan which identifies five goals that reflect the views of our members. These five goals are:

- To develop a volunteer network
- To educate healthcare professionals
- To increase commitment to research
- To increase support for carers
- To develop a model for MSA centres

Research priorities for the MSA Trust

The funding of research grant projects with the aims of finding the cause of MSA and improving treatments for people with MSA, through drug discovery and translational studies including, for example, the treatment of important symptoms in MSA.

To seek collaborative partnerships with other organisations involved in neurodegenerative research, to increase research capacity, share resources and generally raise the profile of the disease.

To encourage engagement with the pharmaceutical industry, in particular around target identification and drug discovery, working in collaboration with the Trust-funded MSA UK Network. The Network will provide a biobank, enabling sharing of samples amongst the MSA research community and ultimately facilitate the participation of patients in clinical trials.

To develop interest amongst clinical and non-clinical scientists to undertake MSA research by demonstrating the on-going commitment of the Trust to fund research, and by building links with existing research structures (e.g. the National Institute for Health Research and the Dementias and Neurodegeneration (DeNDRoN) Specialty), thereby organically growing the MSA scientists and clinicians of the future.

To support international scientific collaboration, enabling participation in European initiatives and considering overseas grant applications from researchers with a demonstrable link to a UK based Principal Investigator or institution.

The Role of the Nurse Specialists

The MSA Trust Nurse Specialist's primary role is information and support to those living with MSA, their carers, families and the professionals supporting them. They attend specialist MSA clinics across the UK by invitation from Neurologists with an interest in MSA, and offer education sessions to anyone supporting someone with MSA. The MSA Nurses also liaise closely with Parkinson's Disease Nurse Specialists, Community Matrons and Palliative Nurse Specialists.

Why is this role needed?

People's worlds fall apart. They don't know where to turn. They are frequently overwhelmed and unable to act. Often Health Professionals are not familiar with MSA. As people's experience of MSA is individual and symptoms and challenges are constantly changing, ongoing trusted support is vital.

What does the role involve?

- Answering (and initiating) calls and emails to people living with MSA and their carers and families, including Health and Social Care Professionals. Last year the nurses dealt with over 2500 telephone and 14000 email enquiries. Commonly asked questions are "How long have I got?", "Am I going to pass this onto my children?" and "How will I die?"
- Attending specialist MSA clinics. Last year the nurses attended 55 clinic sessions at 11 locations, reaching 345 patients.
- Providing advice and practical help at Support Groups: last year the nurses attended 34 support groups, with 177 attendees.
- Teaching – formally at conferences, and informally with local services. Thirty-seven training courses were given last year.
- Contributing to raising the profile of MSA and the Trust at meetings e.g. National Palliative Care and contributing to policy work e.g. NICE guidelines.
- Acting as a resource to the Trust, supporting colleagues in communications and fund-raising.

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Cell based therapies for glaucoma

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Key take home messages:

- Stem cells could be useful in the treatment of glaucoma by improving aqueous outflow to lower eye pressure, by protecting retinal ganglion cells directly against glaucoma damage or by facilitating optic nerve regeneration.
- Stem cell treatments have been shown to reduce retinal ganglion cell death in animal models of glaucoma, demonstrating their potential to slow vision loss due to glaucoma.
- Future research may pave the way for successful transplantation of stem cells to the retina and enable differentiation into mature retinal ganglion cells able to restore functional connections to the brain, but formidable challenges remain to be overcome.

Glaucoma is the leading cause of irreversible blindness worldwide, and its global prevalence is predicted to exceed 100 million people by 2040.[1] The disease is often, but not always, associated with elevated intraocular pressure (IOP) and leads to progressive loss of retinal ganglion cells (RGCs) in the optic nerve, potentially causing blindness.[2] Current therapeutic approaches consist mainly of self-administered eye drops, surgical or laser treatment to enhance aqueous outflow and thus lower IOP. However, in many cases IOP reduction does not successfully prevent the degeneration of RGCs, and poor patient adherence to prescribed treatment regimes treatments can render them ineffective. Furthermore, symptomatic reduction in vision typically arises only late in the disease, after significant damage has been incurred. Thus, there is an urgent need for treatments which not only lower IOP and protect RGCs from dying, but also promote the growth and navigation of implanted or regenerated RGC axons through the optic nerve and restore functional vision.

Stem cells could potentially provide a compelling treatment strategy for glaucoma, either by protecting vulnerable tissues or by providing a source of mature cells to replace those lost due to disease. Stem cells are defined by their potency, that is, their potential to undergo differentiation into any cell type. At successive stages of normal development, cells enter increasingly narrow niches, moving from the totipotency of the fertilised egg to the multipotency of, for example, neural stem cells. Stem cells exhibit self-renewal, meaning populations can be maintained in culture, allowing for expansion of small cell numbers into robust therapeutic doses. A number of different stem cell approaches have already been used to treat a wide variety of diseases in research studies, several involving the eye. As an example, clinical trials for age-related macular degeneration and Stargardt's disease are already underway, with promising early results.[3]

Addressing glaucoma with stem cell approaches will be challenging. The retinal cell layers are intricately organised, and RGC axons must project long distances from the eye to visual targets in the brain. Replacing RGCs with exogenously derived stem cells will require careful control of the transplanted cells' differentiation state and integration into the complex architecture of the host tissue. Beyond that, new cells must then navigate the length of the optic nerve and synapse at proper brain targets. More immediate applications for stem cells in glaucoma are likely to come from endogenous sources, which may be isolated from patients' own tissue prior to autologous transplantation, limiting the risk of tumour formation. Stem cells have been shown to exert protective effects on neurons and may play a role in repairing the damaged TM. This review discusses the current spectrum of cell-based therapies for glaucoma, emphasising the need for endogenous neuroprotection and regeneration in the retina and optic nerve.

Cell-based Therapies

Aqueous Outflow Modulation

Aqueous humour fills the anterior chamber of the eye between the iris and the cornea, and the balance between production and outflow of this fluid through the TM determines IOP. Increases in the resistance of the aqueous outflow pathway, often due to decreased TM cellularity and reduced phagocytosis of debris in the extracellular matrix (ECM) as compared with healthy TM cells, contribute to elevated IOP and thus to the degeneration of RGCs.[4] Current glaucoma therapies target this pathway, using pharmacological or surgical intervention to decrease outflow resistance. Drug side effects and surgical complications therefore comprise primary risks of glaucoma treatment. Delivering a dose of stem cells that produce a sustained, long-term reduction of IOP would at least partially alleviate these concerns.

The TM occupies a space of relative immune privilege and endogenous stem cell populations have been discovered in the TM, which express characteristic markers of mature TM cells and perform a similar phagocytic function as that observed *in vivo*.[5] Other recent approaches have differentiated induced pluripotent stem (iPS) cells into TM-like cells for transplant and recovery of TM function.[6,7] TM dysfunction frequently occurs in eyes with glaucoma and often worsens with age, adversely affecting aqueous outflow and thus contributing to

IOP elevation. Restoring TM function using stem cell therapies could therefore potentially limit glaucomatous damage to RGCs and thus help prevent further vision loss in treated patients.

Retinal Neuroprotection

Transplanted stem cells can have a protective effect in the CNS, by mechanisms which may include regulation of inflammation and secretion of neurotrophic factors (NTFs). A potential therapy based on stem cell transplantation could arise from these characteristics: rather than implantation and integration of a graft in the retina, which requires exceedingly intricate control, a sustained-release approach using stem cells may directly reduce RGC death in glaucoma. A phase I clinical trial has already utilized encapsulated mesenchymal stem cells (MSCs) to deliver ciliary neurotrophic factor (CNTF) and slow retinal degeneration in patients with retinitis pigmentosa.[8] NTF deprivation likely contributes to cell death in glaucoma, and diffusible factors secreted by stem cells have shown protective effects on neurons in animal models.[9] Both MSCs and neural stem cells (NSCs) have demonstrated neuroprotection of RGCs.[10-12] Both have likewise undergone successful modifications to enhance their NTF production, although whether these modifications confer significant increases in protection remains controversial.[10,13] Despite these challenges, therapies involving stem cell-mediated neuroprotection via NTF secretion or immunomodulation have shown promise and are positioned to become an important priority for future research.

Replacement of RGCs

Conceptually, the most definitive cell-based approach to glaucoma would involve transplantation of differentiated stem cells to the damaged retina, followed by graft integration into the inner nuclear layer and projection of long axons through the optic nerve, terminating with synapses at visual targets in the brain. Naturally, each step of this complex path poses unique hurdles. Firstly, transplanted cells must migrate to the injured retina and integrate with surviving cells. This process may be impeded by local inflammatory cells, reactive Muller glia, or inhibitory molecules in the ECM.[14] Altering the gene expression of implanted cells to modify their response to external stimuli, removing inhibitory factors in the retina, or supplying exogenous NTFs may alleviate these inhibitory effects and improve graft integration.[15] Secondly, stem cells must differentiate into mature RGCs. Recent efforts have shown success in generating functional RGC-like cells in vitro from iPS cells.[16] Such cells have yet to demonstrate a differentiated RGC-like phenotype *in vivo*.

Even if grafted cells survive and differentiate into RGCs, they must then navigate the inhibitory environment of the optic pathway and generate synapses at visual targets that maintain the retinotopic map of the retina. Most research on axon projection derives from regeneration studies of endogenous RGCs, and the behaviour of transplanted cells may not mirror that of surviving cells. Nonetheless, several groups have shown success in using combinatorial treatments to stimulate RGC axon regeneration in animal models. These typically include both intrinsic methods such as genetic manipulation of RGCs, and extrinsic changes including modification of inhibitory ECM components, peripheral nerve grafts, or inflammatory stimulation. One such experimental approach yielded full-length regeneration of a small population of neurons in mice, with reported gains in visual function and behaviour.[17]

Future Directions

For short-term clinical impact, stem cell-based therapies for glaucoma will most likely rely on proven effects of IOP lowering and retinal neuroprotection. Optimising these treatments may slow degeneration of RGCs and ensure that a larger proportion of cells survive for longer periods. Stimulating regeneration of these surviving cells could then provide a mechanism by which visual function, even at relatively low levels, may be recovered, thus dramatically improving the quality of life for patients with severe vision loss. As these studies move forward, it may become possible to facilitate exogenous transplantation and integration of new RGCs with active connections to the brain, although many formidable challenges remain to be overcome.

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The agitated patient on the neurology ward

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Few clinical scenarios have as much potential to evoke ill-feeling and inter-disciplinary tension as the agitated patient. Though unfortunate this is understandable. With agitation comes disruption of normally efficient ward routines, fear of aggression and even actual injury. Staff who feel threatened and 'out of their depth' struggle to provide optimal patient care, a problem potentially magnified when misinformation is seen as fact (see Table 1) and the view this 'should be someone else's problem' gains purchase. The reality is alternative placements are rarely available for medically unwell agitated patients. Consequently tempers fray, a misinterpretation of 'zero tolerance' policies is used to justify disengagement, and the care of often particularly sick patients suffers with potentially devastating consequences. Thankfully however with adequate preparation staff can increase their confidence in working with these patients, derive much satisfaction from providing good quality care, and greatly improve outcomes.

Emergency management of agitation

Agitation is instantly recognisable, but harder to define. It encompasses both subjective distress and motor restlessness (pacing, wringing hands etc). Though crises such as aggression or attempts to abscond are what typically precipitate senior staff being summoned, they rarely occur without warning. Generally they follow a prodromal period of increasing irritability, possibly with glaring, fidgeting or pacing.[1] Management of aggression training emphasises recognising this escalating agitation and intervening to avert crises. This involves calmly and empathically engaging the patient, attempting to ascertain the causes of their increasing agitation and attenuating them before overt aggression supervenes. Crucial questions are whether the patient is delirious or has a major psychiatric illness. Clearly however, this assessment must be done in tandem with planning for violence, guarding personal safety and ensuring adequate staff to restrain the patient should this prove necessary. Oral medication should be offered, but intramuscular medication also prepared. This will normally be Haloperidol, though if medical contraindications or alcohol/sedative withdrawal is suspected Lorazepam is preferred. Doses are determined more by medical fitness rather than level of agitation. A starting dose of Haloperidol 0.5mg (or Lorazepam 0.5mg if antipsychotics contraindicated but emergency tranquilisation essential) would be indicated in a frail elderly woman, whereas a psychotic young man may receive both Haloperidol 5mg and Lorazepam 2mg.

Assessment

In medical inpatients delirium is the cause of agitation until proved otherwise. It is characterised by an abrupt onset, altered conscious level and fluctuating course. Impaired attention, with associated disorientation, is the key clinical finding. It can be identified through simple bedside tests such as serial 7 subtractions or, still sensitive but less influenced by education, listing the months of the year backwards.[2] Additional disturbances in cognition (particularly memory, executive and visuospatial functions) are also often present, sleep is fragmented, and perceptual disturbances, especially illusions and visual hallucinations, can occur. Previously regarded as a transient disturbance from which recovery was the norm, delirium is now recognised as a medical emergency. It is associated with high mortality, and even optimally treated can have long term consequences for survivors. Twenty percent of delirious patients still exhibit symptoms 3-6 months after onset,[3] and it is associated with an increase in incident dementia.[4] Prospective studies demonstrate this association after controlling for potential confounders, indicating delirium does not just predict dementia but directly contributes to cognitive decline. Animal studies suggest mechanisms by which this could occur, demonstrating that in animals with neurodegenerative disease systemic inflammation can have a neurotoxic effect.[5] Prevention should be a hospital priority, and early detec-

Table 1: Commonly encountered misconceptions in managing agitated patients

Psychotic symptoms mean a patient has schizophrenia
Only a psychiatrist can detain a patient
A patient can only be restrained or medicated against their will if they have been detained*
If a patient is detained under the Mental Health Act they must be transferred to a psychiatric hospital
If a patient is detained mental health services must provide a psychiatric nurse
Psychiatric services can only accept a patient when 'an organic cause has been excluded'+

*Detention may be indicated, but in an emergency this can occur under incapacity legislation. In exceptional circumstances, when there is not even time for a capacity assessment, interventions in life threatening circumstances can occur under common law.

+The crucial question is, of course, which setting can best meet a patient's care needs

Table 2: Disorders which can be confused for delirium

	Delirium	Dementia	Mania	Depression	Schizophrenia	Anxiety states	Personality Disorder
Onset	Abrupt	Chronic	Can be acute	Subacute	Insidious	Chronic or acute in context of major stressor	Chronic with acute exacerbation of symptoms/ decompensation in context of stressors
Delusions	Persecutory. Fleeting, changeable, poorly formed. First rank symptoms uncommon	Delusions may develop, generally late-stage, simple and persecutory	Grandiose, 'mood congruent'	Nihilistic or persecutory 'mood congruent'	Fixed, false system of beliefs with complex logical structure. 'First rank symptoms'	Absent	Though may have 'overvalued ideas', true delusions absent
Hallucinations	Predominantly visual	Both auditory and visual can occur in later disease (visual common in Lewy-body dementia)	If present generally auditory and 'mood congruent'	If present generally auditory, 'mood congruent'	Auditory hallucination core feature, especially 'third person'	Absent	Not true hallucinations; 'pseudo-hallucinations'
Attention/ working memory	Impaired	Relatively normal until advanced stages	Distractable, but attentional impairment less pronounced than delirium	Minimal impairment, though poor motivation may result in poor performance on assessment	Relatively intact	Intact	Intact
Arousal	Abnormal: hypoalert or hyperalert	Relatively normal	Hyperalert	May be hypoalert	Relatively normal or mildly hyperalert	Relatively normal or hyperalert in panic	Normal or mildly hyperalert
Orientation	Generally disorientated to time and often place	Disorientated in advanced cases	Orientated	Orientated	Orientated	Orientated	Orientated
Episodic Memory	Impaired	Impaired, temporal gradient to memory loss.	Relatively intact	Selective or patchy impairment, may complain about memory impairment	Relatively intact	Intact	Intact
Motor activity	Increased or decreased	Varies, often normal	Increased	Generally decreased	Generally fairly normal though may be apathetic and can be catatonic	Often increased	Normal unless acutely agitated
Affect	Labile, though may be fearful or seem depressed	Variable	Elevated mood, though may be irritable and labile	Sustained low mood	Perplexed	Anxious	Anger
Speech	Slow/rapid, incoherent	Word finding difficulty but reasonably coherent until late stage	Pressured, 'flight of ideas'	Slowed, monotonous	Disjointed, 'loosening of association'	Relatively normal, may be slightly pressured	Normal
Sleep-wake cycle	Very disturbed, cycle may be reversed	Some fragmentation	Reduced sleep without sleepiness	Disturbed, often early morning wakening	Relatively normal, though sleep phase disorders common (especially delayed)	Initial insomnia characteristic	Relatively normal
Course	Fluctuating, lucid intervals can mislead	Stable from day to day	Alternate between elation and irritability	Diurnal variation in mood, worst in morning	Stable once established with deterioration generally consequent to medication non-compliance	Stable with potential episodes of panic	Stable

*Lewy-body dementia poses particular difficulties in distinguishing from delirium given visual hallucinations are prominent, the course is fluctuating and consciousness can be impaired

Table 3: Optimising the care of delirious patients
Correct sensory deficits (glasses, hearing aids)
Orientation (calendar, clock and verbal)
Maximise natural light in day, minimise light and noise at night
'Side-room' may increase sensory deprivation
Minimise catheters, treat constipation
Correct malnutrition/dehydration
Minimise sedatives and anticholinergics
Ensure pain optimally treated
Early mobilisation, walking aids, ROM exercises

tion and intervention is crucial. There is no shortage of well validated screening tools (e.g. the 4AT, www.the4at.com) and they should be more widely used; the 'time is brain' maxim may also be very applicable to delirium. Moreover, though the agitated patient is being discussed here, remember these are the minority of delirious patients; hypoactive or mixed presentations are more common. Hypoactive delirious patients often go unnoticed though they probably represent more severe disturbance with a greater likelihood of mortality.[6]

While the most likely cause of agitation in a hospital is delirium, there are other possibilities. These, together with features which distinguish them, are detailed in Table 2. Agitation does of course occur in dementia, but with the exception of Lewy-body dementia hallucinations are generally not prominent until the advanced stages. Though they may not be orientated, demented patients are normally alert, onset is insidious rather than acute, and sleep cycle disturbance is much less pronounced than in delirium. Patients with schizophreniform or manic psychosis are generally orientated and have preserved recent memory. Though they may be distractible, they will not have the gross attentional disturbance of delirium. The lethargy and psychomotor retardation of hypoactive delirium can be confused for the avolition and withdrawal of severe depression.[7] As with other 'psychiatric' conditions hallucinations in depression are usually auditory rather than visual. Like delusions they are mood congruent, and generally focused on ideas of guilt, death and decay.

On occasion agitation may result as an inappropriate response to a stressor in the absence of delirium or a major psychiatric illness. This may reflect the difficulties in interpersonal functioning and impulse control characteristic of personality disorders. If this is the diagnosis there will likely be an established history of similar conduct. Behaviour is regarded as volitional and may warrant removal from the ward and potentially prosecution. Keep in mind though that these patients can evoke very strong emotions which can cloud clinical judgement, and evidence of personality change should raise the possibility of an underlying neurological (or other medical) disorder. Withdrawal from a variety of abused substances can precipitate agitation. In the case of sedative agents (e.g. alcohol, benzodiazepines) this may precipitate delirium. Opiate withdrawal is associated with intense irritability, restlessness and craving; though treatment of withdrawal may be necessary to enable the patient to receive necessary medical treatment, it is not life threatening and consciousness is clear.

With a clear psychiatric diagnosis, transfer to psychiatric care is generally indicated. Behavioural disturbance in dementia (once delirium is excluded) is also generally managed in psychiatric settings. Though in exceptional (and relatively medically stable) cases risk may necessitate transfer to psychiatric care, delirious patients will overwhelmingly be managed on medical wards. It is important for physicians to appreciate just how limited the medical capabilities of psychiatric wards actually are. Mental health nursing is a distinct undergraduate degree from medical nursing, so it is unsurprising psychiatric nurses do not feel confident caring for medically unwell patients and intravenous administration of drugs and fluids is generally not feasible. Additionally resources for basic monitoring such as pulse oximetry are generally absent and even obtaining a chest X-ray often means travel to a different site.

Delirium

The treatment priority in delirium is identifying and addressing precipitants and maintaining factors. Multifactorial causation is the norm not exception, meaning consideration of potential contributors should not cease when a putative precipitant is identified. Remember that the threshold for developing delirium in compromised brains (be it because of dementia, MS, Parkinson's disease, traumatic brain injury or even, possibly, depression[8]) is lowered. If very vulnerable, relevant precipitants (such as sleep disturbance, hunger or simply being in a strange environment) may seem trivial. Their potential importance can be understood however when delirium is conceptualised as arising through a complex interaction of pre-existing vulnerabilities, direct brain insults (such as drug effects and metabolic abnormalities) and aberrant stress responses. The latter are increasingly being elucidated and likely include aberrant HPA axis activity and primed microglia amplifying intracerebral inflammatory effects.[9] Though heterogeneity in causation makes discussion of a 'final common pathway' in delirium facile, reduced acetylcholine and increased dopamine are often thought important.[10]

Treatment of delirium

Optimising the environment is crucial. Many features of delirium-friendly care should be routine practice (see Table 3) and, though controlled studies are understandably hard to conduct, their implementation has been demonstrated to reduce delirium incidence.[11] Distressed patients may require 1:1 nursing care, the 'sitter' providing orientation and reassurance with simple repeated statements e.g. 'You are in hospital. You are safe.' Family can be a useful resource, their effectiveness optimised by

Table 4: Antipsychotic doses when treating delirium

	Advantages/Disadvantages	Sample dosing regime	
		Fairly robust adult	Frail elderly
Haloperidol	Always obtainable, IM and IV formulation, staff familiarity, very prone to cause EPSEs, possibly higher risk QTc prolongation	Initially 2mg bd* (2.5mg qds not unusual; higher doses are used, but unlikely further gain beyond 10mg a day)	0.5 mg bd (0.25mg in extreme frailty)
Risperidone	Slightly less prone to cause EPSEs, orodispersible formulation	Initially 1mg bd. Doses beyond 3mg bd unusual	0.5mg bd (0.25mg in extreme frailty)
Olanzapine	Less prone to cause EPSEs or QTc prolongation, more sedation, orodispersible formulation	Initially 5mg at night (may require 10mg and occasionally higher). Split dose if daytime agitation prominent	2.5mg at night (1mg in extreme frailty)

*In a young, acutely agitated but physically fairly robust delirious patient in an 'at risk' situation, an immediate dose of Haloperidol 5mg may be required. Regular doses are generally lower however. In cases where there are particular concerns about using antipsychotics (e.g. epilepsy, or the patient is particularly medical unwell) even in a young adult it is prudent to start with 1mg bd if possible.

It is important if treating delirium that antipsychotics are prescribed regularly, not 'prn'. Clearly however the prescription of regular antipsychotics is generally not appropriate when managing an episode of agitation the cause of which is not yet clear. Given their potential adverse consequences antipsychotics should be reduced/stopped after symptoms resolve.

Table 5: Situations in which antipsychotics are not first choice for treating agitation

Clinical situation	Alternatives
Medical contraindications e.g. myocardial infarction	Lorazepam can be used for sedation. Aripiprazole and possibly Olanzapine less cardiac risk than many other antipsychotics but not 'safe' and crucial to monitor ECG.
Alcohol or sedative withdrawal	Benzodiazepines (long half-life such as Diazepam or Chlordiazepoxide). Pabrinex may be required. In GHB (Gamma-hydroxybutyrate) withdrawal Baclofen can usefully augment benzodiazepines.
Parkinson's disease/Lewy body dementia	Cholinesterase inhibitors, avoid antipsychotics (except Clozapine, though use of this drug is generally not practical), if use of sedation is unavoidable Lorazepam. Pimavanserin will likely be licensed for PD/LBD psychosis, but is not currently available.
Post-traumatic amnesia	Propranolol or possibly Trazodone for agitation. Antipsychotics useful if sustained psychotic symptoms.
Psychotic depression	Antipsychotics augment treatment with antidepressants. ECT may be required.
Post-ictal delirium or psychosis	Seizure control, exclusion of other medical issues and supportive care is priority. Generally resolves spontaneously. Lorazepam preferred over antipsychotics for management of agitation but low dose Haloperidol may be required.

delirium education and guidance on how to interact with the patient.[12]

Medication can be helpful in delirium, but is not a substitute for optimising care. Antipsychotics are generally the agents of choice; NICE recommends Haloperidol or Olanzapine, though Risperidone is also a reasonable choice (Table 4). Though the latter two drugs may be associated with quicker response and are less likely to give rise to extrapyramidal side effects,[13] in practice Haloperidol is generally first choice. Olanzapine is actually fairly anticholinergic which is a theoretical disadvantage; this does not generally cause problems, but its sedative properties mean it is not first choice in hypoactive delirium. All antipsychotics can cause akathisia, important to remember in patients becoming more restless as doses increase. The association between antipsychotic use in dementia and increased mortality is well established,[14] so they should be stopped as soon as possible. Despite being the first drug identified to increase risk of stroke, the hazard ratio for mortality associated with Risperidone in demented patients may be less than with Haloperidol, and that with Olanzapine lower still.[15] Though antipsychotics may augment treatment if psychotic symptoms are present, benzodiazepines are the cornerstone of treatment for delirium precipitated by withdrawal from sedatives such as alcohol or benzodiazepines. A typical regime for alcohol withdrawal would start with Diazepam 10mg four times a day, but doses are titrated to symptoms and may be much higher. Other circumstances when drugs other than antipsychotics are the first choice for agitation (due to delirium or other cause) are considered in Table 5.

Novel treatment options for delirium

Given the consistent finding of reduced acetylcholine in delirium, cholinesterase inhibitors would be expected to be helpful. Increased mortality when Rivastigmine was trialled as adjunctive treatment to Haloperidol in delirious ICU patients curbed initial enthusiasm.[16] These extremely unwell patients with multiple organ failure are quite different from the typical delirious population however, and targeted use of anticholinergics may in time find a role. They may be most useful in delirious patients with a pre-existing cholinergic deficit, such as patients with Alzheimer's disease. Given the prominence of sleep disturbance, Melatonin or even 'bright light therapy' may find a role.[17,18] Dexmedetomidine, an alpha 2 agonist, is associated with reduced incidence of delirium when used for sedation in ICU; it decreases centrally mediated sympathetic activity and, if hypotensive/bradycardic side effects can be tolerated, may in time be used to treat delirium out-with ICUs.[19]

Conclusions

Agitation is a common problem throughout hospitals, with neurology patients being particularly vulnerable. Poor management can have disastrous consequences, but an engaged staff team adhering to some fairly common-sense principles can greatly improve outcomes. Prevention and early detection of delirium must be a priority. Though evidence for the use of antipsychotics in the treatment of delirium is good, skilled nursing care can make a huge difference and the centrality of this must be recognised and skill development supported.

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'Measuring the burden of hospitalisation in multiple sclerosis: A cross-sectional analysis of the English Hospital Episode Statistics database 2009-2014' Review by: Claire McCarthy

Multiple sclerosis (MS) is estimated to affect 89,790 people in England.[1] This report, published in November 2015, looked at the reasons why people with MS are admitted to hospital and the cost implications. It has been produced by the NHiS Commissioning Excellence group in conjunction with the MS Trust. The first question I asked was who are the NHiS? The answer came from a news review by ACNR in April 2015. NHiS are a UK-based, private organisation who specialise in managing, analysing and interpreting healthcare data. The Commissioning Excellence directorate focuses on data relating to neurological conditions with an aim to allow commissioners and service providers to identify service gaps. NHiS collected data from the English Hospital Episode Statistics (HES) database which contains 1 billion records of patients who have been treated in hospital trusts in England.

The headline finding was that in 2013/14 non-elective (emergency) hospital admissions for people with MS in England cost the NHS £43 million.[1] There were 23,665 non-elective admissions of people with MS, 37% of emergency admissions were repeat admissions.[1] Unsurprisingly the most common reasons for admission were: urinary tract infections (14%), MS itself (10%), pneumonia and pneumonitis secondary to food aspiration.[1] From 2010/2011 to 2013/14 the number of elective MS admissions increased due to the increase in day-case provision of disease modifying therapies.[1] 27% of the total admissions were emergency admissions but this equated to 46% of the overall spend on care for people with MS in hospital.[1] Wide variations in admission rates and costs were noted nationally between CCGs. As there is no current, accurate record of MS prevalence across England the report could not conclude whether this variation was due to a difference in the numbers of patients with MS or a problem with community services in these areas.

The report concluded that MS Specialist Nurses, GPs and community rehabilitation teams are key in the prevention of hospital admissions for people with MS. It also supported the NICE recommendation that everyone with a diagnosis of MS should have an annual specialist review.[2] Further work is needed to establish accurate local prevalence data for MS, which is essential for future service commissioning/planning.[1]

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Clinical Signs in Neurology. A Compendium

The aim of this book can be summarised by defining the word Compendium, a point that is perhaps laboured slightly in the preface. A "concise compilation of a body of knowledge" does, however, accurately describe the contents, whose emphasis is on discussing those signs which have value in clinical practice.

An additional aim of the book is to increase the reader's familiarity with a selection of signs so specific to certain conditions that, upon recognition, the diagnosis can be made. Although the term "spot diagnosis" is perfectly adequate in describing these scenarios, I much prefer the descriptive term "augenblickdiagnose" used in the book. Campbell points out, through the medium of Goethe, that "One sees only what one knows". This emphasises the utility in familiarizing oneself with the small print of one's speciality, whilst incidentally enriching the Teutonic theme.

Although the target audience is not specified, one can infer from the wide-range of topics covered that this book has the jobbing Neurologist in mind. In my opinion, it would better serve the post-graduate neuro-enthusiast than it would the (potentially befuddled) undergraduate.

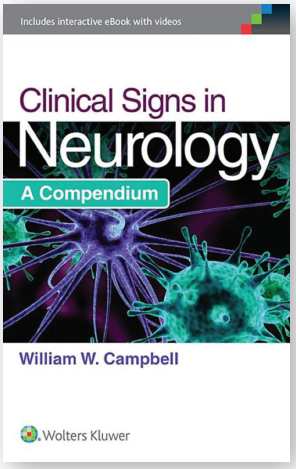
The book is organised in alphabetical order, rendering the contents page somewhat redundant. It reads like a succinct and exquisitely illustrated encyclopaedia, with a startling variety of clinical signs covered. These signs are indexed at the back, allowing for quick reference if you have a specific query. Like any book of this nature, the style is somewhat self-referential. This is not obtrusive however, and does not interfere with the reading experience. It never falls into the tedious, involutional loops of direction and re-direction that can be encountered in some reference texts.

The addition of an e-book gives a wealth of demonstrative video content. These videos were largely provided in the form of in-text links, which re-directed to a number of sources, quite a few of which appeared to be readily accessible to the intrepid googler. However, the curatorship provided in collecting these high quality resources, combined with the £0 price tag on the e-book justifies their inclusion.

I was disappointed that the author did not take the opportunity in the e-book to offer any alternatives to the alphabetical categorisation system employed in the print edition. Organisation of the signs by disease or relevant part of the neurological examination would be a useful alternative; I would have thought it well within the capabilities of the e-book.

At £45, this book represents excellent value. I might find myself reaching for it – beset by obscure, eponymous signs in historical letters, encountering a 'heretofore' unheard of finding during grand rounds or, when trying shamefully to add a little grandeur to my own examination findings in clinic. For these reasons, I think an institutional copy would be ideal.

However, I think the book's greatest success is the manner in which a brief perusal can drastically reduce the readers "unknown unknowns". This harks back to one of the original aims, to increase familiarity with one's speciality. In this, I think the book can be considered a triumph. I would recommend a personal copy to anyone with a genuine curiosity about neurology: it is as equally suited to specific interrogation as to idle exploration, with rewards to be gained from both.



Author: William W Campbell.
Published by: Wolters Kluwer.
ISBN: 978-1-4511-9445-6.
Price: £45.
Pages: 406.

Reviewed by: Ronan O'Malley, Specialist Trainee in Neurology, Royal Hallamshire Hospital, Sheffield.

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Reviewer: Luca Nart, Clare College, Cambridge.

Tauopathies are a diverse set of neurodegenerative disorders associated with the aggregation of a modified native protein – Tau – in nerve tissue. Uncovering why, where and when Tau misbehaves is one of the cornerstones of Alzheimer's research and has been a focus of funding since the central role of Tau was discovered in the late 1980s. Recent work by Myeku et al. reveals Tau's direct inhibition of a cellular refuse system, the proteasome, allowing further Tau aggregation and neuron loss in murine models. Excitingly, Myeku et al. also reveal how this inhibition can be relieved and cognitive decline reversed in vivo with use of a drug widely used in research, Rolipram.

The 26S proteasome is the destination for cellular proteins that have reached the end of their lifespan, degrading peptides for reuse or metabolism. Myeku et al used transgenic rTg4510 mice expressing a mutant tau– an animal model commonly used in tauopathy research. Primary tauopathies and tau-associated conditions such as AD commonly present as insoluble plaques of oligomeric Tau and it is these that are associated with neuronal dysfunction and eventual death. An aspect of this accumulation is reduced breakdown of Tau. Previous work by Dickey et al has confirmed the upstream effects of Tau in turning off the chaperone system that guides the protein, but the direct effects of Tau on the proteasome had remained obscure until this recent publication.

The study begins by confirming the role of reduced Tau degradation in a murine model expressing pathogenic P301L tau. They noted reduced peptidase activity and increased ubiquinated protein (the cellular tag for proteins destined for the proteasome), later confirmed in vitro with the use of ubiquinated GFP. These isolates were later shown to be physically associated with Tau, rather than interference with an upstream process. This reveals Tau's role as a proteotoxin, driving further aggregation and further proteasome inhibition. This association was further found to be restricted to pathogenic, insoluble tau rather than healthy wild-type Tau. Such a positive feedback mechanism seems to be a key of tauopathy pathogenesis.

Myeku et al extended these investigations to the role of the cAMP-PKA pathway - a crucial signaling mechanism in cells with wide-ranging effects. Increasing the activity of this system through using the phosphodiesterase (PDE4) inhibitor Rolipram restored proteasome activity both in vivo and in vitro. rTg4510 mice inoculated with Rolipram saw improved cognitive performance and spatial reference compared with control counterparts. These effects were observed when Rolipram was provided both prophylactically and at early-moderate stages of disease progression, but not at later stages of their conditions. Myeku et al later hypothesised that phosphorylation of PKA prevented possible binding of Tau to the ATPase domain of the proteasome (that provides energy for the process), similar to PrPsc seen in scrapie.

Perhaps most compelling is that these cognitive benefits are provided by Rolipram, a PDE4 inhibitor initially developed as an antidepressant in the 1990s. In spite of Rolipram being discontinued in clinical trials due to a narrow therapeutic window, the significant gastrointestinal side effects appear to have been surmounted in other PDE inhibitors licensed for use in the US, including Roflumistat for COPD. Pfizer and Merck have both entered PDE4 inhibitors into Phase II clinical trials for use in AD but results have yet to be published.

Moreover, the reversal (rather than delayed onset) of behavioural changes seen in this mouse model demonstrates an important clinical implication. Our current lack of biomarkers for cognitive impairment leaves us unable to accurately anticipate these changes in AD patients and as such treatment is often restricted to when patient cognition has already declined. A drug that has efficacy even after onset of impairment would have important applications. However, the underlying pathology of Alzheimer's still remains unclear – unlike a primary tauopathy the role of tau in AD aetiology is unclear and other major factors such as Amyloid-β aggregation are at play. It remains to be seen whether this animal model and Rolipram's effects are applicable to human AD pathogenesis.

The attraction of a small molecular drug that is affordable, with analogues in current clinical use and which can be repurposed for its neuroprotective effects is undeniable. This enthusiasm must of course be tempered by the lack of data regarding reproducibility in patients, the effects of other PDE4 inhibitors and safety concerns, but there is room for optimism yet.

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The author declares that there are no conflicts of interest.

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th Apr, 2016

February

Dementia 2016
11-12 February, 2016; London, UK
T. 020 7501 6762, www.dementiasconference.com

Is it criminal? Acquired brain injury, challenging behaviour and rehabilitation Partnerships in Care Brain Injury Services Conference 2016
24 February, 2016; Cambridge, UK
www.partnershipsincare.co.uk or contact samantha.coburn-kett@partnershipsincare.co.uk

March

An Interdisciplinary Team Approach to the Management of Patients in Prolonged Disorders of Consciousness
3 March, 2016; London, UK
E.institute@rhn.org.uk, T. 0208 780 4500 x5140, www.rhn.org.uk/events

Mental Health: Moving Forwards – The Five Year Plan
March 10, 2016; Manchester, UK
E. tickets@openforumevents.co.uk
T. (0161) 376 9007

A Multi-disciplinary Team Approach to the Assessment and Management of Huntington's Disease
16 March, 2016; London, UK
E.institute@rhn.org.uk, T. 0208 780 4500 x5140, www.rhn.org.uk/events

Treating Depression 2016
24 March, 2016; London, UK
T. 020 7501 6762, www.mahealthcareevents.co.uk

Neurology 2016: leading edge neurology for the practising clinician
30th March - 1st April 2016; London, UK
E. Jean.reynolds@ucl.ac.uk, T. 020 344 84460

April

Brain Repair Spring School – Restoring Function
6-8 April, Cambridge, UK, www.brc.cam.ac.uk

SMART Assessor Training
25-29 April, 2016; London, UK
3 March, 2016; London, UK
E.institute@rhn.org.uk, T. 0208 780 4500 x5140, www.rhn.org.uk/events

May

Managing Behaviours that Challenge in Brain Injured Individuals: The Positive Behaviour Approach
5 May, 2016; London, UK
E.institute@rhn.org.uk, T. 0208 780 4500 x5140, www.rhn.org.uk/events

An Introduction to Thermoplastic Splinting of the Upper Limb in Neurological Conditions
16- 8 May, 2016; London, UK
E.institute@rhn.org.uk, T. 0208 780 4500 x5140, www.rhn.org.uk/events

ABN Annual Meeting 2016
17-19 May, 2016; Brighton, UK
T. 020 7405 4060, E. info@abn.org.uk

Pain Therapeutics
23-24 May, London, UK
E. tarri@smi-online.co.uk, T. 020 7827 6162

2nd Congress of the European Academy of Neurology 2016
28-31 May, 2016; Copenhagen, Denmark
www.eaneurology.org/copenhagen2016

The Alzheimer's Association International Conference (AAIC) 2015

Conference details: 18-23 July 2015, Washington DC, USA. ***Report by:*** Dr Catherine Slattery, Dr Camilla Clark, and Dr Ross Paterson, Dementia Research Centre, UCL Institute of Neurology, London, UK.

In July over 4000 researchers from 60 countries came together in Washington D.C. for the Alzheimer's Association International Conference (AAIC) 2015; the world's largest gathering of researchers focused on Alzheimer's disease and other dementias.

The conference opened with a plenary talk exploring 'What will it take to end Alzheimer's disease?' As the proportion of people with dementia doubles for every five year increase in age, being able to delay the age of onset by five years is estimated to halve the number affected. The field continues its search for the elusive but much needed disease modifying therapy for Alzheimer's disease. A lively debate saw Nick Fox and Rachelle Doody discuss the relative importance of disease modification for therapies in clinical practice. This set the scene for Paul Aisen to announce the most publicised news of the conference, the open label extension of the Phase III Solanezumab Expedition Program in mild Alzheimer's disease. In brief this delayed-start analysis pooling data from two previous studies provided evidence that, whilst the effects of Solanezumab on cognitive decline were relatively small, there appeared to be a significant and sustained benefit in those who had been on active therapy the longest, consistent with a disease modifying effect. It is hoped that EXPEDITION 3, a multicentre Phase 3 solanezumab trial in mild AD expected to report in December 2016, and several ongoing studies in pre-symptomatic disease, will shed further light on these promising early findings.

Molecular PET imaging using amyloid and tau tracers in patients and pre-symptomatic individuals continues to be an area of huge interest, with ongoing studies to optimise clinical utility, standardise analytical techniques for assessing longitudinal change, and understand how results relate to other biomarkers. Michael Scholl won the Alzheimer's Imaging pre-conference prize for his presentation on in-vivo Braak staging using 18F-AV 1451 Tau PET imaging. Studies examining tau PET in atypical presentations of Alzheimer's disease showed that tau deposition is more topographically related to regional hypometabolism than amyloid deposition. A comprehensive study of amyloid PET and CSF amyloid, demonstrated that the two modalities seem to be highly comparable.

There was considerable interest in novel CSF biomarkers for aiding preclinical diagnosis, predicting disease progression and response to treatment. CSF Neurogranin, a post synaptic protein, is emerging as a promising biomarker of synaptic dysfunction, evidence that it may be an early disease marker and may predict progression from mild cognitive impairment (MCI) to dementia. Henrietta Wellington from University College London won the student poster prize for demonstrating that Neurogranin elevation may be specific to AD. With regards to novel analytical techniques, a number of elegant CSF proteomic studies demonstrated the utility of mass spectrometry in biomarker discovery and development. Kaj Blennow from the University of Gothenburg presented data suggesting an impressive performance from a fully automated ELISA platform for biomarker quantification between centres. From a clinical perspective, a large study of over 2000 individuals undergoing lumbar puncture (LP) in Amsterdam provided much needed data on the safety and risks of routine LP: low rates of headache and other complications were reported.

Bruce Miller addressed 'Frontotemporal Dementia: A quarter century of progress' and the importance of being able to predict molecular pathology from patient phenotype was emphasised now that drug therapies for FTD are beginning to emerge. Arguably the most promising are histone deacetylase (HDAC) inhibitors for individuals carrying the progranulin gene mutation. In her plenary, Li Gan explained that even a very modest boost in progranulin levels of 5-8% can be neuroprotective in animal models.

Work on vascular cognitive impairment demonstrated that neuropathologically determined microinfarcts are underdiagnosed on conventional MRI and that these lesions may contribute to the degree of clinical heterogeneity seen in amyloid positive individuals. Other personal highlights included studies of the 'oldest old' cognitive super-agers, the use of 'big data' in early detection of AD and the rise of retinal imaging for studying neurodegenerative disease.

A professional interest day organised by the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) provided the opportunity for Professional Interest Areas to meet and collaborate. At the Neuroimaging PIA, Michael Grothe summarised neuroimaging advances over the last year to the Alzheimer's Imaging Consortium, and Alan Evans's plenary on the 'Human Connectome' presented how functional brain networks defined with resting-state functional magnetic resonance imaging can be recapitulated using measures of correlated gene expression in post mortem brain tissue. With further work, this could help explain the basis of regional vulnerability in neurodegenerative disease. At the blood-based biomarkers PIA there was discussion about the challenges that continue to face the field of blood biomarkers. The online resource Alzbiomarker (www.alzforum.org/alzbiomarker), which collates knowledge of the wet biomarker field and provides meta-analysis data for key fluid biomarkers, was unveiled and will go live in Autumn 2015.

Junior researchers benefited from pre-conference sessions on basic neuropathology, animal models, and an introduction to neuroimaging in dementia. ISTAART also organised lunch time workshops on 'How to write a grant' and 'How reviewers view your manuscript' which included lots of practical tips for writing and submitting scientific papers from journal editors.

Almost 500 oral presentations and 1,500 poster presentations were given during the five day main conference. The focus remains twofold: establishing a better understanding of disease pathophysiology to identify new therapeutic targets; and developing and refining sensitive and specific biomarkers to establish the earliest onset of clinically relevant Alzheimer's pathology and to track clinically meaningful changes in response to novel therapies. Whilst there are undoubtedly many hurdles and much work remaining to be done, there are grounds for cautious optimism that drugs including Solanezumab and HDAC inhibitors may herald the start of a new era of disease modification in Alzheimer's disease and other neurodegenerative dementias.

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Wessex Dementia Collaboration Conference: Quality care, research and risk reduction in dementia

Conference details: 21 October 2015, Southampton, UK. ***Report by:*** Angus Prosser, NIHR CLAHRC Wessex, University of Southampton.

On 21st October 2015, over 150 people from more than 70 organisations involved in dementia care from Hampshire, the Isle of Wight and Dorset in the UK braved grey skies and rain to attend the 2nd annual Dementia Collaboration Conference in Southampton. The conference aimed to share and showcase good practice and innovative work in dementia care across the region, in addition to identifying actions and potential collaboration projects to further improve the support provided to dementia patients and carers. The day was hosted by three organisations – The Wessex Academic Health Science Network, Public Health England, and the Wessex Mental Health, Dementia and Neurological Conditions Strategic Clinical Network.

After an introduction by Dr Christopher Kipps, Clinical Director for the Strategic Clinical Network, the day was opened with a personal account of dementia by Nicci Gerrard, co-founder of John's Campaign. John's Campaign is a campaign to allow the families and carers of people with dementia the same rights as parents of sick children: to have the right to remain with them in hospital for as long as they are needed. Nicci Gerrard highlighted how carer-support in hospital can contribute to patients' well-being, and provide a level of attention that cannot be provided by clinical staff with time restraints. The presentation was followed by Alison McGinnes and Rachel Hayden, Clinical Nurse Specialists for long term conditions and dementia respectively, who spoke of their experience supporting John's campaign at Hampshire Hospitals NHS Foundation Trust.

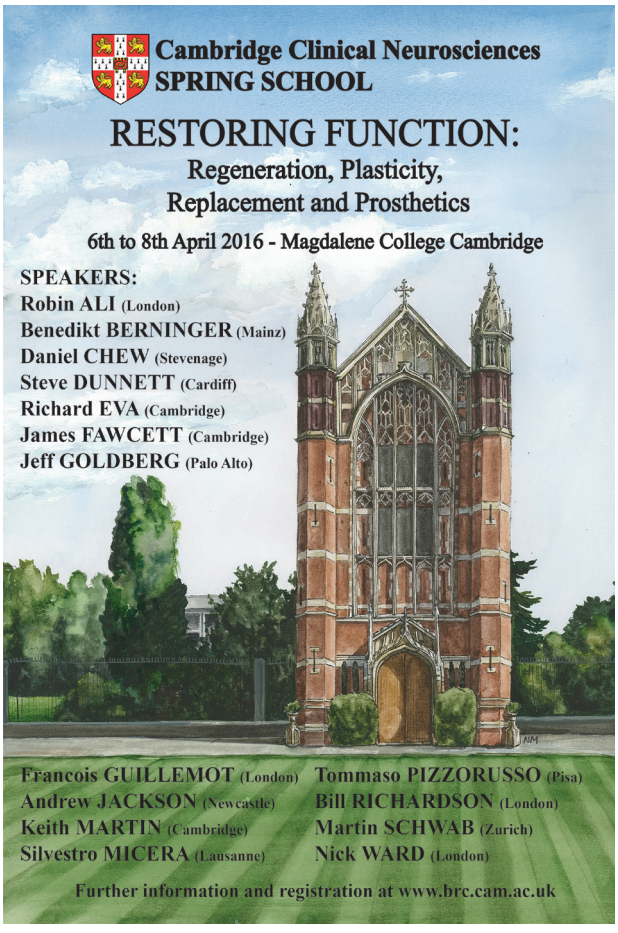
Elaine Rashbrook, Public Health England's National Lead for Older People, provided a talk on dementia risk reduction, and how it is the 'low hanging fruit' in dementia – "at best it will do good, at worst it will do no harm". Public Health England's national dementia programme was discussed, as well as the 'One You' national social marketing campaign aimed at raising awareness of actions people can take to reduce their dementia risk. Heart well-being, mood, smoking, drinking and cognitive ability were highlighted as changeable factors which could reduce the risk of dementia and delay its onset.

Professor Alistair Burns, NHS England's National Clinical Director for Dementia, presented a national dementia update that emphasised the importance of improving care across all stages of the dementia pathway, including some examples of guidelines and organisations looking at preventing well, diagnosing well, supporting well, living well and dying well. Professor Burns commended the delegates for their work across these areas.

Dr Christopher Kipps was welcomed back to the podium to officially launch the Wessex Dementia Timeline. The Wessex Dementia Timeline is a project that was developed as a visual display of dementia projects that are taking place in Wessex, with an aim to aid collaboration to improve dementia care. Dr Kipps explained that the Dementia Timeline contains over 130 projects, grouped into pre-diagnosis, diagnosis, post-diagnosis, and end of life projects. The Dementia Timeline can be viewed at http://wessexhealthlines.nhs.uk/

To round off an enjoyable and informative day on dementia care in and around Wessex, Dementia Timeline awards for projects of exceptional quality were presented. The award for the best pre-diagnosis project went to "The Journey of Dementia", an interactive theatre experience run by James Wilson aimed at raising awareness of the family experience prior to receiving a diagnosis. The "Early Diagnosis Project Wiltshire 2012-2015", which used volunteers to improve dementia knowledge at community locations to increase diagnosis rates, took away the award for the best diagnosis project. The "Dementia and Fire Safety Collaborative Working" project by the fire service and Southern Health's older people's mental health team won the post-diagnosis award for their work to reduce the risk of injury or death from fire in the home for those with dementia. The Dementia and Fire Safety and Collaborative Working project was also awarded the directors choice award by Professor Alistair Burns, who thought the project was an outstanding example of how collaborations can make a large impact in the care of people with dementia. The end of Life project award went to "End of Life care dementia training programme" by Jane Brennan, which sets out to train health and social care staff and carers of those with dementia on end of life care.

The conference provided multiple workshops throughout the day for delegates. These included interactive sessions on dementia risk reduction and prevention, utilisation of information using the Dementia Intelligence Network, workplace development for person and relationship centred dementia care, embedding dementia research into clinical practice, and creating dementia friendly environments in GP and acute care settings. Posters on current research from pre-diagnostic to end of life care in dementia research were displayed, and dementia organisation exhibition stands showcased their work.



Meningitis and Septicaemia in Children and Adults 2015

Conference details: 4-5 November, 2015, London, UK. ***Report by:*** Anna Jones, Research Officer, Meningitis Research Foundation.

Meningitis Research Foundation's 10th international conference opened with a moving talk from GB Paralympian and MRF ambassador Aaron Phipps. This patient's perspective of meningococcal disease certainly set the scene for the international audience of nearly 300 clinicians, researchers and public health professionals gathered at the Royal Society of Medicine in London. Over the two days, presentations from globally renowned experts addressed the most important issues of the day, including meningococcal, pneumococcal and Group B Streptococcal (GBS) prevention strategies, prospects for herd protection, advances from research and issues in the clinical management of sepsis and meningitis.

The packed programme of plenary sessions began with a look at current issues in clinical management of meningitis and sepsis, including a review of the new UK Joint Specialist Societies' Guideline on Acute Meningitis and Meningococcal Sepsis in Adults, two weeks ahead of its official launch. A treatment algorithm for the early management of suspected meningitis and meningococcal sepsis in hospital has been updated in accordance with the new guideline and is available free from MRF (www.meningitis.org).

In a session dedicated to Group B Streptococcus and neonatal infection, delegates heard that Malawian children with neonatal sepsis without overt meningitis have a 6.6-fold increased risk of developmental delay at 1 year of age, whilst meningitis was associated with a 17-fold increased risk. Back in the UK setting, we learned that incidence and case fatality rates of bacterial meningitis in UK neonates are unchanged over the last two decades. An in-depth study of healthcare delivery for children < 90 days old with bacterial meningitis has demonstrated unacceptable variation in clinical management. Lessons learned from this UK study are being packaged as a treatment algorithm and educational e-tool aimed at junior doctors. The session ended with a presentation about prospects for the prevention of GBS, with a maternal vaccine currently under development by GSK.

The programme then moved on to meningococcal carriage and herd protection. Data presented by Professor Sir Brian Greenwood showed that the introduction of serogroup A meningococcal vaccine (MenAfriVac) in Chad substantially reduced carriage rates and halted an epidemic caused by the bacterium. The subsequent talk considered how herd protection contributed to the huge success of the MenC conjugate vaccines in the UK and presented preliminary evidence that the decline in meningococcal disease in the UK since 2001 is likely the result of substantially reduced carriage rates. There was lively debate about whether immunisation against meningococcal B disease should be immediately introduced for adolescents, the main carriers of the bacteria.

Professor Philippe De Wals

'Preventing pneumococcal disease' was the focus of the final plenary session of day one, where delegates heard that, although highly successful UK PVC7 and PVC13 programmes have resulted in an overall reduction in invasive pneumococcal disease, this reduction is now being eroded by progressive increases in non-PVC13 serotypes and a surprising recent increase in Serotype 19A, which should be covered by PVC13. Novel pneumococcal protein vaccines currently under development (many in Phase II trials) could be used in the future to address the issue of replacement disease.

Day two opened with a fascinating presentation about the genomic techniques used to characterise a novel and highly virulent MenW ST-11 strain currently causing a year on year increase in disease cases in the UK. A later talk revealed that this same MenW strain recently expanded in Chile leading to the introduction of the MenACWY vaccine for all Chilean 9 month to 5 year olds from 2012. Although the vaccine provided direct protection for the targeted age group, no herd protection was observed in unvaccinated age groups and overall incidence rates remained similar in 2013 and 2014. This data has helped inform vaccination schedules in other countries. In the UK, the MenACWY vaccine was introduced in August 2015 in 14-18 year olds and university freshers and is intended to induce herd protection.

The morning ended with an encouraging presentation from Dr Marie Pierre-Preziosi, head of the Meningitis Vaccine Project, who described the huge success of the monovalent group A meningococcal vaccine (MenAfriVac). Since introduction of the vaccine, over 220 million persons have been vaccinated in 16 countries of the African Meningitis Belt, leading to a dramatic reduction in carriage and invasive disease. However, despite this promising news, the following presentation reported the current high incidence of MenC in Nigeria and Niger with 5000 and 8000 cases reported, respectively, between February and June 2015. This is the highest incidence of MenC ever reported in Africa. The outbreak has been attributed to a unique strain (ST10217) belonging to an unassigned clonal complex.

With the recent introduction of the MenB vaccine (Bexsero) to the UK routine childhood immunisation schedule in September 2015, many delegates were interested to learn about Public Health England's plans for enhanced surveillance and evaluation of the vaccine, during the final plenary session. Evidence for the impact of Bexsero abroad has been mixed; there have been no vaccine failures in Quebec since Bexsero was used to immunise all 2 month to 20 year olds from the end of 2014, however, vaccine induced immunogenicity against an outbreak strain at Princeton University was found to be fairly low.

In addition to the plenary sessions, 58 academic posters were displayed throughout the conference and covered a range of topics including: Epidemiology & Surveillance, Clinical diagnosis, treatment & sequelae, Vaccinology, Pathogenesis and Public Health. The prize for the best poster was awarded to Hayley Lavender's work on how genetic variation of host FH related proteins is likely to contribute to the risk of developing meningococcal disease.

Abstracts and presentation slides from the plenary sessions can be accessed at www.meningitis.org/conference2015.

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Please refer to the Summary of Product Characteristics (SmPC) for full details of Prescribing Information

COPAXONE® (glatiramer acetate) 40mg/ml Solution for Injection, Pre-filled Syringe Abbreviated Prescribing Information

Presentation: Glatiramer acetate 40mg solution for injection in 1ml Pre-filled Syringe. **Indications:** Copaxone is indicated for the treatment of relapsing forms of multiple sclerosis (MS) (see Section 5.1 of the Summary of Product Characteristics (SmPC) for important information on the population for which efficacy has been established). Copaxone is not indicated in primary or secondary progressive MS. **Dosage and administration:** Patients should be instructed in self-injection techniques and should be supervised by a healthcare professional the first time they self-inject and for 30 minutes after. A different site should be chosen for every injection. The recommended dose in adults is 40mg of Copaxone (one pre-filled syringe) subcutaneously three times a week with at least 48 hours apart. It is not known for how long the patient should be treated. A decision concerning long term treatment should be made on an individual basis by the treating physician. *Children and adolescents:* No specific studies. *Elderly:* No specific data. *Impaired renal function:* No specific studies. Monitor renal function during treatment and consider possibility of glomerular deposition of immune complexes. **Contraindications:** Known allergy to glatiramer acetate or mannitol. Pregnancy. **Precautions and warnings:** Subcutaneous use only. Initiation to be supervised by Neurologist or experienced MS physician. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Convulsions and/or anaphylactic or allergic reactions can occur rarely. Rarely, serious hypersensitivity reactions may occur. If severe, treat appropriately and discontinue Copaxone. **Interactions:** No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation:** Contraindicated in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Effects on ability to drive and use machines:** No studies have been performed. **Adverse reactions:** Serious hypersensitivity reactions have been reported rarely e.g. bronchospasm, anaphylaxis or urticaria. *Very Common:* Infection, influenza, anxiety, depression, headache, vasodilatation, dyspnoea, nausea, rash, arthralgia, back pain, asthenia, chest pain, injection site reactions, pain. *Common:* Bronchitis, gastroenteritis, herpes simplex, otitis media, rhinitis, tooth abscess, vaginal candidiasis, benign neoplasm of skin, neoplasm, lymphadenopathy, hypersensitivity, anorexia, weight increased, nervousness, dysgeusia, hypertonia, migraine, speech disorder, syncope, tremor, diplopia, eye disorder, ear disorder, palpitations, tachycardia, cough, seasonal rhinitis, anorectal disorder, constipation, dental caries, dyspepsia, dysphagia, faecal incontinence, vomiting, liver function test abnormal, ecchymosis, hyperhidrosis, pruritus, skin disorder, urticaria, neck pain, micturition urgency, pollakiuria, urinary retention, chills, face oedema, injection site atrophy, local reaction, oedema peripheral, oedema, pyrexia. Consult the Summary of Product Characteristics in relation to other side effects. **Overdose:** In case of overdose, patients should be monitored and the appropriate symptomatic and supportive therapy instituted. **Price:** Packs of 12 Pre-filled syringes £513.95. **Legal category:** POM. **Marketing Authorisation Number:** PL 10921/0026. **Marketing Authorisation Holder:** Teva Pharmaceuticals Ltd, Ridings Point, Whistler Drive, Castleford, West Yorkshire, WF10 5HX, United Kingdom. **Job Code:** UK/MED/15/0096. **Date of Preparation:** January 2016.

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 Teva UK Limited on 0207 540 7117 or medinfo@tevauk.com

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