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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

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Pre-existing depression may be unmasked during benzodiazepine use. Tolerance and physical and/or psychic dependence may develop, especially during prolonged use. Discontinuation of the therapy may result in withdrawal or rebound phenomena. Abuse of benzodiazepines has been reported. When used as an adjuvant in the treatment of epilepsy, this preparation may in rare cases cause restlessness and muscle weakness. Consult SPC for further information. **Product License Number:** PL 00156/0322 (5 mg/5 ml), PL 00156/0323 (10 mg/5 ml). **Product License Holder:** Martindale Pharmaceuticals Ltd T/A Martindale Pharma, Bampton Road, Harold Hill, Essex RM3 8UG. **Basic NHS Price:** £128.61 (5 mg/5 ml); £134.25 (10mg/5ml). **Legal Category:** POM. Further information: Martindale Pharma, Bampton Road, Romford, RM3 8UG. Tel: 01277266600. **Date of Preparation:** June 2015.

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References:
1. Tapclob 5mg/5ml Summary of Product Characteristics and Tapclob 10mg/5ml Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc /
2. MHRA. Antiepileptic drugs: new advice on switching between different manufacturers' products for a particular drug. Letter to healthcare professionals from the Commission on Human Medicines November 2013.

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PUBLISHER AND ADVERTISING Rachael Hansford
T. 01747 860168 M. 07989 470278 E. rachael@acnr.co.uk

COURSE ADVERTISING Cathy Phillips E. Cathy@acnr.co.uk

EDITORIAL Anna Phelps E. anna@acnr.co.uk

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Mike Zandi, Editor.

Diana Olszewska, Allan McCarthy, Emer Fallon, and Tim Lynch from the Mater Misericordiae University Hospital, Dublin, open this issue of ACNR with 12 clinical vignettes of genetic Parkinsonism. Six autosomal dominant (late onset), three autosomal recessive and three atypical juvenile forms are presented, as well as a discussion on the complex genetics of Parkinson's disease. Miles Levy, Leicester Endocrinologist writes on the pituitary and headache. When should one image the pituitary and arrange pituitary profile blood tests in headache disorders? And what should we make of the pituitary incidentaloma? Miles Levy writes a helpful account to provide guidance to these questions. Should antiplatelet agents be restarted after a haemorrhagic stroke, or avoided? Rustam Al-Shahi Salman, Edinburgh, and Simon Bell, Sheffield, discuss previous attempts to answer this question which have not done so definitively, and their RESTART randomised trial, which is already recruiting across 114 UK hospitals so far. A similar trial to address this question with anti-coagulant therapy is in the funding application stage. Andrew Larner turns to historical descriptions of echo phenomena, including echolalia, echopraxia and the bat-like echolocation, and their utility in refining a dementia diagnosis and relevance to catatonia.

Most of us reading will know the key mentors in our careers, and realise the immense importance of finding and keeping an effective and supportive mentor. We are all in positions to be mentors and several schemes are now providing guidance. Helen Devine and Jon Rohrer in this issue discuss the Association of British Neurologists Trainees' mentoring scheme, in which neurology registrars can be mentors to junior doctors considering a career in neurology. Other schemes include that run by the Academy of Medical Sciences for clinical academics at later stages in their careers.

We have five conference reviews in this edition, amongst which the recent 19th International Congress of Parkinson's Disease and Movement Disorders in San Diego, covered in depth by Tom Foltynie, UCL. The Grand rounds, Video Olympics and blue ribbon highlights return us to the article by Olszewska et al at the beginning of this issue, with clear and memorable clinical vignettes. We hope you enjoy this issue of ACNR and have a restful summer.

Mike Zandi, Editor
Email. Rachael@acnr.co.uk

Erratum. Wood R, Chan D. ACNR 2015;15. A draft version of this article was inadvertently published in the paper copy of our last journal and not the final proof. This is now available on line.

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.

Sian Alexander is Co-Editor of ACNR and Social Media Co-ordinator. She is an NIHR Academic Clinical Lecturer in Neurology at the University of Cambridge. She divides her time between clinical work as a Specialist Registrar in the East of England, and research into the cellular mechanisms of neurodegeneration.

Andrew Bateman is ACNR's Rehabilitation Editor. He is Clinical Lead for NeuroRehab in Cambridgeshire Community Services NHS Trust and Affiliated Lecturer in Dept of Psychiatry at University of Cambridge. He is Head of Department at the Oliver Zangwill Centre for Neuropsychological Rehabilitation, where alongside clinical work he has led research & educational activity.

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.

Rhys Davies is Editor of our Book Review Section. He is a consultant neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool and at Ysbyty Gwynedd in Bangor, North Wales. He has a clinical and research interest in cognitive neurology.

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.

Imran Noorani is Assistant Conference News Editor. He is an Academic Neurosurgery Foundation Trainee in Southampton General Hospital having trained in Cambridge. His academic interest is oculomotor neurophysiology, specifically models of saccadic decision and their potential application to neurological disorders.

David Werring is ACNR's Stroke Editor. He is Reader in Clinical Neurology, UCL Institute of Neurology,National Hospital for Neurology and Neurosurgery,Queen Square, WC1N 3BG.

Alastair Wilkins is our Case Report Co-ordinator. He is Senior Lecturer in Neurology and Consultant Neurologist, University of Bristol. He trained in Neurology in Cambridge, Norwich and London. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis.

Peter Whitfield is ACNR's Neurosurgery Editor. He is a Consultant Neurosurgeon at the South West Neurosurgery Centre, Plymouth. His clinical interests are wide including neurovascular conditions, head injury, stereotactic radiosurgery, image guided tumour surgery and lumbar microdiscectomy. He is an examiner for the MRCS and is a member of the SAC in neurosurgery.

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 University Lecturer in Neuroimmunology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.

Recognising the phenotype of genetic forms of Parkinson's disease in clinical practice

Diana Olszewska *
is a Neurology Research Fellow at the Dublin Neurological Institute, Mater Misericordiae University Hospital with a particular interest in genetics of Parkinson's disease.

Dr Allan McCarthy *
is a Locum Consultant Neurologist at The Adelaide and Meath Hospital in Dublin with interest in movement disorders.

Ms Emer M Fallon
is a Research Coordinator at the Dublin Neurological Institute, Mater Misericordiae University Hospital.

Professor Tim Lynch
is a Consultant Neurologist at the Mater Misericordiae University Hospital, Director of the Dublin Neurological Institute, and Clinical Investigator at the Conway Institute, University College Dublin. Professor Lynch is a widely known expert in Movement disorders with a particular research interest in Parkinson's disease, genetics of Parkinson's disease, Parkinsonism, and genetics of atypical dementia.

Correspondence to:
Dr Diana A Olszewska,
Dublin Neurological Institute,
Mater Misericordiae University Hospital,
Dublin.
E: diana.angelika.olszewska@gmail.com

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Introduction

Parkinson's disease (PD) is a heterogeneous, neurodegenerative disorder affecting 6.3 million people worldwide and 1.2 million in Europe.[1] The annual cost to Europe is estimated at 13.9 billion euro[2,3] and the numbers are predicted to double by 2030.[4] PD places a huge socio-oeconomic burden on Western economies and poses a major challenge for patients and society. Only symptomatic treatment is available. Traditional linkage analysis, gene cloning and Genome Wide Association Studies (GWAS) have identified several loci and genes associated with monogenic PD. The study of monogenic forms of PD may lead to the identification of new targets for pharmacotherapy and these may ultimately translate into new therapies for sporadic PD. However, treatment developed using these new technologies may only be effective for specific genetic mutations eg. kinase inhibitors for *LRRK2* mutations. GWAS and linkage analysis have identified 18 Parkinson's disease loci (*PARK*) numbered in a chronological order. This classification is imperfect as it contains both confirmed and unconfirmed loci (loci not replicated) and the causative gene remains unknown for many loci. Additionally one of the proposed loci was later found to be previously reported (PARK4 and PARK1).[5]

Mutations in seven genes cause either autosomal dominant (*SNCA, LRRK2, VPS35),* or autosomal recessive *(Parkin, DJ1, PINK1, ATP13A2*) familial PD.[5] Moreover some of these genes contain polymorphisms which act as risk factors for the development of PD.[6]

Clinical signs can be used to suggest 'typical' or 'atypical' forms of PD. Age-of-onset is used to classify PD into juvenile-onset (< 20 years), early-onset (between 20 and 40 years) and late-onset (>60 years) disease (Figure 1). The majority of patients have sporadic disease.[6] Although the true Mendelian forms of PD are rare (occuring in 30% of familial and 3-5% of sporadic PD)[5] there is a positive family history in 10% of patients with apparently sporadic PD.[6]

The pattern of inheritance may be elusive at times e.g. reduced penetrance associated with autosomal dominant inheritance may mimic recessive disease. In addition, heterozygote mutations in certain 'recessive' genes have been associated with late onset disease, possibly because of partial expression of the corresponding protein.[5]

Autosomal dominant mode of inheritance: (Table 1)

1. *SNCA (PARK1/PARK4)*, OMIM: 163890

In 1997, the first mutation linked to autosomal dominant monogenic PD was reported by Polymeropulous.[7] The mutation (A53T) in a large Italian kindred (the Contoursi kindred) occurred in the synuclein gene (*SNCA*). *SNCA* encodes α (alpha)-synuclein (*PARK 1/PARK 4*) which is a small, 140-amino-acid protein[8] abundant in Lewy bodies. Subsequently two other point mutations A30P (described in one German family) and E46K (one Basque family) were described.[5,9] All three mutations are very rare, with A53T being the most common (reported in one Italian, eight Greek, two Korean and one Swedish families).[5,9] Aside from point mutations, multiplications of *SNCA* may also occur. Duplications were found in thirteen families with monogenic PD and four sporadic PD cases, while triplications were described in three independent families.[5]

The age-of-onset in the A53T families is typically between 40 and 50 years of age, and is associated with asymmetrical bradykinesia, rigidity,[7] good levodopa-responsiveness, dysautonomia, and less commonly rest tremor.[10] The course of the disease is rapidly progressive (the interval from the onset to death is 10 years) (Table 1).

The A30P mutation is associated with a later age-of-onset (60 years (+/-11)), and mild dementia may occur.[11] The E46K mutation is linked with dementia and visual hallucinations (dementia with Lewy bodies)[11] (Table 1).

Disease-onset associated with duplications occurs at around 50 years and the age-of-onset associated with triplications is earlier at 38 years (+/-13).[10] Therefore a gene dosage effect is present, in which triplications are associated with a 100% increase in protein expression resulting in a younger age-of-onset and more rapid disease progression. In comparison duplications are associated with a 50% increase in protein expression[12] and later-onset monogenic PD with slower disease progression and cognitive and psychiatric decline.[10] Triplications are commonly linked with dysautonomia.[13]

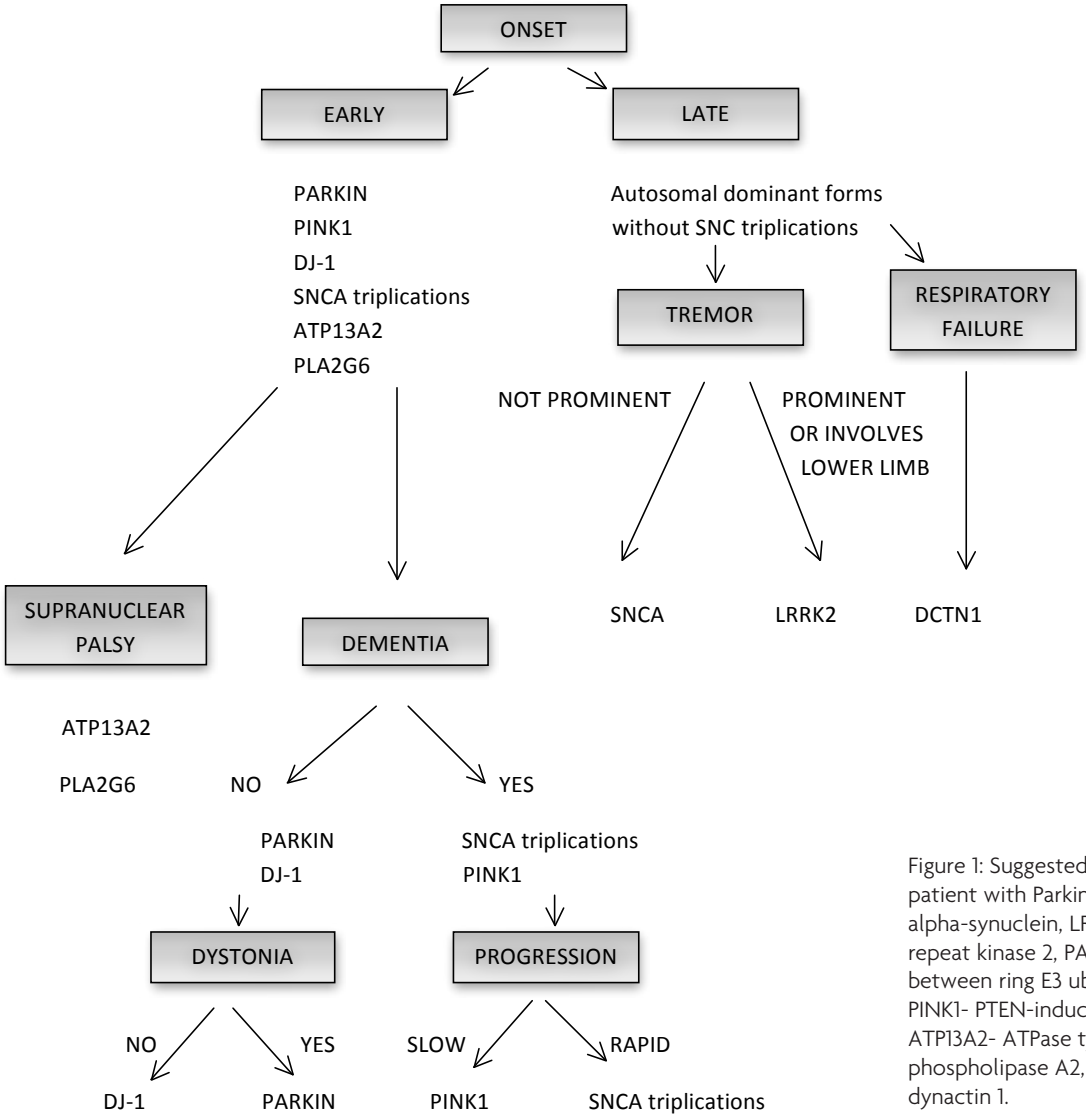

Figure 1: Suggested approach to a patient with Parkinson's disease: SNCA-alpha-synuclein, LRRK2-leucine-rich repeat kinase 2, PARKIN-parkin ring in between ring E3 ubiquitin protein ligase, PINK1- PTEN-induced putative kinase 1, ATP13A2- ATPase type 13A2, PLA2G6-phospholipase A2, group 6, DCTN-1-dynactin 1.

Therefore *SNCA* duplications and triplications should be considered in patients with an early-onset Lewy body disease picture in which early cognitive impairment and autonomic dysfunction is seen (Figure 1).

In 2013 two new *SNCA* point mutations were reported: H50Q and G51D. The H50Q mutation was described in a British patient with onset at 71 years and a Canadian-British patient origin with onset at 60 years. Disease was characterised by good levodopa-response and cognitive decline.[11,14] The G51D mutation was reported in seven patients from British and French families and it was associated with dysautonomia, pyramidal signs, depression, anxiety,[10,11,14] and cognitive decline.[12] Age-of-onset was before 40 years, levodopa-response was moderate, and the monogenic PD had a rapid course with death within 10 years.[12]

2. *LRRK2* (Leucine-rich repeat kinase 2) (*PARK8*), OMIM: 609007

LRRK2 mutations in PD were identified in 2004 and subsequently were found to be the most common cause of autosomal dominant monogenic PD. *LRRK2* is a large gene with 54 exons, encoding a 2527 amino-acid protein.[13] It is responsible for 5-15% of autosomal dominant familial, monogenic PD and approximately 1% of sporadic PD in Caucasian patients.[6] Previous studies in Ireland reported 1 mutation in 236 sporadic patients (<1%) and 1 mutation in 35 familial patients (3%).[15] However, our follow up study of 133 Irish patients with familial PD found only 2 patients (1.5%) with *LRRK2* mutations and 1 (0.26%) patient of 388 in sporadic PD.[16,17] Therefore we found 3 (0.58%) patients with *LRRK2* mutation in 521 patients with familial and sporadic PD.

Over 100 gene variants[18] have been described with 7 mutations proven to be pathological.[12] The most common mutation is G2019S[12] and is most prevalent in the Middle East, Portugal, Spain and Italy with a north-south gradient evident in Europe.[12,15,18] In Ashkenazi Jews the frequency is 29.7% in familial cases and 13.3% in sporadic cases and increases to approximately 40% in sporadic and in familial cases in North African Berbers.[6,15] Onset is by age 59 with slower progression, less frequent dementia, and a more benign course than sporadic PD[6] (Table 1). Tremor is the cardinal symptom, reported in 60-99% of patients.[10] An abduction-adduction leg tremor is more prevalent in *LRRK2*-associated disease.[18] The most common pathological features are Lewy bodies with tau and ubiquitin staining being less common. Symptomatic treatment is typically required later in the disease course and patients are less prone to dyskinesia.[18] Patients with the G2019S mutation are more prone to dystonia in the first two years.[18] Penetrance increases with age with a risk estimation of 28% at 59 years and 74% at 79 years.[15]

3. *VPS35* (Vacuolar sorting protein 35), OMIM: 601501

In 2011 a mutation p.Asp620Asn (D620N) in *VPS35* gene was described[12] in familial and rarely in sporadic PD. It is the only pathogenic *VPS35* mutation found to date and was the first PD-related pathogenic mutation discovered using next generation sequencing. The phenotype resembles sporadic PD with an earlier age-of-onset at 60 years, rare dementia and a good response to levodopa[12] (Table 1). Depression is more common.[19] Pathological features include gliosis, tau and alpha-synuclein inclusions.

Table 1: Known Parkinson's disease phenotype characteristics:

AD – autosomal dominant, AR – autosomal recessive, Park – Parkinson's disease loci, *SNCA* – alpha-synuclein, *LRRK2* – leucine-rich repeat kinase 2, *VPS35* – vacuolar sorting protein, *EIF4G1* – eukaryotic translation initiation factor 4 gamma 1, *DCTN1* – dynactin 1, *DYT12* – rapid onset dystonia-parkinsonism, *UCHLI* – ubiquitin carboxyl-terminal esterase li, *HTRA2* – htrA serine peptidase 2, *PARKIN* – parkin ring in between ring E3 ubiquitin protein ligase, *PINK1* – PTEN-induced putative kinase 1, *ATP13A2* – ATPase type 13A2, *PLA2G6* – phospholipase A2, group 6, *FBXO7* – F-box protein 7.

Pattern of inheritance	Loci / Gene	Mutations described	Mean age of onset	Clinical phenotype	Levodopa response	Course
AD	*PARK 1/4 SNCA*	A53T (most common)	40-50	Asymmetrical bradykinesia, rigidity, dysautonomia rare tremor	Good	Rapid
		A30P	60 (+/-11)	Mild dementia		
		E46K		Dementia, visual hallucinations		
		Duplications	50	Cognitive, psychiatric		Slower
		Triplications	38 (+/-13)	Cognitive, psychiatric dysautonomia		Slower, More severe
AD	*PARK 8 LRRK2*	G2019S	59	Less frequent dementia, tremor common abduction-adduction leg tremor, dystonia in the first 2 years, rarely before dopamine replacement	Rx later than IPD, less dyskinesia	Slow, More benign than IPD
AD	*VPS 35*	D620N	60	Resembles IPD, rare dementia, depression more prevalent	Good	
AD	*EIF4G1*	A1205H	Late	Cognition intact	Good	Slow
AD	*DCTN 1*	8 mutations described	50-60	Depression, weight loss, hypoventilation, Respiratory failure, mild parkinsonism	Moderate	
AD	*DYT 12*	ATP1A3	20-30	Dystonia>parkinsonism, dysphagia, dysphonia, depression, psychosis, alternating hemiplegia, explosive onset	Poor	
Role questionable AD	*PARK 5 UCHLI PARK 11 GIGYF2 PARK 13 HTRA2*	1 family only	49-51	Typical	Good	
AR	*PARK 2 PARKIN*	Over 200 mutations described	36	Early dyskinesia, motor fluctuations, dystonia, no dementia, diurnal variation with sleep, no LB	Excellent	Slow
AR	*PARK 6 PINK1*	Over 60 mutations described	24-47	Dementia, anxiety, depression	Good	Slow
AR	*PARK 7 DJ-1*	10 mutations described	20-40	Psychiatric features	Good	Slow
AR (Atypical)	*PARK 9 ATP13A2*	10 mutations described	11-16	Pyramidal signs, dementia, supranuclear gaze palsy, reports of more typical PD		Rapid
AR (Atypical)	*PARK 14 PLA2G6*	Many described	Infant (<2)	Spasticity all limbs, cognitive decline, bulbar dysfunction, dystonia, cerebellar ataxia	Responsive, but short-lived, incomplete and associated with early dyskinesia	
		4 mutations described	Early adult	Dystonia-parkinsonism, pyramidal signs, cognitive dysfunction, LB, absence of cerebellar signs reported, reported iron accumulation in a brain.		
AR	*PARK 15 FBXO7*	4 mutations described	Juvenile	Pyramidal signs, early dystonia	Responsive	Progressive

4. *EIF4G1* (Eukaryotic translation initiation factor 4 gamma 1), OMIM: 600495.

In 2011 mutations in *EIF4G1* were reported in monogenic and sporadic PD.[20] The only confirmed mutation associated with PD is A1205H, described in French families and one Irish patient (Table 1) who is a 66-year old Irish man with levodopa-responsive parkinsonism. He developed dyskinesia 15 years after onset treated successfully with deep brain stimulation. He later developed visual hallucinations and dementia 29 years after onset[17] There is inconclusive evidence as to whether other EIF4G1 mutations could be pathological.[6]

5. *DCTN1* (Dynactin 1) mutations in Perry syndrome, OMIM: 601143

While rare, the syndrome has a very characteristic clinical profile of early-onset parkinsonism, depression, severe weight loss and hypoventilation which can culminate in respiratory failure[21] (Table 1). Eight autosomal dominant mutations described in 16 families are causative.[22] Patients typically present in the fifth or sixth decades, with mild parkinsonism and a moderate response to levodopa. Patients succumb to respiratory failure; early diagnosis may improve quality of life and potentially offset episodes of respiratory failure with the use of nocturnal bipap or a diaphragmatic pacemaker (Figure 1).

6. Rapid onset dystonia parkinsonism / DYT12, OMIM: 182350

The rapid onset of dystonia over a period of days to weeks, frequently after times of stress with associated dysphagia, dysphonia and parkinsonism in the second and third decades

of life are the cardinal clinical features of this autosomal dominant disorder (dystonia more prominent than parkinsonism)[23,24] (Table 1). Non-motor symptoms such as psychosis, depression and anxiety may be present. Mutations in the *ATP1A3* gene are causative. More recently mutations in this gene have been associated with alternating hemiplegia of childhood with early-onset dystonia (<18 months), developmental delay and fluctuating consciousness.[23]

Autosomal recessive forms:

Some of the unique characteristics, with some overlap, associated with *Parkin*, *PINK1* and *DJ-1* are described below[5] (Figure 1).

1. *PARKIN (PARK2)*, OMIM: 602544.

Parkin was the first autosomal recessive gene linked to PD.[5] It encodes a 465 amino-acid protein, the second largest gene in the human genome.[5] Parkin is responsible for 50% of autosomal recessive monogenic PD and 15% of the sporadic early-onset (<45) PD.[12] Parkin-related disease has a mean age-of-onset of 36 years (associated with homozygous and compound heterozygous mutations)[25] and an excellent response to levodopa therapy.[26,27] Over 200 mutations have been described (up to May 2015).[28] The phenotype is characterised by early dyskinesia in feet and legs,[29] motor fluctuations, symmetric onset, hyperreflexia, frequent dystonia[6] and a slow disease course without dementia (Table 1).[30] The lowest effective levodopa dose should be prescribed. The recognition and diagnosis of parkin-related disease has implications for both treatment and prognosis in these younger patients. Diurnal variation with sleep benefit occurs.[9] Lewy bodies are not present.[26,27] Parkin can be thought of as a 'nigropathy', a less diffuse process without the development of cognitive impairment or anosmia.[27,31] Pathology is predominantly restricted to brainstem without Lewy bodies similar to that found in the "frozen addicts" post MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine).

2. *PINK1* (PTEN- induced putative kinase 1), (PARK6), OMIM: 608309

PINK1 is a 581 amino-acid protein kinase with over 60 mutations reported.[5] Mutations in *PINK1* are responsible for 2-4% early-onset monogenic PD in Caucasians and 4-9% in Asians.[6] Similarly to the phenotype associated with Parkin mutations disease progression is slow and response to levodopa is good. Sense of smell is less likely to be affected than in sporadic PD.[31] Psychiatric co-morbidity and gait disturbance is common in PINK1 compared to Parkin (Table 1, Figure 1).[32,33] The one reported post-mortem of a patient with compound heterozygote mutation showed substantia nigra pars compacta neuronal loss, Lewy bodies and aberrant neuritis in brainstem, pars compacta and nucleus of Meynert with sparing of the amygdala and locus ceruleus.[32]

3. *DJ-1 (PARK 7)*, OMIM: 602533

DJ-1 occurs in 1-2% of an early-onset of monogenic PD and there are 10 mutations described to date. The phenotype is similar to that of *Parkin* with an early-onset disease between the ages 20 and 40, good levodopa response and slow progression (Table 1, Figure 1).[6] Psychiatric (cognitive impairment, anxiety and depression) features are also reported.[6]

Genes associated with juvenile onset, atypical forms of parkinsonism:

1. *ATP13A2* (ATPase type 13A2), (*PARK9*) (Kufor-Rakeb syndrome), OMIM: 610513

ATP13A2 is a large gene encoding a 1180 amino-acid protein with 10 known pathogenic mutations.[5] Kufor-Rakeb syndrome is named after a village in Jordan, where the disease was first described in 1994.[33] The phenotype is one of very early-onset disease between the ages of 11 and 16 years, recessive pattern of inheritance, rapid progression, atypical features, pyramidal signs, supranuclear gaze palsy[5] and dementia, and facial-faucal-finger minimyoclonus (Table 1).[6,12] Recent reports describe more typical early-onset PD.[13]

2. *PLA2G6* (Phospholipase A2, group 6) (*PARK14*), OMIM: 603604.

PLA2G6 displays recessive inheritance, with disease onset ranging from infantile to early adulthood. In infants the onset is before the age of two years[35] and is associated with spasticity in all limbs, cognitive decline, bulbar dysfunction, dystonia and cerebellar ataxia. Homozygous mutations in *PLA2G6* can occur in adults with a levodopa-responsive dystonia-parkinsonism, pyramidal signs, cognitive dysfunction, Lewy body disease and sometimes iron accumulation in the brain (table 1).[6,12,36] There is a debate as to whether heterozygote "carriers" manifest the disease. For example a 28-year-old woman had a single heterozygote (c.238 G>A p.A80T) mutation in *PLAG2G6* with a phenotype in keeping with *PARK14*. She had difficulty speaking, marked tremor, bradykinesia, rigidity, ataxia and anxiety at the age of 18. She developed laterocollis, retrocollis, hand dystonia, dysarthria, dysphonia, limited vertical and horizontal gaze, freezing episodes, marked on dyskinesia and suboptimal response to levodopa. There was a late-onset parkinsonism with dystonia in two paternal grand aunts.

3. *FBXO7* (F-box protein 7) (*PARK 15*), OMIM: 605648

FBXO7 encodes a 522 amino-acid protein with four known mutations causing juvenile, progressive, recessive levodopa responsive Parkinsonism. Pyramidal signs and early dystonia also occur (Table 1).[37,38]

Genetic risk factors:

1. *GBA*, OMIM: 606463.

Recessive mutations in *GBA* (glucocerebrosidase) gene cause Gaucher's disease, while heterozygote mutations increase by five fold the risk of developing late-onset PD.[39] Mutations in GBA are more prevalent in Ashkenazi Jews (19.6% in comparison to 6.9% of non-Ashkenazi Jewish patients in one study).[5] The phenotype is levodopa-responsive parkinsonism with a slightly earlier age-of-onset,[12] early motor complications and higher prevalence of dementia.[40]

2. *LRRK2* risk factors and protective loci

Ross et al. carried out an assessment of 121 exonic *LRRK2* variants in 8,611 patients and 6,929 controls from Caucasian, Asian and Arab Berber populations.[41] Carriers of known mutations were excluded and risk associations were described for polymorphisms in Caucasians (p.M1646T) and Asians (p.A419V). Risk association in Asians with p.G2385R was confirmed, while no association was described for p.R1628P. Lastly P.Y2189C could possibly be a risk factor in the Arab-Berber population.[41]

Ross et al. also identified a common three-variant haplotype (N551K-R1398H-K1423K) that seemed to act in a protective manner and suggested that the reduced penetrance found in LRRK2-associated monogenic PD might be due to variants acting in cis or trans with the pathogenic variant. It is possible that LRRK2 activity influences symptom onset and any future therapeutic suggestions that lower risk in LRRK2 associated monogenic PD might protect against symptomatic onset in sporadic PD. For example the protective R1398H variant has reduced kinase activity suggesting this Roc domain substitution might be the most likely functional allele on the haplotype.[41]

Conclusion

While PD is a complex disorder, certain clinical features combined with age-of-onset may guide the clinician as to which gene should be tested. The clinician should decide on a pattern of inheritance guided by a family pedigree first. When PD occurs in every generation, with one parent or 50% of children affected, it suggests an autosomal dominant pattern. In autosomal recessive inheritance the disease skips generations, parents are not affected (carrier state) and only 25% of the siblings have PD (although reduced penetrance in autosomal dominant inheritance may mimic recessive disease).[5] Secondly, it is important to establish the age-of-onset of PD and associated clinical features. In general, late onset PD is associated with autosomal dominant forms (except *SNCA* triplications) with prominent tremor or tremor involving the legs suggesting *LRRK2* (adduction-abduction leg tremor)[18,40] and lack of tremor associated with *SNCA*-related disease (Figure 1). Information about the ethnicity of the patient may be useful. For example an autosomal dominant picture in a patient originating from the Middle East, of Jewish ancestry or from North Africa is highly suggestive of the G2019S *LRRK2* muta-

tion. Patients with late forms of the disease associated with rapid progression, weight loss and respiratory failure should prompt screening of the *DCTN1* gene associated with Perry syndrome (Figure 1). Early onset PD is associated with autosomal recessive forms and SNCA triplications (Figure 1). While the patient with early onset PD with dementia and rapid progression should be tested for *SNCA* triplications, patients with dementia but slow progression should be screened for *PINK1* (Figure 1). Patients with early-onset monogenic and sporadic PD and normal cognition, slowly progressive disease, good levodopa response, early dystonia or leg dystonia should have *PARKIN* screening performed. If Parkin testing is negative or dystonia is not a feature then *DJ1* screening should be considered. Juvenile-onset disease associated with atypical features can often point toward a specific gene. Early-onset parkinsonism with supranuclear palsy, pyramidal signs and dementia is characteristic for mutations in *ATP13A2* and *PLA2G6* (Figure 1). Suggested approach to the genetic testing in a PD patient is proposed in Figure 1.

Parkinson's disease is responsible for a growing burden on society and health care services. As more genetic associations are described for this complex disorder, more potential therapeutic targets will emerge. While no drugs have yet come to market based upon genetic data, new insights are uncovering the molecular pathways involved in disease pathogenesis. Future therapies may only benefit patients with a particular genetic profile and certain side effects may be predicted in others. The advent of cheaper next generation sequencing technology will lead to even further associations and risk loci being uncovered. Large scale clinical studies to tease out genotype-phenotype correlations may lead to genomic 'risk' profiles. For example, individuals harbouring *SNCA* duplications may benefit from knock-down therapy while those with *LRRK2* mutations may benefit from a kinase inhibitor, probably with treatment commencing in the pre-disease 'at risk' state. However, a much clearer understanding of the biological pathways involved will be needed to ensure that the correct molecular targets are identified while minimising the potential side effects.

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Pituitary headache

Miles J Levy
is a Consultant Endocrinologist and Honorary Senior Lecturer at the University Hospitals of Leicester and Leicester Medical School.

Correspondence to:
Email: miles.levy@uhl-tr.nhs.uk

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The ready access to brain imaging has resulted in an increased detection of incidentally discovered pituitary lesions. Radiological and post mortem studies report the prevalence of pituitary incidentalomas to be as high as 10%.[1] Exclusion of secondary headache is a frequent clinical indication for brain imaging. It is therefore not uncommon to be faced with a patient with both headache and a pituitary abnormality. The clinician must decide if the pituitary lesion is of any relevance to headache or a purely incidental finding. The aim of this article is to review the association between pituitary tumours and headache, and to suggest a pragmatic approach to investigation and management.

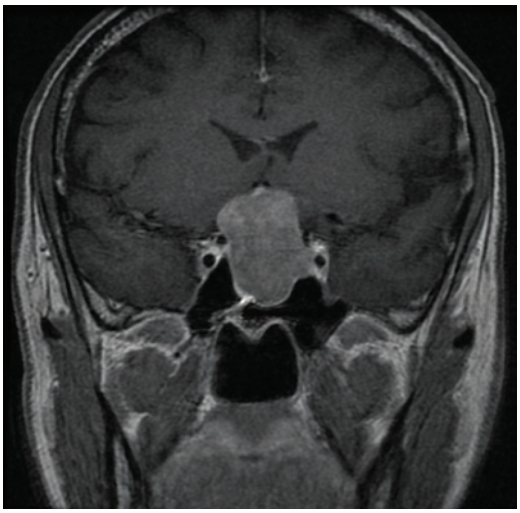

Figure 1: Large pituitary macro-adenoma with no headache

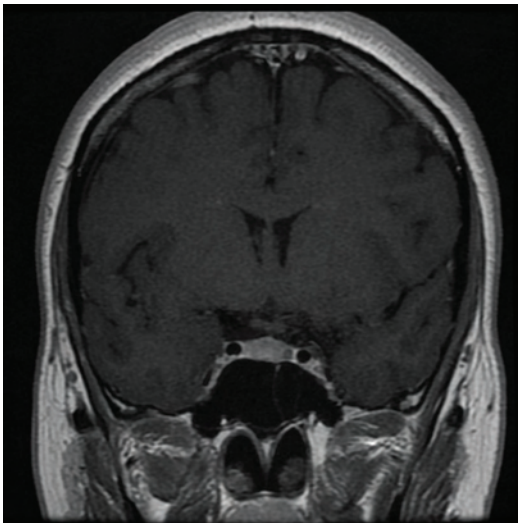

Figure 2: Small micro-adenoma may present with severe headache

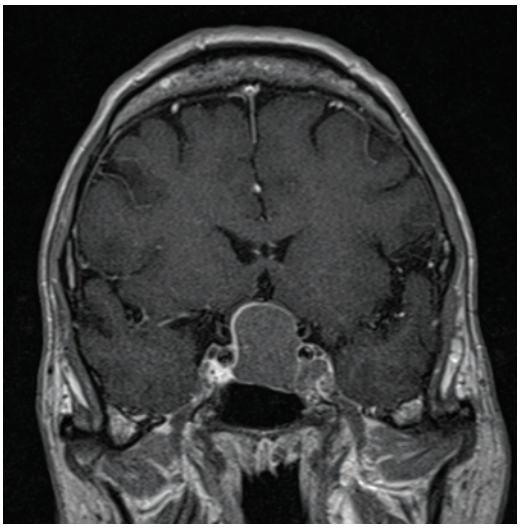

Figure 3: Left-sided cavernous sinus invasion with ipsilateral headache

Mechanism of headache in pituitary tumours

Pituitary tumours come to clinical attention as a result of their endocrine activity, the physical consequences of the lesion, or both. Whilst visual loss and hypopituitarism are clearly a result of compression of local structures, it is not clear if headache is a purely physical phenomenon. The traditional explanation of headache in pituitary tumours is dural stretch, but there is little evidence of an association between tumour size and headache.[2] Large pituitary lesions can present with no headache at all (Figure 1), whilst small secretory micro-adenomas (<1 cm) may cause debilitating headache (Figure 2). Therefore, whilst headache is undoubtedly common in pituitary tumours, with a prevalence of 30-70%,[3,4] the mechanism is far from clear.

The cavernous sinus contains the first and second branches of the trigeminal nerve and the internal carotid artery, which are potentially significant structures as regards headache (Figure 3). Despite this, prospective studies have shown no relationship between ipsilateral cavernous sinus invasion and headache.[2,5] This further suggests that physical mechanisms are not a satisfactory explanation for pituitary headache. Despite these negative studies, the cavernous sinus cannot be completely dismissed as some pituitary tumour patients have cavernous sinus disease with severe ipsilateral headache.[6] Headache with ipsilateral cavernous sinus invasion may have pronounced cranial autonomic features, which can dramatically improve after medical or surgical treatment.[7-9] There are several reports of patients with macroprolactinomas invading the cavernous sinus presenting with ipsilateral refractory headache, which resolves within days of dopamine agonist treatment.[7-9] Pituitary apoplexy is a specific situation whereby an acute vascular event within a pre-existing pituitary tumour gives rise to severe headache and diplopia. The mechanism of pain and cranial nerve palsy

in apoplexy is probably via irritation of the 5th nerve, and 3rd, 4th and 6th nerves respectively.

There is no doubt that endocrine activity of the tumour can be relevant to pituitary headache. Acromegaly commonly has headache as an early feature, and this can be a useful clinical marker of disease activity. Somatostatin analogues, commonly used in the medical management of acromegaly, can have an immediate analgesic effect on headache. Interestingly, the control of headache and growth hormone (GH) suppression do not always go hand in hand, suggesting that the mechanism of somatostatin analgesia is not directly related to GH per se.[10] It is hypothesised that pituitary headache may be caused by the secretion of an un-measured pro-nociceptive peptide that is suppressed by somatostatin. Prolactinoma and TSHoma patients may be associated with headache that is reproducibly aborted by somatostatin, supporting the idea of a hitherto unidentified pain-producing peptide being actively secreted in pituitary tumours.[11]

The hypothalamo-pituitary axis is known to be an important anatomical area in the pathophysiology of primary Trigeminal Autonomic Cephalgias (TACs). Functional imaging studies (fMRI and PET) demonstrate ipsilateral hypothalamic and cavernous sinus activation.[12] Pituitary tumours have a higher prevalence of TACs than the general population,[6] re-enforcing the view that this part of the brain is important in headache.

The genetic susceptibility of patients to headache may be as significant as tumour properties per se. A family history of headache is a predictive associative factor for pituitary headache.[6] Therefore pituitary headache is likely to be a heterogeneous phenomenon dependant on the biochemical and physical characteristics of the tumour, as well as the genetic susceptibility of the patient to headache.

Pituitary incidentaloma

When an incidental pituitary lesion is discovered, it is important to rule out clinical signs of endocrine disease. Women should be asked about hyperprolactinaemic symptoms, including menstrual irregularity, fertility problems and galactorrhoea. Clinical signs of acromegaly and Cushing's syndrome should be looked for. In early acromegaly subtle soft tissue signs may be present including carpal tunnel syndrome, increased snoring due to palatal oedema, and mild facial changes. Old photographs or previous self-images on mobile phones are useful to look for changes in appearance that patients and their families may not have recognised. In suspected Cushing's syndrome, the presence of bruising and thinning of skin are particularly useful discriminatory features.

Serum prolactin is the most cost effective single test for a pituitary incidentaloma, a level > 1000 miU/L usually signifying a prolactinoma if no other causes of hyperprolactinaemia are found.[13] In suspected acromegaly, a random GH and IGF-1 level is useful, although a formal OGTT with failure to suppress GH confirms the diagnosis. Assessment of thyroid status with fT4 and TSH will exclude TSH deficiency (low T4 with low or normal TSH) and TSHoma (high T4 and non-suppressed TSH). Screening tests for Cushing's syndrome include 24h Urine Free Cortisol, overnight Dexamethasone Suppression Test (DST) or formal low dose DST, and are only needed if clinically indicated.

Clinical Features of Pituitary Headache

The International Headache Society (I.H.S) Headache Classification System allows the clinician to formally classify headache attributed to hypothalamic or pituitary hyper- or hyposecretion (I.H.S 7.4.4). It is useful to biologically phenotype the headache, because appropriate headache treatment will often lead to clinical response without the need to treat the pituitary lesion per se. The commonest headache phenotype in patients with pituitary tumours is chronic migraine.[6] It is likely that the endocrine changes caused by a pituitary lesion trigger migraine in a predisposed individual. This is particularly common in young women with micro-prolactinoma, the same demographic as those predisposed to migraine. Hyperprolactinaemia commonly causes exacerbation of migraine via alteration in female hormones, rather than as result of any mass effect. The full range of TACs has been described in association with pituitary tumours, including cluster headache, SUNA, paroxysmal hemicrania and hemicrania continua, at a higher prevalence than the general population.[4,6] TACs occur with small and large, non-functioning and functioning pituitary tumours and the precise mechanism is unclear. A sub-group of patients have headache that can only classified under I.H.S 7.4.4 and we have suggested modification of this to include the presence or absence of cavernous sinus invasion.[6] Future studies are required to determine which specific clinical features are exclusive to pituitary tumours.

Management Approach

The clinician must always consider that the pituitary lesion is incidental to headache. Standard pharmacological prophylactic or abortive headache treatment often leads to improvement in symptoms. If there are signs of endocrine excess, the pituitary lesion should be treated conventionally. Normalisation of endocrine status may lead to resolution of headache without the need for specific headache treatment. Dopamine agonist treatment of prolactinoma will usually lead to improvement of associated headaches. In acromegaly, surgical or medical treatment will often lead to abolition of headache, although somatostatin analogue over-use should be avoided.[14] Surgical treatment of macro-adenoma will lead to improvement in headache in nearly 50% of patients.[6] A difficult problem can be the patient with a pituitary macro-adenoma who presents with troublesome headache and ipsilateral cavernous sinus invasion. In this situation, headache should not be the sole indication for surgery, as there is no guarantee of resolution of symptoms. The usual indications for hypophysectomy are visual loss as well as endocrine control of the tumour. The American Endocrine Society lists unremitting headache as a relative indication for surgery,[13] but it should be made clear to the patient that headache may not resolve post-operatively. Tumours that invade the cavernous sinus are relatively inaccessible surgically, even with the recent development of endoscopic surgery. Post-operative residual cavernous sinus disease should be managed in a multi-disciplinary setting both by the pituitary team and a dedicated pain or headache specialist. Potential therapeutic options include treatment of the tumour bulk itself with external beam or gamma knife radiotherapy, and specific management of the pain with the use of drugs or specific interventions to down-regulate trigemino-vascular pathway.

Summary

Pituitary tumours commonly present with headache and it is useful for the clinician to have a system for dealing with this problem. Full assessment of the headache phenotype as well as clinical and biochemical characterisation of the pituitary lesion are important to drive appropriate management. From an academic perspective, pituitary tumours may give interesting new insights into the pathophysiology of headache, and there is merit in studying this area more extensively.

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Introduction to the ACNR Stroke Series

In stroke medicine, some of the most worrying decisions clinicians have to make are related to balancing the risk of future occlusive cerebral and systemic ischaemic events (for which antithrombotic drugs are likely to help) and the risk of intracerebral bleeding (which may be caused or aggravated by antithrombotic drugs). Small vessel disease processes that cause most cerebral haemorrhages can also lead to ischaemic stroke (even in the same patient). The stakes here are high because antithrombotic-related intracerebral haemorrhage is often devastating or fatal. In the latest article in ACNR's Stroke series we are therefore delighted to have a timely, authoritative and thought-provoking article on the challenges in managing antithrombotic drug treatment after an intracerebral haemorrhage. In this very clear and concise review, Rustam Al-Shahi Salman and Simon Bell describe the limits of available evidence to guide us, and emphasise the importance of ongoing randomised trials to help resolve this most challenging of modern stroke medicine dilemmas.

David Werring,
Reader in Clinical Neurology,
UCL Institute of Neurology,
National Hospital for Neurology and Neurosurgery,
Queen Square, WC1N 3BG.

Rustam Al-Shahi Salman MA PhD FRCP Edin
is a MRC Senior Clinical Fellow and Professor of Clinical Neurology at the University of Edinburgh, and an Honorary Consultant Neurologist in NHS Lothian. He is interested in anything that might bleed, or has bled, in the brain.

Simon Bell BSc (Hons) MB ChB MRCP
is a Neurology Specialist Trainee at the Sheffield teaching Hospitals NHS Foundation Trust. His undergraduate studies were performed at Bristol University. He has received neurosciences training in Gloucester, Bristol, Brisbane (Australia), Leeds and Sheffield. His research interests are both cerebrovascular and dementia neurology.

Correspondence to:
Rustam Al-Shahi Salman
Centre for Clinical Brain Sciences (CCBS), FU303i, First Floor, Chancellor's Building,
49 Little France Crescent,
Edinburgh EH16 4SB, UK.

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The contemporary conundrum of antithrombotic drugs after intracerebral haemorrhage

Summary

- Stroke due to intracerebral haemorrhage (ICH) causes more lost disability-adjusted-life-years than ischaemic stroke
- Acute stroke unit care and blood pressure reduction for secondary prevention of stroke improve outcome for ICH survivors
- When patients suffer an ICH, almost half are being treated with an antithrombotic drug
- But should survivors of antithrombotic-associated ICH restart or avoid antithrombotic drugs?
- Join the on-going collaboration of 114 hospitals in the UK helping to answer this question in the REstart or STop Antithrombotics Randomised Trial (RESTART, www.RESTARTtrial.org, ISRCTN71907627)

Stroke due to intracerebral haemorrhage (ICH) is a burden

Stroke due to non-traumatic intracerebral haemorrhage (ICH) affects roughly 15,000 adults in the UK and ~2 million adults elsewhere in the world each year.[1] Despite ICH accounting for only 10-15% of all strokes, ICH causes more lost disability-adjusted-life-years than ischaemic stroke.[1] ICH accounts for an even larger proportion of strokes in low-middle income countries,[2] where hypertension is particularly prevalent.[3]

First, the good news…

Stroke due to ICH is treatable

Acute stroke unit care is just as much of a life-saving management strategy for patients with ICH as for their counterparts with acute ischaemic stroke.[4] Furthermore, acute blood pressure lowering within six hours of ICH onset is safe, and seems to reduce disability (but not death).[5] The recently updated European Stroke Organisation (ESO) ICH guidelines strongly recommended acute stroke unit care for patients with ICH and made a weak recommendation for acute blood pressure lowering. The writing group did not find evidence from randomised trials to support other interventions for acute ICH, such as surgical evacuation.[6]

Stroke due to ICH is preventable

The PROGRESS randomised trial involving 6,105 patients with prior ischaemic stroke, ICH or transient ischaemic attack has shown that reducing blood pressure is the most important intervention for secondary prevention after ICH.[7] PROGRESS showed that over a mean follow-up of four years, the overall relative risk of recurrent stroke was reduced by 28% in the group treated with an ACE inhibitor (perindopril) with/without a diuretic (indapamide) compared to the placebo group.[7] The benefits of blood pressure reduction were greatest for patients with ICH,[8] regardless of the presumed underlying small vessel disease and whether or not the patient was 'hypertensive',[9] prompting the ESO ICH guidelines to strongly recommend reducing blood pressure after ICH.[6]

Table 1: Outcomes associated with starting antiplatelet drugs after intracerebral haemorrhage

Study	Design	Inception point	Total follow-up (person years)	Patients on anti-platelet drugs (n)	Intracerebral haemorrhage		Ischaemic stroke		Myocardial infarction / acute coronary syndrome		Serious vascular events	
					n (/1,000 PY, 95% CI)	HR for anti-platelet therapy	n (/1,000 PY, 95% CI)	HR for aspirin	n (/1,000 PY, 95% CI)	HR for aspirin	n (/1,000 PY, 95% CI)	HR for aspirin
Flynn et al. 2010[20]	Scotland Community All primary ICH 1994-2005	Hospital discharge	1,510	120 aspirin	2 (9.4, 1.1–34.0)	1.07, 0.24–4.84[1]	1 (5.1, 0.1–28.5)	0.23, 0.03–1.68	–	1.77, 0.49–6.49	-	0.73, 0.42–1.28
				297 none	12 (9.8, 5.1–17.1)		28 (23.1, 15.4–33.4)		–		–	
Biffi et al. 2010[18]	USA Hospital Lobar CAA-ICH 1994-2006	90 day survivors	353	16 aspirin	3	1.72[2]	-	NS	–	–	–	–
				88 none	26		-		-		-	
Chong et al. 2012[19]	Hong Kong Hospital All primary ICH + SAH + SDH 1996-2010	30 day survivors	2,281	56 aspirin	3 (22.7)	–[3]	5 (44.4)	p=0.03	12 (6.9)	p<0.01	52.4	p=0.04[4]
				384 none	44 (22.4)		24 (12.7)		13 (92.3)		112.8	

ICH = intracerebral haemorrhage. SAH = subarachnoid haemorrhage. SDH = subdural haemorrhage. HR = hazard ratio. NS = not statistically significant.

[1]HR 1.52 (95% CI, 0.31–7.39) for 235 lobar ICHs (not calculable for deep ICH).

[2]95% CI not given (but not significant). HR 3.95 (95% CI, 1.6–8.3) in a multivariable analysis involving previous lobar ICH, microbleeds, and CT-defined white matter hypodensity in posterior brain regions.

[3]Not provided overall, not calculable for patients with lobar ICH, and not significant for patients with deep ICH (38.7/1,000PY on Aspirin versus 20.8/1,000PY not on Aspirin).

[4]In a sub-group analysis restricted to 127 patients with "standard clinical indications for anti-platelet therapy" (coronary artery disease, ischaemic stroke, atrial fibrillation, and diabetes mellitus), they did not provide a hazard ratio but did provide a p value.

But what should be done about antithrombotic drugs after ICH?

Patients with ICH often have co-morbid ischaemic diseases and other 'vascular risk factors' in addition to hypertension. Because evidence in recent decades has shown the benefits of antithrombotic (i.e. antiplatelet and anticoagulant) drugs for the prevention of major cardiovascular events,[10,11] it is unsurprising that the use of antithrombotic drugs at the time of ICH has risen to 40-50% during the same timespan.[12,13]

Given ICH patients' co-morbidities, they are at considerable risk of further major vascular events; overall, ischaemic events appear to be at least as frequent as recurrent ICH.[14] Ischaemic events may be even more common in ICH survivors with a past history of ischaemic events, but there are few data about this sub-group of interest.

So this raises the not infrequent clinical dilemma of whether to restart or avoid antithrombotic drugs in survivors of ICH who have a clear indication for these drugs.[15]

Unfortunately, there are no randomised trials addressing this uncertainty about secondary prevention treatment.[6,16] It is therefore unsurprising that there is variation in clinical practice when it comes to restarting these drugs, which does not appear to be explained by any patient characteristics.[17]

Figure 1: The REstart or STop Antithrombotics Randomised Trial (www.RESTARTtrial.org, ISRCTN71907627)

Antiplatelet drugs

Three published observational studies describe the outcomes associated with restarting or avoiding antiplatelet drugs after ICH (Table 1).[18-20] One study found a two-fold reduction in all major vascular events among patients who restarted aspirin after any ICH.[19] None of the studies found an increase in the risk of recurrent ICH associated with restarting aspirin in univariate analyses. However, one of these studies of 104 adults with lobar ICH identified 29 recurrent ICHs during a median follow-up of almost three years.[18] In a multivariable analysis of this small cohort, there was an association between aspirin use after ICH and recurrent ICH (adjusted hazard ratio 3.95, 95%CI 1.6-8.3), which was possibly explained by microbleeds.[18]

The logical response to this uncertainty, in the light of variation in practice, the lack of dramatic effects in observational studies, and the possibility of confounding by indication in observational studies, is a randomised trial. The REstart or STop Antithrombotics Randomised Trial (RESTART, www.RESTARTtrial.org, ISRCTN71907627, Figure 1) started to address this uncertainty in May 2013, and has recruited 168 participants at 114 UK hospitals at the time of writing. RESTART ultimately seeks to determine whether restarting antiplatelet drugs results in a beneficial reduction in all major vascular events. The trial is currently powered to address the safety of doing so. Given an annual risk of recurrent symptomatic ICH of about 1.8 to 7.4% per annum[14] and observational studies showing a 1- to 4-fold relative increase in the risk of recurrent ICH on antiplatelet drugs (Table 1), if RESTART recruits 720 patients it will have excellent power (after all participants have been followed for at least two years) to detect a doubling of the rate of ICH if the true rate is 4.5% per annum, or 93% power at the 5% significance level to detect a 4-fold increase in risk of recurrent ICH if the annual risk is only 1%.

Stroke-friendly UK Neurologists are encouraged to join the RESTART collaboration by contacting RESTART.trial@ed.ac.uk to help us resolve this clinical dilemma.

Anticoagulant drugs

At least twelve observational studies have compared the outcome of restarting or avoiding oral anticoagulant drugs after intracranial haemorrhage, but only four of these

Table 2: Outcomes associated with starting oral anticoagulant drugs after intracranial haemorrhage

Study	Design	Inception point	Follow-up	Patients by antithrombotic drug use (n)	Intracranial haemorrhage		Ischaemic events		Death of any cause	
					% per year	Association with OAC	% per year	Association with OAC	% per year	Association with OAC
Majeed et al. 2010[21]	Sweden and Canada; Hospitals; All primary ICH + SAH + SDH, on warfarin, INR>1.5; cardiac indication for OAC; 2002-2008	Day 7 after stroke onset	227 person-years	45 resumed warfarin (median 5.6 weeks)	7.6%	HR 5.6 (95% CI 1.8-17.3)	–	–	–	–
				87 did not resume warfarin	6.0%		–		–	
Yung et al. 2012[22]	Canada; Hospitals; First-ever ICH + SAH on warfarin; AF, mechanical heart valves, VTE; 2003-2008	Stroke onset	1 year	91 resumed warfarin	15.4%	–	–	–	48%	OR 0.8 (95% CI 0.4-1.4)*
				193 did not resume warfarin	15.0%		–		61%	
Nielsen et al. 2015[23]	Denmark; Hospitals; First-ever ICH + SDH + SAH, previously on oral anticoagulant for 6 months or more; AF; 1997-2013	6 weeks after hospital discharge	1 year	303 resumed warfarin or NOAC	8.6%	HR 0.9 (95% CI 0.2-2.8)*	5.3%	HR 0.6 (95% CI 0.3-1.0)*	9.7%	HR 0.6 (95% CI 0.4-0.8)*
				1,089 took no antithrombotic drugs	8.0%		10.4%		19.1%	
				360 received antiplatelet drug(s)	5.3%	–	10.3%	–	19.5%	
Kuramatsu et al. 2015[24]	Germany; Hospitals; Primary ICH on warfarin for AF, INR >1.5; 2006-2012	Hospital discharge	1 year	110 resumed warfarin	–	–	5.5%	OR 0.3 (95% CI 0.1-0.8)	8.2%	OR 0.15 (95% CI 0.1-0.3)
				456 did not resume warfarin	–		14.9%		37.5%	

AF = atrial fibrillation. HR = hazard ratio. ICH = intracerebral haemorrhage. NOAC = non-vitamin K oral anticoagulant. NS = not statistically significant. OAC = oral anticoagulant. OR = odds ratio. SAH = subarachnoid haemorrhage. SDH = subdural haemorrhage. * = adjusted measure of association

studies were sufficiently described and large enough to inform the dilemma about whether or not to restart oral anticoagulation (Table 2).[21-24] These four studies were of adults with either purely intracerebral[24] or various types of intracranial haemorrhage[21-23] and a variety of indications for oral anticoagulation (although analyses were restricted to patients with atrial fibrillation in two studies[23,24]). Although the studies chose different inceptions points, they all described outcomes over approximately one year of follow-up. However, the studies described a variety of different outcome events, so only the most frequently reported are shown in Table 2, but the frequencies of these events vary probably because of differences in study design. Nevertheless, these studies described promising associations between oral anticoagulants and reductions in: death of any cause,[23,24] all ischaemic events,[23,24] ischaemic stroke,[21] and ischaemic and haemorrhagic events combined.[23] Three studies described non-significant associations between oral anticoagulants and haemorrhagic events[22-24] and one study found a significant increase in the risk of haemorrhagic events on oral anticoagulants.[21]

Again, the associations seen in these observational studies and the possibility of confounding by indication mean that a randomised trial is warranted to investigate whether resuming an oral anticoagulant results in a beneficial reduction in all major vascular events. The non-vitamin K oral anticoagulants are particularly attractive for such a trial, because of their lower risk of intracranial haemorrhage in comparison to warfarin.[25] Stroke-friendly UK Neurologists are encouraged to contact RESTART.trial@ed.ac.uk if they would be interested in joining our efforts to obtain funding for this trial.

Conclusion

Double-edged swords generate many of the contemporary dilemmas in stroke medicine: cerebral small vessel diseases may manifest with ischaemia or haemorrhage; biomarkers such as brain microbleeds are associated with the occurrence of both haemorrhagic and ischaemic clinical outcomes; and antithrombotic drugs cause beneficial reductions in ischaemic clinical outcomes at the expense of an increase in the risk of haemorrhagic clinical outcomes.

These "first world" dilemmas are becoming increasingly frequent as survival after stroke improves and society ages, and will become a problem elsewhere in the world as epidemiological transitions occur in low-middle income countries. However, treatment uncertainties arising from these dilemmas require resolution in large randomised trials, with embedded advanced imaging sub-studies to explore the potential of stratified medicine approaches.

The only hope for us to resolve dilemmas such as these is large-scale collaboration within 'learning healthcare systems' that embed clinical research in the routine of everyday clinical practice.[26,27]

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Neurological Signs: Echo Phenomena

AJ Larner
Cognitive Function Clinic,
Walton Centre for Neurology
and Neurosurgery, Liverpool,
L9 7LJ, UK.

Correspondence to:
Email: a.larner@
thewaltoncentre.nhs.uk

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A number of echo phenomena are described in the neurological literature,[1] some of which are briefly considered here.

Echophenomena/Imitation behaviour

Much acquired human social behaviour is imitative in origin, both adaptive and maladaptive, but in neurological practice the term "imitation behaviour" is reserved for the reproduction by the patient of the examiner's words or gestures without preliminary instruction to do so ("naive imitation behaviour") or even despite explicit instruction not to do so ("obstinate imitation behaviour").[2] The term echophenomena has sometimes been used interchangeably with imitation behaviour.

To be labelled as such, the behaviours must be consistent and, as implied in the "obstinate" terminology, have a compulsive quality to them. Echophenomena may be accompanied by frontal release signs and utilisation behaviour (another reflection of environmental dependency), and are usually attributed to frontal lobe dysfunction, though have been associated on occasion with either basal ganglia or thalamic lesions, and exceptionally with parietal lesions.

Kahlbaum's 1874 description of catatonia included the symptoms of echophenomena, and echolalia and echopraxia feature amongst the symptoms listed in the criteria for catatonia in DSM-5. Obstinate imitation behaviour has been reported to distinguish frontotemporal dementia from Alzheimer's disease,[3] but I think this is likely to be a specific (few false positives) but not very sensitive (many false negatives) sign.

Echolalia

Echolalia is the involuntary repetition of an interviewer's speech utterances (as opposed to the voluntary mickey-taking which characterises an irritating game typical of childhood, but sometimes indulged in by adults). As well as frontal lobe lesions, catatonia, and dementia syndromes, echolalia may also be encountered in children with autism, in Tourette syndrome,[4] and rarely as an ictal phenomenon, possibly with a left supplementary motor area origin.[5]

Echolalia may also occur in certain aphasia syndromes, for example in transcortical sensory aphasia, a fluent aphasia with well-preserved repetition skills. The aphasia of Alzheimer's disease has sometimes been likened to transcortical sensory aphasia, and a "mixed transcortical aphasia" with echolalia has been reported in Creutzfeldt-Jakob disease.

In contrast, "effortful echolalia" has been reported in left medial frontal lobe infarction including the supplementary motor area with a non-fluent output typical of transcortical motor aphasia.[6]

In "dynamic aphasia" speech output is characterised by a difficulty in initiation, with the phenomenon of "incorporational echolalia" when the patient uses the examiner's question to help to form an answer. This has sometimes been conceptualised as a form of transcortical motor aphasia, and may sometimes be seen in progressive supranuclear palsy.

Echopraxia

Echopraxia is the involuntary repetition of an interviewer's movements or gestures. As with echolalia, this may be seen in frontal lobe disorders, catatonia, Tourette syndrome,[4] and rarely as an ictal phenomenon.[5] A mechanism for echopraxia in schizophrenia has been postulated which invokes activity in mirror neurons providing representation to the inferior frontal gyrus and motor cortex which becomes an executed movement due to decreased inhibition and/or increased arousal.[7]

Echolocation

An entirely separate echophenomenon is echolocation.

Visiting the Liverpool Asylum for the Blind in 1805, the American chemist Benjamin Silliman (1779-1864) reported:

"How ... can we account for the acuteness of hearing which enabled a particular blind man, by means of the echo produced by his whistling, to decide when he was approaching any object of some magnitude ...".[8]

Echolocation is the comparison of outgoing sound pulses with the returning echoes in order to navigate or hunt. Though echolocation is most familiar (and studied) in bats and dolphins,[9] some blind individuals have developed the ability to use self-generated sounds, such as tongue clicks or finger snaps, as a form of sensory substitution to perceive the environment (Youtube has some informative videos). Sighted individuals can also be trained to do this.

A possible answer to Silliman's question has been provided by a functional MR imaging study of two blind echolocators which found that calcarine ("visual") but not auditory cortex was activated when the subjects listened to recordings of echolocation clicks and echoes, suggesting a possible role for cross-modal brain plasticity in the development of this faculty of compensatory enhancement.[10] It would be interesting to learn if this was also the case in sighted individuals trained to echolocate.

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Next Generation Neurology: The ABNT mentoring programme

Helen Devine
is a Neurology ST4 in KSS deanery and completing a PhD at the MRC Centre for Neuromuscular Diseases, NHNN. She is chair of the ABNT.

Dr Jonathan D Rohrer
MRC Clinician Scientist and Honorary Consultant Neurologist at the National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology.

Correspondence to:
E: h.devine@ucl.ac.uk

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In May 2014, the Association of British Neurologists Trainees (ABNT) introduced a mentoring scheme in which neurology trainees act as mentors to junior doctors to develop their interest in neurology and to encourage recruitment into the specialty. Changes in medical school curricula and junior doctor training mean that many doctors have less exposure to neurology than previously. The aim of the mentoring scheme is to support individuals who show an interest in neurology, enabling them to manage their career development in an effective and efficient manner. As well as being of benefit to junior doctors, it is hoped that the scheme will give neurology trainees valuable experience in mentoring, which is a skill encouraged by the General Medical Council.[1] This article will describe how the ABN mentoring scheme was developed.

The benefits of mentoring

The educational literature reports that the advantages for doctors of receiving mentoring are: improved performance, career opportunity and advancement, improved knowledge and skills, and greater confidence.[2] Mentoring has been shown to have a role in career guidance and a survey of junior doctors in the USA found that mentored junior doctors were nearly twice as likely to describe excellent career advice and preparation than those who did not have a mentor.[3]

Mentoring has a long tradition in neurology,[4] and has increasingly been recognised as a successful means of promoting career development and retention within physicians established in academic neurology.[5] However, career advice in neurology can be "difficult to find, is not necessarily intuitive and is likely to be given on an informal basis".[6]

The ABNT mentoring scheme

A working party was set up to develop the ABNT mentoring scheme by following a best practice example. The London Deanery mentoring programme now has over 500 mentees.[7] Key features of this programme were identified as: the delivery of mentoring by appropriately trained and supported doctors, confidentiality for the mentees, avoidance of dependence, the presence of a mentoring working party and administrative support team, and a choice of mentors of the same sex or ethnicity.

The working party created an outline for the scheme of a two-year mentoring relationship between mentee and mentor with two or three face-to-face meetings per year and email contact. This was to ensure the mentees felt supported by the relationship and the mentors did not feel overburdened. Application forms for prospective mentees were written to include information about demographics, career aspirations and previous career experience.

Junior doctors in medical training posts throughout the UK were invited via an email from their deanery to become mentees in the mentoring scheme. Foundation programme directors and administrators and CMT programme directors and administrators in each deanery were contacted to allow this. The scheme was also advertised on the ABNT website, and emails were sent to students and junior doctors who had an expressed an interest in being involved in the scheme at the RCP Career Day. Interested mentors were identified within the ABNT through the ABNT website and newsletter as well as in discussions at the ABN conference in May 2014.

The mentee-mentor pairings were made in a meeting of the ABNT mentoring working party. This decision was made to limit administrative burden as this is a small but nationwide scheme and allocations were made based on location and interests. Forty-one mentor-mentee pairings have now been in contact and evaluation of the mentoring scheme will occur at the end of the year.

A training day for mentors was held in June 2014 at the ABN offices to ensure that mentoring is delivered by appropriately trained doctors. The ABN office team is providing administrative support and mentors and mentees have been encouraged to contact the ABNT mentoring working party if practical support is required.

The mentoring scheme and its evaluation will comply with the ethical guidelines produced by the British Educational Research Association.[8] The mentors and mentees have the right to withdraw at any stage in the study and the data collected will be anonymised and the responses will be confidential.

Evaluation and dissemination

The goal of evaluating the mentoring scheme is to gain an understanding of the mechanisms of mentoring in providing career advice and guiding junior doctors to consider neurology as their chosen career. It will also aim to assess the benefit to the neurology trainee mentors as an educational experience. A distinctive feature of many evaluative reports is the emphasis on recommendations;[9] therefore, the report will include practical recommendations clearly derived from the data. The report will be available on the mentoring scheme section of the ABNT website and will be presented as a poster at the ABN conference.

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The French Connection

On the 13th of March 2014 I woke up to unfamiliar surroundings. Working in hospitals for the last few years had taught me enough to recognise that I was in one, and my clothes (or lack of them) let me know that I was a patient. I could not recognise this hospital and so I racked my brain to think about how I got here. Through the fog of confusion, I could vaguely remember being on a ski trip but could not remember much else. I tried to look for more clues, but didn't get far as I found myself tied to the hospital bed. Thinking that this must all be a bad dream, I was happy and relieved to find my father (a GP) at my bedside. He filled me in on the events of the last week.

We had been snowboarding in Tignes, France. The weather was fantastic, snow was crisp and the après ski epic. Not much more you can ask for on an annual ski holiday. By day three the weather had changed, as had my luck. Now overcast with visibility poor, we had spent the morning traversing the valley, deciding that this wasn't much fun we broke for lunch. With no improvement by the afternoon, we decided to stay put and spend it in a snow park.

A few runs in, I foolishly decided that I wasn't getting enough air on a particular jump. So I hit it again with double the speed and double the run up. Big mistake! I lost control at the peak of my airtime, overshot the landing and used my face as a brake on the ice. Lying lifeless thirty yards from the ramp my friends ran to my aid. Finding me unconscious they called for help and 30 minutes later the ski paramedics reached me. It was documented that my initial GCS was 3 and I was Cheyne-Stokes breathing. Concerned by the size of haematoma forming on my right temple the ski paramedics were convinced I must have smashed my skull. Once stabilised we awaited the helicopter. With the same conditions as the morning it was two hours before a weather window opened and the helicopter could land. I was taken from the slopes to the local medical centre where I was intubated, before a second air ambulance took me to the ICU in Grenoble Hospital a few hundred miles away. This was to be my new home for the next few weeks.

On arrival I was taken straight to the CT scanner. I had multiple petichial cerebral haemorrhages, a counter coup subarachnoid haemorrhage, gross cerebral oedema, bilateral first rib fractures, significant pulmonary contusion injuries and extensive soft tissue swelling outside my cranium. Fortunately I had not fractured my skull. My father arrived at Grenoble a few hours later with a 300 euro taxi bill. At this time, I was stable in my coma and the plan for the first day was to watch and wait. By day two I wasn't showing the improvement

Jump before the accident

Landing of the accident

My lift

the doctors had hoped for, they considered drilling micro burr holes to decompress my skull and relieve some of the intracranial pressure. Subconsciously I must have heard them at this point, because I started to stir. Shortly after I was extubated.

Now awake it was noted that I had a right hemiparesis and homonymous hemianopia on the same side. Considering the scale of my injuries the doctors and my father thought I would be left like this for the rest of my life. With such a grim outlook there was little more that could be done other than keeping me comfortable and seeing how I recovered. My father was by my bedside for as much of the time he was allowed, he kept everybody back home updated (including my work) and read to me. He sat on my left. I owe him a lot.

Traumatic head injuries are classified based on the clinical history and the examination findings. Severity is separated between mild, moderate and severe head injuries based on initial GCS, duration of coma, duration of anterograde amnesia and the need for neuro surgical intervention. This helps to predict an initial outcome/prognosis for the individual. With an initial GCS of 3, a coma lasting over twenty four hours and having a prolonged period of anterograde amnesia, I was well into the severe category. The understanding and management of acute brain injuries is under much debate currently in medical literature, with new concepts such as Brain Impact Apnoea in which the respiratory centre in the brain stem shuts down after a significant head injury producing a period of apnoea. Although only proven in animal models this demonstrates the importance of good basic life support. Acute management is also up for debate – the DECRA study talks about the potential benefits of aggressive decompressive craniotomy in acute head injury victims. The study did not show favourable results. Although there is no clear plan on acute management currently I feel in the next decade there will be drastic changes in the world of acute management of head injuries.

Fortunately, slowly I started to improve. Although conscious for this initial period, I was not myself and have no recollection of events and my actions. The cerebral irritation had made my behaviour unruly and unpredictable. I pulled out every IV cannula, I was verbally abusive, and accused everyone of trying to kill me (including my dad). Eventually I was tied down as I was a danger to myself as much as everyone else. The use of restraints is unclear in the UK. Many doctors simply state that it is illegal. The real answer is that it is legal but very questionable. Ethically restraining a patient against their will is a breach of their autonomy

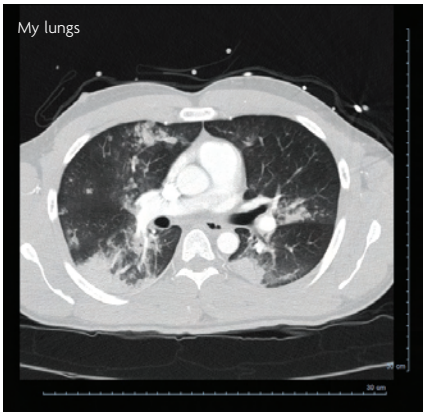
(one of the 4 basic pillars of the Beauchamp and Childress model of biomedical ethics). Currently in the UK the GMC states everyone has autonomy even if they don't have mental capacity and so restraining anyone against their will is a breach of autonomy. I am not going to attempt to answer or comment on the logic of this issue. To address this issue would take a separate article if not a book to scrape the surface of questions asked. With everything being said, I am happy that they tied me down.

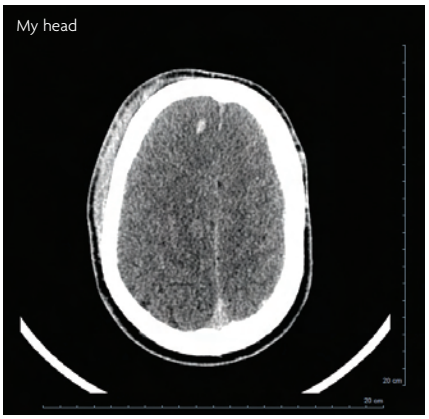
A week or so passed before I started to feel more like my normal self. I had forgotten most of my hardships (intubation, central line, parenteral nutrition, urinary catheter). On Day 9 I was sat out of bed, day 10 I was walking around the ward. The hemiparesis and homonymous hemianopia had fortunately faded at this point and I was just left (and still am) with a few upper motor signs in my right leg (Occasional clonus and mild hyper reflexia).

My memories come in at around day 11 and as a result I had lost all sense of time. I had been due back at work the week before, fortunately dad had kept them informed. I was keen to get back home and get on with my life. A few days later, I was discharged and my insurance company got me on to a busy easyjet flight back to the UK. Still feeling quite jaded and fragile on arriving home, I intended to take a week off to recover before returning to work. It wasn't till I saw a very reputable Neurologist (Dr R Kent) specialising in neuro-rehabilitation that I realised my return to work wouldn't be so simple. She explained my increased risk of having a post traumatic epileptic event, and insisted I needed to take a minimum of three months off, avoid driving, sleep deprivation, alcohol, and anything else that could lower my seizure threshold. The DVLA has specific rules on driving after a severe head injuries. The patients have the responsibility to inform the DVLA and normally take 6-12 months off driving based on a doctor's review. These rules are a precaution only for the increased epilepsy risk.

I was seven months into my FY2 year when this accident occurred. I met with my hospital to explain what had happened and the discussion I had with my Neurologist. Everyone was very supportive and understanding. I was referred on to Occupational Health and a professional support group who both provided much assistance. There are many facilities available for people who have suffered a brain injury. Although I didn't require any of them I was informed and always knew there was someone I could turn to if required. In cases of head injuries needing support my advice is to ask your local Neurologist to tell you about the services available in your area.

Getting used to my new pace of life was difficult. Initially, I just felt odd. I suppose unless you have had a head injury it's difficult to fully understand the feeling, but I will try to explain. I was slower at everything both physically and mentally. It took me two months to be able to write legibly again and any physical activity beyond walking was mentally exhausting. I knew I would have to work hard at this.





The cerebral irritation had made my behaviour unruly and unpredictable. I pulled out every IV cannula, I was verbally abusive, and accused everyone of trying to kill me (including my dad).

Physically I like to be active and not being able to do things was initially frustrating. If I wanted to go for a run, I would have to tax my brain thinking really hard about running and five seconds later I would move. To continue this momentum I would have to keep up this train of thought and after around five steps I would fall over. My balance was all over the place, it felt like I was running on ice. Still, I persisted, and around a month after the accident I managed my first 5K. Everything improved slowly over time, and at seven months I managed to run the Cardiff half marathon. The ultimate physical test was at one year when I went snowboarding again. Physically I was back.

Mentally rehab was even more difficult. I started back at work on a phased return around four months post-accident. I found myself easily tiring and so it was hard at first. Just like the running it became easier day by day as I acclimatised and got back into the swing of things. My hospital looked after me very well, they took my return slowly and checked up on me regularly. I wanted to prove to myself as much as everyone else that my brain was still up to it. So at nine months I sat MRCP part 2 and managed to pass. Revision or simple mental tasks are very good for the recovering brain. My Neurologist recommended *Brain Injury Work Book* by Powell and Malina, I found this hard to locate online so I used the MRCP revision book *Rapid Review of Clinical Medicine* by Sharma and Kaushal. It worked for me. After the exam I was back to working full time although my Neurologist (Dr R Kent) did not want me working night shifts till at least one year post accident. This allowed the risk of me developing post traumatic epilepsy to be kept to a minimal as possible level.

At one year I was put on the emergency unit full rota. Truth be told I didn't know how my brain would cope over my first set of nights. So starting with a four day Easter bank holiday wasn't ideal but I managed fine. I guess I'm back mentally as well.

This incident has taught me a lot about medicine and life in general. I now have an even greater empathy and understanding for anyone who has sustained a head injury whatever the severity. In my case it took a lot of hard work and even more luck for me to get to be where I am. I hope others who have suffered with brain injuries can read my story and see that there is a chance that they can reach a good outcome. Although frustrating, time is the only thing that can truly show the final neurological outcome. So I recommend be patient, trying to be strong and hold on.

The message I pass on to my medical colleagues is that every head injury is individual and no matter what grade of injury the recovery/outcome is unique and must be handled on an individual basis. Recovery can be so vastly individual, sustaining a mild head injury can result in a lifetime off work when severe head injuries might require minimal time off work. Studies have shown that there are limited prognostic markers beyond the initial phase of recovery. In the end it is only time that will show how much neurological recovery is possible and rushing the process does not help and can often hinder it. That's why as physicians we also have to be patient and treat patients on an individual basis focusing on their unique concerns and expectations.

I am grateful for all that I have learned from this experience (even though it almost killed me) and will strive to use this knowledge to better my medical practice as well as that of my colleagues. The incident has also got me thinking about other issues such as life and philosophy, but that is another article. All I will say is that sometimes life will get you down and ultimately there isn't too much you can do about it, so just accept it is what it is and get on with it.

Dopaminergic control of autophagic-lysosomal function implicates Lmx1b in Parkinson's Disease, Nat Neuroscience

Reviewer: Lucy Collins PhD Student at the John Van Geest Centre for Brain Repair Cambridge.

Reprogramming of somatic cells to alternative lineages is an attractive strategy for modeling inaccessible cells in pathological conditions such as diabetes mellitus, myocardial infarction and in neurodegenerative conditions like Parkinson's Disease. Induced neuron (iN) technology offers an experimental method to potentially enable the manipulation of disease relevant cells. Dermal fibroblasts isolated from a skin biopsy can be directly converted into neurons using defined transgenes introduced into the cell through viruses. This technique is new in the field and many groups are striving to optimise many aspects of this conversion process.

A recent paper aiming at deriving iN cells from Zhao et al, reported that the factor Neurogenin 2 (Ngn2) enhances the production of iN's. This factor was previously reported by Liu and colleagues, also to be an important pro neuronal factor for converting adult fibroblasts (Liu et al., 2013). Many combinations of transgenes have been tried but the best combination for adult fibroblast conversion has yet to be decided on. Marius Wernig and colleagues defined the set criteria for iN cells and acknowledged that various degrees of reprogramming can be achieved in the dish but complete reprograming should produce a cell with a distinct morphology that expresses neuronal genes and fires action potential with evidence of synaptic transmission (Yang, Ng, Pang, Südhof, & Wernig, 2011).

In this current paper by Zhoa et al, the starting population of fibroblast are devoid of any neuronal markers, and after conversion levels of Tuj and MAP2 in these reprogrammed cells were detected as well as more specific neuronal markers such as GABA and vGlut. These converted cells also fired action potentials and had neurotransmitter receptors present.

The limitations of this work and indeed all iN work is that the efficiency of conversion of adult iN cells is still very low. The iN end product remains a heterogenous population of starting dermal fibroblast with iN cells at various degrees of reprogramming. Until such times as this is resolved the value of these cells will remain limited.

Liu M-L, Zang T, Zou Y, Chang JC, Gibson JR, Huber KM, & Zhang C-L. *Small molecules enable neurogenin 2 to efficiently convert human fibroblasts into cholinergic neurons.* Nature Communications, 2013:4;2183. doi:10.1038/ncomms3183

Yang N, Ng YH, Pang ZP, Südhof TC, & Wernig M. *Induced neuronal cells: how to make and define a neuron.* Cell Stem Cell, 2011;9(6):517-25. doi:10.1016/j.stem.2011.11.015

Zhao P, Zhu T, Lu X, Zhu J, & Li L. *Neurogenin 2 enhances the generation of patient-specific induced neuronal cells.* Brain Research 2015. doi:10.1016/j.brainres.2015.04.027

Neurogenin 2 enhances the generation of patient-specific induced neuronal cells

Reviewer: Lucy Collins PhD Student at the John Van Geest Centre for Brain Repair Cambridge.

An improved understanding behind the selective loss of dopaminergic (DA) cells in Parkinson's disease needs to be understood in order to develop better therapies. A recent publication in Nature Neuroscience investigates what is particularly sensitive about DA cells and what factors maintain their cellular function over a lifespan. LIM homeobox transcription factor (Lmx1a and Lmx1b) proteins are known to be developmental drivers of DA neurons. Genetic variations in these proteins have also been flagged up in genome wide association studies as being implicated in PD, and in recent stem cell modeling studies such as induced pluripotent stem cells (iPS) and induced neurons (iN) conversions show that the Lmx1 transgenes are important transcription factors for DA specification.

The function of Lmx1b in adult DA neurons is unclear, to investigate this Laguna et al, use Cre recombinase under the dopamine transporter (DAT), to selectively deplete the Lmx1 proteins in adult mouse DA neurons. Laguna and colleagues found that loss of Lmx1b resulted in dysfunction of the dopaminergic synapse, inclusions of electron-dense protein aggregates in neuronal terminals and degeneration of DA neurons mimicking early cellular degeneration in PD. The transgenic animals also reflected some of the common motor impairments and also early anosmia associated with PD (Laguna et al., 2015).

The authors also found loss of Lmx1b expression also resulted in downregulation of key proteins involved in the lysosome autophagosome pathway (ALP) including LC3I-II, Lamp1 and 2, beclin, p62 cathepsin D and TFEB. The lysosomal pathway has been implicated in PD from genetic and environmental observations. The commonest single genetic risk factor for the development of PD are mutations in the lysosomal enzyme glucocerebrosidase GBA, which when homozygous or compound heterozygous cause Gaucher's disease.

Therefore this paper highlights a dual role of Lmx1b, namely it is important in the maintenance of DA neurons and their functioning ALP and as such agents that can affect its expression maybe of benefit in more than one way in PD patients.

Laguna A, Schintu N, Nobre A, Alvarsson A, Volakakis N, Jacobsen JK, et al. *Dopaminergic control of autophagic-lysosomal function implicates Lmx1b in Parkinson's disease.* Nature Neuroscience, 2015;18(6):826-35. doi:10.1038/nn.4004

Hold on Hope?

Reviewer: Dr Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals NHS Foundation Trust, UK.

Is optimism a good thing? In most situations the ability to see a hopeful outcome from a difficult set of circumstances is probably helpful allowing an individual to persevere in spite of the daunting challenges they face. What about optimism which is pegged onto the most unlikely of outcomes?

These are the themes that stalk many conversations with family members of those who are recovering from brain injury. The reactions and coping mechanisms are often different between groups of people, but how should we approach the fine line between expectation and optimism? The dichotomy of encouraging optimism versus fostering realism is something that fills discussion with family members in the context of brain injury. There are a number of different viewpoints on how to manage this difficulty within the psychological literature but little in the way of defined evidence.

This paper explores familial optimism in the post-acute stage of acquired brain injury from the inpatient setting and onto discharge. By comparing questionnaires assessing a number of different domains around emotional wellbeing and perceived control administered longitudinally over the course of 18 months, 5 hypotheses were evaluated;

1) Family members are unrealistically optimistic in the post-acute phase.
2) There is a negative emotional impact when optimistic expectations are not fulfilled.
3) Discharge triggers a downward adjust-

ment of expectations and consequent emotional crisis.

4) Optimism about consequences and controllability will lead to better emotional wellbeing and less anxiety and depression.
5) Optimism about controllability will result in greater engagement in the rehabilitation process.

Unfortunately (and, perhaps, predictably) family members were usually over-optimistic in their estimations of how effective treatment and rehabilitation were likely to be while underestimating the impact that the brain injury would have on the family as a whole. Where family members' expectations were not fulfilled there was a negative emotional impact (with a correlation between decline in emotional wellbeing and large variances in expectation and outcome). In spite of this, discharge home was not found to precipitate emotional crises in family members. In the initial stages following the brain injury, optimism is associated with greater emotional wellbeing and it would seem that the negative impact of unrealistic optimism is only manifest later on in the post-acute period. Familial optimism is associated with a greater engagement in the rehabilitation process, which is obviously of great importance particularly where family members are going to adopt a caring role on an ongoing basis.

Although perhaps none of these results on their own are particularly surprising and there may be little that can done to affect an individual's perspective and expectations following brain injury, taken as a whole they serve as a valuable reminder of the importance of consistent, clear and realistic communication with families from the earliest stage. A poorly considered prognostic discussion on the neuro ITU may have profound and long-lasting effects on a family's perceptions and hopes. The preservation of the emotional wellbeing of family members is important both in keeping them involved with the rehabilitation process and for their own health.

Riley GA, Hough A, Meader LM, Brennan AJ. *The course and impact of family optimism in the post-acute period after acquired brain injury.* BRAIN INJURY 2015;14:1-9.

Elisabeth is Missing

In the prologue to this book, Maud finds half a compact mirror that used to belong to her sister Sukey, who disappeared just after the war. The story describes how Maud, despite advancing dementia, leads her daughter Helen to crack the mystery of Sukey's disappearance. The sleuthing is complicated by Maud's growing conviction that Elisabeth, a friend in whose garden the mirror discovery was made, has also disappeared. The ensuing dramas unfold in parallel, but in chronologically opposite directions – the reader and protagonist, each experiencing their own versions of delirium, moving to and fro between the parting narrative furrows.

The author's style is appealing, and vividly conveys Maud's growing sense of visceral certainty that embodied within her is information that would explain Sukey's disappearance. She is even more certain, however, of her decreasing facility to remember and to communicate any such information.

Maud's house is littered with notes-to-self – paper plaques of remembrance designed to release her from the entanglements of her condition, which must be Alzheimer's disease. The ignominy, the drudgery and the rage born of her enfeeblement are juxtaposed with the light comedy and social farce of a misfiring intellect. The author's credentials shine the brightest as she describes the brutal reality of life as a carer, with no warning of, or respite from, the next bedroom or restaurant ransacking. The incremental ratcheting-up of dependence without gratitude reduces daughter Helen to tears of frustration and bereavement. She does have the support of her own daughter, Katie, who defuses and diffuses both the harrowing and hilarious alike. Her brother, by contrast, seems unencumbered by any awareness of what might be his responsibility or of the simmering tensions within the family, as he pops in to pass comment.

The tempo of Maud's condition sets the rhythm of the book (try humming the 'Jaws' sound track, but start much earlier, and hum much more slowly). The nature of the condition is also a useful plot device whereby certain events become nail-biters, terrifying for Maud simply because of her inability to interpret: I will never again look at or listen to a slow-moving stair lift in the same way.

As a cognitive haze starts to form denser clouds over the islands of preserved memory, the race is on. Can Maud find and collect the dots, and join them, before debility supervenes? Increasingly, she lacks the ability to hold in her mind the information required for deduction and, with each page-turn, a satisfactory conclusion seems less likely. The silver lining, however, is that as her ability to retain new information diminishes (including important information about Elisabeth, presumably), more attention can be devoted to her relatively preserved long-term memory. Despite living in an increasingly confused present, she simultaneously re-lives her own long-term memories, often vividly and with life-affirming clarity. Her descriptions of the chaotic post-war years, of the close bond she had with her sister, and of her parents' reaction to their daughter's disappearance give this part of the tale a raw and gritty 'kitchen-sink' feel. The addition of a significant maniacal wandering woman and a brooding lodger provide the post-war plot with a necessary dollop of intrigue.

With its mysteries solved, it is this novel's upgraded account of experiencing dementia as a patient and, in particular, as a carer that lives on in the memory. Do carers deserve to be given a diagnosis even more than the patients? Do we need the same approach to the diagnosis of early dementia as we do to early pregnancy, with the dementia equivalent of antenatal classes and briefings from the beginning about the varied experiences and the differing means of delivering care as the final date approaches?

The more the general public reads about the natural history of dementia and its effects on patients and on those closest to them, the better prepared society will be for the increasing prevalence of this affliction: this is a book for everyone.

Author: Emma Healey
ISBN: 0241968186
Published by: Penguin
Price: £4.99
Pages: 288

Reviewed by:
Dr Tom Hughes,
Consultant Neurologist,
Cardiff, UK.

Liverpool Neurological Infectious Diseases Course 2015

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When a patient presents with a typical infectious illness, he or she will often provide a basic history, identifying key risk factors and their pre-morbid health state, cooperate with an exam while displaying valuable clinical signs, helpfully cough up or urinate a sample for culture, and respond fairly quickly to targeted therapy.

Infections of the nervous system present barriers to all of the above. Confusion obtunds the historian and hampers the exam, yielding limited and non-specific findings. We cannot easily sample the brain parenchyma. The Cerebrospinal fluid (CSF) provides an alternative, although direct observation of the pathogen may be limited; we may only be able to track its footprints via serology and Polymerase Chain Reaction (PCR). Lumbar punctures (LP) may be feared by patients. Neuro-imaging findings are often non-specific, and timely Magnetic Resonance Imaging (MRI) can be difficult to obtain. Finally, the optimal delivery of treatment across the blood-brain barrier requires expert knowledge, optimal regimes and, for some drugs, doses verging on toxic.

Many doctors would agree that neurology is their Achilles heel, and infectious diseases of the Central Nervous System (CNS) are among the most difficult areas of medicine to diagnose and treat. This course is for them.

Running over two days, with over 100 attendees from as far as Australia, the Liverpool Neuro-Infectious Diseases (ID) course 2015 was organised to provide helpful instructions in managing common neuro-infections as well as many stimulating discussions on current research and rarer, more exotic cases. We learned the essentials of interpreting MRI studies from Dr Maneesh Bhojak, and put our skills into practice in Dr Andy Ustianowski's session on HIV patients with lesions such as toxoplasmosis, Tuberculosis (TB), CNS Lymphoma and Progressive Multifocal Leukoencephalopathy (PML). Dr Jonathan Folb gave us the microbiology expertise on diagnosing meningitis, as well as common pitfalls; Dr Katherine Ajdukiewicz presented an update on managing these patients, as well as reviewing the evidence for current practices such as adjunctive steroids, and the changing pattern of infection with pneumococcus and different meningococcal sero-groups. These examples illustrate how well-structured a course this was, with sessions scheduled to build on established knowledge.


Professor Avindra Nath

There were practical guides on recognising neurological diseases in returning travellers, including a detailed session on Tick Borne Encephalitis (TBE) from Dr Ales Chrdle, an infectious disease (ID) specialist working in the Czech Republic where the disease is highly prevalent. Dr Chrdle has vast experience of the disease and his expertise was very enlightening; certainly this condition will be in my mind when seeing patients with recent travel to Bohemia. Interactive case presentations from ID and neurological experts covered rarer diseases such as Chikungunya, Tetanus, Sub-acute Sclerosing Pan Encephalitis and Rabies. These allowed us to engage in the diagnostic process, as well as hear expert advice on best management. Notably the course covered paediatric and adult conditions, providing broad appeal to many trainees.

There were multiple presentations from researchers from international units, and a poster competition featuring topics such as CD8 Encephalitis, complement factor deficiency, Neurosyphilis manifesting as Optic Neuritis, and Anti-NMDA Encephalitis arising in the context of herpes simplex infection.

The Richard T Johnson keynote lecture was delivered by Professor Avindra Nath of the National Institute of Neurological Disorders and Stroke in the USA, who described his hugely successful career as a neuro-infection specialist, including his work into the 'nodding disease' epidemic in Uganda, the discovery of genetically coded retroviruses in subtypes of Motor Neuron Disease, key virulence factors in neurological HIV, and perhaps most importantly, the art of performing fundoscopy in an Ebola suit.

The lectures raised recurring questions. How do some patients shrug off a pathogen which unleashes a hugely destructive illness in others? How much neurological damage is directly mediated by the pathogen and how much is induced by the inflammatory response, and might this be useful for treatment? Dr Nick Davies' presentation on overlapping viral and autoimmune encephalitides demonstrated there may well be elements of both. Finally, with the changing patterns of migration, climate, and evolution of resistance, what is the future of neuro-ID going to look like?

In addition to the high-quality presentations, this was a highly sociable course. The first day closed with a drinks reception followed by dinner in a Thai restaurant. For the more physically active attendees, a five kilometre 'fun run' took place at 7am the following morning, offering a guided tour of Liverpool by Professor Tom Solomon at a merciless pace (his twitter handle is @RunningMadProf!).

This course would be useful to anyone daunted by neurological infections, of which there are likely to be many of us. The variety and balance of content was excellent, and speakers were engaging and enthusiastic about their subjects. I would recommend it to those who are considering a career in neurology or ID, and for anybody who is at all curious about this fascinating and expanding subject. The course also offered 10 CPD points towards delegate professional development portfolios. For more information on the Neuro-ID course run by Professor Tom Solomon and colleagues at The Liverpool Brain Infections Group, University of Liverpool please visit www.liv.ac.uk/neuroidcourse


Conference organisers and delegates

19th International Congress of Parkinson's Disease and Movement Disorders

Conference details: 14-18 June 2015, San Diego, USA. ***Report by:*** Dr T Foltynie, UCL Institute of Neurology.

This meeting was my first visit to San Diego – if I'd have known better I would have brought my wetsuit and surfboard (I've learnt for next time), but this time I easily contented myself with the usual high standard of movement disorders presentations.

Plenary sessions

The first session presented by Werner Poewe, included a description of Rytary (IPX066), which is a prolonged release formulation of L-dopa now available in the USA, which alongside novel COMT (opicapone) or MAO-Bi (safinamide) agents represent further progress in the attempts to prolong the half life of L-dopa and reduce motor fluctuations. These of course parallel the previously demonstrated benefits of continuous infusions of intrajejunal L-dopa (marketed as Duodopa or Duopa). Alexander Storch followed on with recommendations on the symptomatic treatment pathway in PD, and then (pleasingly for me) called for further investigation of GLP-1 agonists such as exenatide as potential disease modifying treatments in PD (a phase 2 double blind randomised trial is ongoing at Queen Square).

A session on rehabilitation therapies in the treatment of PD featured an excellent talk by Lynn Rochester. This included both "Exercise" in its broadest definition and "Compensatory strategies", such as cueing techniques, both proven to have clinical efficacy in reducing freezing and falls. Lynn described how this evidence can be usefully "individualised" in the clinic i.e. starting group therapy in early PD then progressing to individualised risk avoidance, strengthening, endurance training and cueing (in isolation or combination).

Ted Dawson opened the main basic science part of the programme and described the consequences of different LRRK2 mutations on ribosome function, via phosphorylation of (S15) proteins of the ribosomal subunits; this appears to cause a global increase in protein translation in human dopamine neurons, and raises the question regarding which of these proteins are involved in the subsequent pathway of dopamine neuronal loss in this subgroup of patients. He also presented unpublished work related to parkin pathogenesis, further showing the negative consequences of PARIS (parkin interacting substrate) that can be rescued by over-expression of PGC1a, which in turn ameliorates mitochondrial biogenesis. He also described work in transgenic mice, showing that parkin activity becomes impaired as a consequence of alpha synuclein mutations (also reversibly involving PARIS and PGC1a) ….so perhaps unifying a pathway of neurodegeneration with or without alpha synuclein pathology. Additional steps in the pathway involve PARP and c-abl themselves perhaps also representing further targets for therapeutic intervention.

The second unofficial meeting of the Anglo-Irish-Aussie MDS subsection.

The question posed by David Sulzer was how much of this pathogenic process is directly due to genetics (polymorphisms, mutations), or consequent on impaired protein clearance strategies (UPS/ Lysosome chaperone mediated autophagy), and whether there is an additional toxic/infectious precipitant from olfactory or GI tracts (noting the lower risk of PD in individuals post vagotomy), and of course the potential role of additional stochastic/ environmental events.

In the same session, Eliezer Masliah reviewed the progress and potential of alpha synuclein immunisation in alpha synucleinopathies (PD, MSA, DLB etc). As well as the laboratory data supporting the idea that reducing alpha synuclein levels may have a role in preventing dopaminergic neurodegeneration, he presented unpublished work showing that analogous benefits may extend to preserving cholinergic neurons through co-reduction of amyloid beta. He reviewed the science supporting PD AFFITOPE, (an active immunisation programme using antibodies against the C-terminus of alpha synuclein) that reduces alpha synuclein accumulation and neuro-inflammation and indeed enhances clearance of alpha synuclein via microglia with accompanying behavioural effects in animals. Beyond this there has been encouraging safety data from patients exposed to this "PD01" antibody publicised in the last year. In addition, an alternative passive immunisation programme (antibodies against the toxic 9E4 domain of alpha synuclein) is also underway and has been shown to lead to antibody/alpha synuclein endosome formation that prevents cell-to cell propagation of alpha synuclein. This Prothena programme, "PRX002" has also recently reported safety data in patients, with accompanying reduction in alpha synuclein levels (in serum).

So with all this work on immunisation and trying to prevent alpha synuclein spread, should we now simply be considering PD as a prion disease? Warren Olanow thinks so, based on the Braak papers describing the pattern of spread of alpha synuclein within the CNS alongside papers demonstrating its transmission to grafted fetal cells. Furthermore, pre-formed alpha synuclein fibrils, or "Lewy body type tissue" from patients with MSA or PD injected into animal brains (whether transgenic or WT, rodent or primate) can spread and cause histological and behavioural changes reminiscent of human PD. In alpha synuclein knockout animals this does not occur and the laboratory evidence is strongly reminiscent of the "templating" typical of prion disorders. The only non-prion like property of mutated/excessive levels of alpha synuclein is the absence of human to human transmissibility (so far). Following this (in the controversies session), Patrik Brundin again clearly articulated why PD was a prion disease, but admitted to needing to move the goal posts to redefine the term "prion" as not necessarily "infectious", but overall failed to win his debate with Glenda Halliday (despite his desperate analogies about alpha synuclein gut transmission and Australian immigration policy).

Nevertheless, with this growing insight into the spreading pattern of alpha synuclein (and other proteins?), might the time be coming for us to take stock of how we clinically classify movement disorders? David Williams proposed that as clinicians we should start putting more emphasis in the clinic on our knowledge of the likely pathological proteins and their distribution, as a way of classifying the spectrum of clinical syndromes we see, and losing nebulous terms such as "atypical parkinsonism". Consistent with this way of thinking, Yoshinori Higuchi presented his latest work on ways of imaging proteinopathies, including a growing number of new PET ligands for A-beta (18F AV-45), Tau (11C PBB3, 18F-T807), alpha synuclein (11C BF-227) and TDP43, however the precise sensitivity and specificity of these ligands related to "clinical" diagnoses and /or pathological diagnoses remains to be clarified.

While it is clear that there has been great progress in our understanding of PD pathogenesis, to date there has not been a single (proven), disease modifying treatment. Creatine and pioglitazone have recently failed, but with a degree of optimism, Tanya Simuni summarised the ongoing potential surrounding trials of isradipine, inosine, exenatide, nicotine, (alongside the safety data of both the Prothena and Affiris alpha synuclein vaccination programmes described earlier). Unfortunately it seems there's currently precious little happening regarding trials in MSA, but of course the vaccination programmes will potentially also be relevant and there is additional interest in approaches like intranasal insulin (insulin signaling is in fact of growing interest related to a range of neurodegenerative processes).

James Surmeier gave a further critique of recent basic science breakthroughs, including the very recent publication from Peelearts et al, on different alpha synuclein strains; ribbons (easily remembered as linguine) – these undergo thioflavin phosphorylation and cause glial cytoplasmic inclusions similar to MSA, but don't cause dopamine cell loss unless in the presence of over expression of alpha synuclein, whereas fibrils (or spaghetti) cause greater neuronal loss in the striatum. He speculated whether perhaps these differing strains relate to different levels of calcium ions in different neuronal and glial cell populations. He also described work showing that alpha synuclein overexpression actually has a functional change on substantia nigra compacta dopamine neuronal firing pattern through potassium channel down regulation. (Unsurprisingly, given his original work with isradipine), he again speculated whether calcium may be involved in a subsequent spiral of neurodegeneration.

Other movement disorders were also covered including a great session on Dystonia phenomenology (probably the archetypal subject of appeal to clinicians who have evolved to become movement disorders specialists). Victor Fung reviewed both the recent classification, showed some great dystonia videos and emphasised that a movement disorders examination must include assessment of patients performing those specific tasks that provoke their symptoms! Despite the seemingly endless number of genes to remember relating to movement disorders eg Beta propeller associated neurodegeneration, BPAN – (consider when patients have childhood deficits then remain stable through teenage years then have progressive degenerative change in adulthood), what has been reinforced at this meeting is the real importance of adenylate cyclase 5 (ADCY5) – which seems to be a not uncommon cause of childhood chorea or dystonia +/- facial myokymia (autosomal dominant or de novo and usually survive to adulthood)…many videos with this genetic diagnosis were submitted to this year's MDS Video Olympics.

Gunther Deuschl described the lessons that can be learnt by studying tremor in elderly people, measured simply using spiral drawing scores and the simple relationship between

The San Diego skyline, including the salubrious conference venue – The Manchester Hyatt hotel.

these scores, activities of daily living, cognition and mortality. Even after adjusting for potential confounders, "tremor" as a crude measure appears to be an independent risk factor for mortality, in contrast to the subgroup with a confirmed diagnosis of "Essential tremor" in whom mortality is not elevated. Furthermore using functional imaging apparently helps to reveal different neural networks involved in "age related tremor" versus essential tremor, further justifying why these ought not to be "lumped together". (There was no comment where patients with dystonic tremor fitted into all this).

In a session on the overlap between movement disorders and epilepsy, Marina de Koning Tijssen described the myoclonus epilepsy syndromes, while Sarosh Irani discussed the autoantibodies associated with paroxysmal movement disorders including; LGI1 (faciobrachial dystonic seizures best treated with immunotherapy), NMDA receptor (variably presenting as a paraneoplastic ovarian teratoma associated encephalitis ranging to focal unusual chorea/dystonic syndromes), Iglon5 (this is a recently described autoimmune parasomnia causing involuntary movements in REM and non-REM sleep with additional axial signs) and Aquaporin4 (painful tonic spasms can occur as the major feature, not just classic neuromyelitis optica).

Jens Volkmann reviewed the direction of travel of Deep Brain Stimulation highlighting the interest in "adaptive" or closed-loop stimulation – ie only stimulate when the local signals are abnormal, it seems that this approach is better than conventional DBS albeit in small numbers of patients in brief assessments. He also described the use of the PC+S device which may one day enable chronic delivery of closed loop DBS, although stumbling blocks include inter individual variation, and consistent beta (abnormal neuronal activity) was only seen in 7/14 electrodes that his group has tested. The device manufacturers are in stiff competition right now with the possibility of using multiple source current steering (as used in the VANTAGE trial) which allows clinicians to shape the stimulation field (but only along z axis), right alongside the possibility of directional stimulation (in either x or y axes) made possible with segmented electrodes. (Do these "advances" just compensate for poor surgery/imperfectly placed electrodes? A more forgiving view might be that the perfect targeting within the STN is still not clear, thus these approaches allow post operative flexibility.)

Young investigator awards

Drs Maurer & Balint received the young investigator awards for their work on resting state fMRI of functional movement disorders, and another rare antibody association (DPPX antibodies-seen again in the Video Olympics) as a cause of stiff person syndrome, respectively.

The Grand rounds

Our most eminent colleagues (who shall remain respectfully nameless), were then called on to display their history and examination skills on 5 patients drafted in for our education.

1. A 28 year old with recent onset of rest tremor of right hand, mild right hand bradykinesia and dystonic posturing of fingers. MRI imaging showed a cystic lesion in the left upper brainstem associated with a nigrostriatal deficit on DaTSCAN imaging. He responded well to L-dopa. The eventual diagnosis was that of Virchow Robin spaces ??! (not sure how convinced I was of this presumed diagnosis based on the extremely unusual cystic lesion in the midbrain we were shown on his MRI).
2. An 18 year old with onset of intermittent involuntary movements since childhood progressively getting worse, but with normal cognition. Bouts of severe jerks interfered with sleep, she had dysarthric speech, a profoundly weak neck, jaw opening dystonia, facial myokymia, and clonus. She had normal imaging, CSF, muscle biopsy and the diagnosis was (wait for it) yet another patient with an ADCY5 mutation.
3. A 66 year old male with 20 years of hemiparkinsonism (+/- dystonia) who was responsive to L-dopa, had fluctuations and dyskinesia, freezing, loss of olfaction, bradykinesia with decrement and had a family history of Lewy body dementia (father)/ Dopa Responsive Dystonia (daughter). No surprises here – he was found to have a GCH1 mutation.
4. A 43 yr old woman with "cerebral palsy" (immediately think DRD), who had the diagnosis re-explored because of variable abnormal movements and abnormal sleep (the extra clue). She also had delayed milestones, and learning difficulties. The examination revealed slurred monotonous speech, and perhaps some subtle limb posturing. She had no dopa response. After a bit of discussion implicating both dopamine and serotonin biosynthesis problems, she was (of course) found to have sepiapterin reductase deficiency.
5. Finally a 73 year old retired surgeon with a 12 year history of gait and balance difficulty and recent postural and action tremor. Also mild

cognitive impairment – (that the patient repeatedly contested). Examination showed gait ataxia and finger nose ataxic tremor, (surely this was enough of a clue), also a grand-daughter with tremor. The MRI showed abnormal signal in the middle cerebellar peduncle, so (of course) the genetic diagnosis was FXTAS – an FMR pre-mutation (99 repeats).

The Parallel sessions

Of course you can't go to all of these, but the highlights from those I attended (my own interests) included; the role of Deep Brain Stimulation beyond Parkinson's disease as discussed by Michele Tagliati and my colleague Patricia Limousin, with excellent video footage of the utility of DBS in tremor subtypes, primary generalised and focal dystonias, tardive dystonia, and the growing evidence of its potential utility in Tourette syndrome.

Relating to potential disease modifying treatments, Anthony Schapira presented "Prospects for therapy in GBA related PD". While the precise mechanism(s) through which GBA (the commonest genetic risk for PD) causes neurodegeneration is yet unclear; these may include substrate buildup (potentially restored by Miglustat), loss of GCase function (thus may be able to use gene therapy eg GBA-AAV), loss of lysosomal function (potentially increased via Ambroxol mediated increase in TFEB activity), or a toxic buildup of protein within the endoplasmic reticulum (again may be helped by Ambroxol or other small molecule chaperones, or HDAC inhibitors). Importantly these approaches may also have relevance to PD without GBA mutations.

The Video Olympics

This is always an unmissable session – the panel were uniformly quaking in their boots as they walked on stage, but Tim Lynch showed why he's so highly regarded clinically on this international MDS stage.

1. A patient with Narcolepsy type 1 causing cataplexy.
2. A young man with DPPX Ab (a new cause of stiff person syndrome) causing stimulus sensitive jerks with dysautonomia (Raynauds syndrome).
3. Gluten enteropathy (Coeliac disease) related to bilateral leg myoclonus, which persisted during sleep.
4. Myoclonus dystonia caused by a 6q deletion.
5. A lady with childhood seizures and developmental delay who remained stable then she deteriorated and had classic iron deposition in the nigra – this was the BPAN form of NBIA (WDR45 gene mutation).
6. An IGLON5 Antibody syndrome causing cognitive/tongue movements, behavioural problems and a post synaptic dopaminergic deficit.
7. Neurosyphilis causing a subacute ataxic myoclonus syndrome.
8. Monoballismus in a deafferented limb due to a midbrain lesion, and then a further contusion and speculation about how this informs on basal ganglia output.
9. Dystonia Parkinsonism and facial numbness with classical imaging changes due to CLIPPERS.
10. Progressive cerebellar and dystonia and long tract signs with positive OCBs due to anti-GAD Ab.
11. Neurocysticercosis causing epilepsia partialis continua.

Blue Ribbon highlights

This is a great way of catching up with the important bits among the posters that you might otherwise have missed. Davis Standaert and Christine Klein had reviewed >1400 submitted abstracts and presented the following as the most worthy of mention;

a) Work by the Diesseroth group showing the use of optogenetics to switch ON and OFF dopaminergic cell grafts in rodents.
b) Blepharospasm being more common (relative to cervical dystonia) in more southern placed regions with greater sunshine.
c) A family with an A53T alpha synuclein mutation with variable penetrance (although admittedly, perhaps the asymptomatic mutation carriers had not yet passed through the age of risk).
d) A parkinsonian kindred with X-linked dominant inheritance due to a RAB39B mutation.
e) GCase activity in PD patients with and without GBA mutations. (Even those without GBA mutations have lower GCase activity than controls).
f) Non manifesting LRRK2 G2019S mutations have an increase in risk-taking behaviour (perhaps a PD endophenotype).
g) The exosomal microRNA profile (using array based technology) in the CSF of 5 patients with PD, which found a reduction of miR-1587, (which controls PLK2 which plays a role in phosphorylation of alpha synuclein perhaps relevant to how alpha synuclein is normally targeted to chaperone mediated autophagy.
h) Increased clearance of alpha synuclein by enhancing lysosomal function via overexpression of the transcription factor TFEB in rodents.
i) The FRET (fluorescent resonance energy transfer) based system of alpha synuclein detection as a means of measuring "prion-like" forms of alpha synuclein.
j) Deleting mutant huntingtin from microglia in HD mice influences the behaviour of these cells BUT not the behaviour or histology of the animals.
k) The Predict PD study nicely defining the risk factors for incident PD.
l) Monitoring PD progression using smartphone technology.
m) Men with de novo PD have greater presynaptic deficits measured on DATSCAN imaging than females with de novo PD.
n) Tau imaging in 14 PSP patients using 18F AV-1451 showing differences in basal ganglia uptake (especially GPi) between patients and controls.
o) Using metabolomics in CSF and serum samples from DATATOP to measure PD progression identified a 15 compound profile that predicted change in UPDRS 2+3 scores.
p) Subcutaneous L-dopa infusions (ND0612) in 16 PD patients provide steady plasma concentrations.
q) Inhaled L-dopa (CVT301) in placebo controlled trial shows both efficacy (diaries + UPDRS) without increase in dyskinesia and no lung related adverse effects.

So pretty good meeting all in all. Great venue, well organised and augers well for Berlin 2016.

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th August, 2015

2015

September

Faculty of Neuropsychiatry Annual Conference 2015
10-11 September, 2015; London, UK
www.rcpsych.ac.uk/traininpsychiatry/conferencestraining/conferences/neuropsychiatryconference.aspx

Paediatric Oncology Solid Tumours Study Day
14 September, 2015; London, UK
www.royalmarsden.nhs.uk/paedsolidtumours
T. 020 7808 291/2924
E. conferenceteam@rmh.nhs.uk

How to Develop a True 7 Day Stroke Rehabilitation Service
16 September, 2015; Birmingham, UK
T. 01732 897788
E. nichola.cadwallader@sbk-healthcare.co.uk
http://sbk-healthcare.co.uk/home/event/1048/#eventpage

Stroke Rehabilitation Service Delivery
17 September, 2015; Birmingham, UK
T. 01732 897788
E. nichola.cadwallader@sbk-healthcare.co.uk
http://sbk-healthcare.co.uk/home/event/1045/#eventpage

ILAE British Chapter Annual Scientific Meeting
23-25 September, London, UK
www.ilae-ukconf.org.uk

October

The Practical Cognition Course
1-2 October, Newcastle, UK
Contact: Ann Fitchett
E. ion@newcastle.ac.uk
T. 0191 208 8320
www.practicalcognition.com

37th Clinical Neurology Course
5-6 October, 2015; Edinburgh UK
www.ed.ac.uk/schools-departments/clinical-brain-sciences/postgraduate-training/edinburgh-clinical-neurology-course
E. Judi.Clarke@ed.ac.uk

November

Consultant PD Masterclass – Sheffield
Module 1 – 2, 3rd & 4th June 2015
Module 2 – 26th November 2015
(Both modules must be attended)
www.parkinsonsacademy.co.uk for further details.

23rd Annual Meeting of the European Charcot Foundation
26-28 November, 2015; Milan, Italy
www.charcot-ms.org/en/registration-information
E. stephanie.vandenbossche@seauton-international.com

Neurology 2015: Leading-edge neurology for the practising clinician

Conference details: 26-27 March 2015. ***Report by:*** Dr Elisabeth Rounis, Clinical Lecturer in Neurology, University of Oxford

After a positive response when it was introduced last year, Neurology 2015 ran for a second year, aiming to present cutting-edge neurology for the modern clinician. The National Hospital for Neurology and Neurosurgery (NHNN) has historically played a major role in guiding practice in the field. With changes in modern medical practice and evidence-based medicine, this institution continues to be involved in guiding modern practice for the management of neurological disorders. This was exemplified by the high quality of talks provided by leaders in the field, who are currently working at the NHNN.

The course presented an ambitious programme of talks centred around six topics in the field, over two days. It kicked off with clinical sessions relating to leading treatments of acute neurological disorders: starting with a comprehensive talk on the clinical manifestations and treatment of Guillain-Barré Syndrome presented by Dr Howard. He discussed new potential treatments, based on recent understandings of the pathophysiology of the condition. This was followed by a talk on treatment of meningitis by Dr Farmer. He discussed the most common pathogens for the disease, options of antibiotic regimes as well as prospects of vaccination. Professor Shorvon discussed the challenging management of super-refractory status epilepticus with an invitation for all participants to register new cases online for the development of consensus criteria (please visit: https://www.status-epilepticus.net/).

The first topic was followed by a scientific talk from Nobel Prize laureate Professor James Rothman. He presented key findings from his research, namely the discovery of 'SNARE' proteins which are involved in cellular membrane fusion, leading, among other functions, to exocytosis and therefore mediating neurotransmission. His work has implications for several neurological disorders including myasthenia and Lambert-Eaton myasthenic syndrome, in addition to explaining the effects of botulinum (and other) toxins on the nervous system.

Dr Gordon Plant brought the clinical discussion back on the table by presenting eye movement disorders in clinical case-vignettes.

The afternoon topics were centred on the clinical approaches to neuromuscular disorders with talks from Professor Reilly on the diagnosis and management of peripheral neuropathy, noting recent advances on the genetic classification of inherited forms of the disease. Professor Hanna presented a clinical approach to diagnosing muscle disorders. Professor Kullman ended the session with disorders of the neuromuscular junction, in particular myasthenia gravis.

The late afternoon sessions were on the management of clinical disorders: namely headache and Parkinson's disease. Dr Matharu presented an evidence-based approach to migraine and chronic headache, with upcoming treatments proposed, including neuromodulation. Professor Bhatia ended the topic with a discussion on therapeutic approaches to the management of Parkinson's Disease (PD).

The following day started with a topic discussing areas where decisions about therapy can be difficult in neurology. Talks included a discussion on the challenges of selecting among newly developed disease modifying treatments in Multiple Sclerosis, presented by Dr Chataway. He described risks and benefits of each of the treatments and provided an approach on escalation regimes. Dr Rees presented therapeutic approaches to the management of gliomas, with progress in the field including new classification methods introduced by molecular oncology, as well as therapeutic options including the possibility of considering immunotherapy. The final talk in that session was provided by Miss Grieve, Consultant Neurosurgeon, on the management of vascular malformations and aneurysms. She discussed trials comparing treatment options, and new techniques making some neurosurgical approaches a safer treatment option.

This topic was followed by a session on NHS Commissioning with discussions on provision of neurology services with the current political and socio-economic framework, ahead of the elections.

Dr Lunn then presented a Clinico-Pathological Case, in typical UK Neurology and National Hospital tradition, which was answered by Dr Rees.

The afternoon topics centred on Neuropsychiatry and Dementia. This started with a clinical talk by Professor Rossor on the clinical evaluation of patients with dementia, with some video examples. Professor Joyce discussed neuropsychiatric manifestations of PD and their management. Finally Professor Collinge gave an overview of Prion Disease with new advances in diagnostic techniques and the possibility of new therapeutic trials, referencing the impressive work of Professor Mallucci in that field.

The final topic of the course centred on recent advances in the treatment of stroke. Dr Werring presented treatment therapies for acute strokes. Professor Martin Brown discussed stroke prevention.

This course provides an opportunity to learn on various neurological topics from experts in the field. The main positives of the course include the idea of alternating scientific and clinical talks, whilst keeping focused on the latter, and trying to provide the most recent evidence for treatment and therapies. The booklet for the course was nicely put together – containing details of the speakers, most recommended journal article of the topic and historical pictures of the National Hospital. Some of the speakers provided their slides in pdf attachments, which was useful, in view of the sheer volume of material covered. The venue, at the Institute of Education, was appropriate for the size of the event, and close enough to Queen Square if anyone wanted to visit... So we look forward to next year's event, in anticipation of the possibility of a scientific talk to be provided by yet another UCL Nobel Laureate, namely Professor John O'Keefe!

Neuroscience at the 25th Cambridge Science Festival

Conference details: 9-22 March 2015, Cambridge, UK. ***Report by:*** Deniz Vatansever (Department of Clinical Neurosciences) and Liam Wilson (Department of Psychiatry).

Each year, the University of Cambridge welcomes over 40,000 visitors into its historic lectures halls, museums and state-of-the art research facilities, as they explore a world of scientific discoveries and knowledge through the Cambridge Science Festival. People of all ages come together with world-renowned scientists in a series of talks, lectures, theatre, art and interactive exhibitions in order to find out more about the latest advancements in science.

Traditionally, one of the themes that has enjoyed tremendous popularity in this festival is "neuroscience". This year, a number of laboratories and institutes opened their doors to welcome visitors into a world of groundbreaking neuroscience research that brings us one step closer to understanding the brain: that mysterious organ, which to many may appear as a 'black box' holding information too complicated to understand. But neuroscientists unravelled the brain for attendees of the 25th Cambridge Science Festival, giving them the opportunity to take part in real experiments at the Health Psychology Lab, getting involved in hands-on activities at the Cognition and Brain Science Unit, and strolling around the Cambridge University Hospital exhibits. Visitors were also able to attend various public lectures and free talks that have been arranged to tell the fascinating story of progress in neuroscience and discuss the outstanding questions that remain elusive. The discussions spanned not only brain disorders and mental health, but also included the importance of playfulness in child development and adult creativity, what we can learn from studying animals like scrub jays (a member of the crow family), and the impact of science on morality and ethics.

One of the highlights of these neuroscience talks was the public lecture, given by Professor of Behavioural Neuroscience, Barry Everitt, as part of the 27th Cambridge Neuroscience Symposium. Throughout his career, Professor Everitt has made substantial contributions to the field of learning, memory and addiction, receiving numerous awards and recognitions for his work. This year, the main focus of his lecture concerned drug addiction, a disorder affecting over 15 million people worldwide (WHO Report, 2012). Professor Everitt first outlined explanations of the brain mechanisms that underlie compulsive drug-seeking behaviour, before concluding his talk by discussing novel treatments that have emerged to help individuals overcome relapse.

Continuing along the theme of brain disorders, another free talk series entitled "Cambridge Stars," showcased the newly elected Royal Society Fellows as they introduced their research. Dr Karalyn Patterson from the Department of Clinical Neurosciences described her ongoing studies investigating the effects of brain damage and disease on language and memory in adults, including Alzheimer's disease and semantic dementia. Given the ageing population, dementia poses a considerable problem for our society today, with conditions like Alzheimer's disease affecting more families and causing a large strain on both the health system and the economy. Thus, a number of researchers from Alzheimer's Research UK (ARUK) explored what happens to the brain when people develop dementia, covering translational research techniques from stem cells to brain scans, all of which are being used in working towards a cure. The Rising Stars – a group of talented students who have received training in public engagement and educational outreach – reiterated the story of the brain's lengthy journey from health to disease through an interactive theatre session. Penned as a discussion amongst passengers on a train, the play delved into topics such as stems cells and intellectual development.

Professor of Behavioural Neuroscience, Barry Everitt.

Last but not least, Dr Thóra Káradóttir explored the power of stem cells in unraveling and potentially providing a treatment for the damage to the "super-highways" of the brain known as white matter. In her inspirational talk, Dr Káradóttir wowed the audience with colourful images of brain cells, while providing a thorough explanation of their purpose, as well as their links to damage and disease.

But brain disorders were not the only focus of the 25th Cambridge Science Festival. Many artists actually show greater creativity as they get older, and produce their most powerful work later in life. Based on this observation, Dr Karen Campbell from the Centre for Speech and Language, and Dr Charlotte Lee from the Faculty of Modern and Medieval Languages discussed ageing artists and the potential links to the science behind their art. Moreover, in an interactive workshop, Professor Patrick Bateson from the Department of Zoology and the creative facilitators from Playful Being demonstrated the power of playfulness in an interactive workshop – a seemingly important activity not only for the maturation of children, but also for adults. A group of panelists from the Department of Education, led by Dr Sara Baker, Dr David Whitebread and Dr Jenny Gibson, discussed the role of "playing" on the learning and development of children. Finally, an extraordinary team of researchers, including Professor Barbara Sahakian and Dr Jennifer Wild, and columnist Allison Pearson gave practical advice on how to manage day-to-day stress, overcome anxiety and balance work and life commitments in order to maintain a healthy brain.

And so the Cambridge Science Festival celebrated another successful and engaging year, with over 280 activities provided by the kind support of all the scientists, artists and students, as well as the endless generosity of the sponsors. Through this tight-knit network of support, the Cambridge Science Festival shall continue the tradition of providing an opportunity for science enthusiasts to find out more about the groundbreaking research conducted at Cambridge, and to inspire young minds to seek out careers in science.

TNA UK Joint Patient Conference/ Healthcare Professionals' Study Day

Conference details: 6 June 2015, London, UK. ***Report by:*** Dr Mehri Eghtessad, Division of Diagnostic, Surgical and Medical Sciences, Eastman Dental Hospital.

The conference was held in the Grange Hotel Holborn, London, in two adjoining rooms for patients and healthcare professionals from a wide range of different specialities: neurosurgeons, oral surgeons, specialists and physicians, plus dentists and nurses - a total of 33 specialists and 120 patients and carers in all attended this 4th joint meeting.

Professor Zakrzewska, who is the chairperson of the Medical Advisory Board of the Trigeminal Neuralgia Association UK, welcomed healthcare professionals to the meeting. The first presentation was delivered by three Trigeminal Neuralgia (TN) sufferers who had been diagnosed with different types of TN: classic, atypical and symptomatic. All had received medical and surgical treatment, the first patient, a 4th year dental student, had undergone microvascular decompression and is in remission. He is looking forward to completing his course of dental studies and being at the frontline of diagnosis to ensure no one suffers unnecessarily. He also highlighted two issues about TN:

- there are no emergency guidelines to manage severe flare-ups
- psychological management of post traumatic stress disorder related to TN and the fear of pain recurring must be part of the treatment package

Prof Zakrzewska reiterated the importance of a holistic approach as opposed to a medical management only pathway. One of the other patients highlighted how much easier it was dealing with the public when saying she had a small benign tumour rather than trigeminal neuralgia.

Prof Zakrzewska was the next presenter, discussing the need for good communication and the need to listen to patient stories. She discussed the place of narrative medicine and the use of language as well as metaphors in elucidating the characteristics of facial pain. She touched on the challenges of chronic pain, training of medical students to manage chronic pain and the need to listen to patients without interruption.

After a coffee break, Dr Deborah Padfield, a visual artist and research associate, gave her talk on images and the understanding of pain communication, the invisibility and subjectivity of pain, and how some patients can communicate their pain much better via images. She talked about various strands of her project and explained the process of producing the images with the collaboration of the patient. She illustrated this with the example of a patient photograph of an apple rotten to the core "which signified her own sensation of being decomposed".

The next speaker was Dr Clare Daniel, Consultant Psychologist and the lead of facial pain services at the Eastman Dental Hospital.

Patients listening to Prof Joanna Zakrzewska, Chair of TNA UK's Medical Advisory Board

She highlighted how unhelpful the model of pain is, incorporating as it does the concept of dualism or the mind/body split. In patients with chronic pain, psychological and sensory inputs are at work in pain processing. It is important to consider the impact of all chronic pain on physical, psychological and social aspect of patients' lives. Clinicians must uncover patients' beliefs about their symptoms, their future treatment goals and the investigations they think they need. Patients and clinicians must have the same model of pain and patients cannot be helped unless they develop a better understanding of their pain and its drivers.

Mr Owen Sparrow, Consultant Neurosurgeon from Southampton General Hospital, discussed posterior fossa procedures for patients with trigeminal neuralgia. There are three absolute indications for surgery: correct diagnosis, uncontrolled pain not responding to drugs and severe side-effects towards drugs. He highlighted that as well as the most conventional procedure of microvascular decompression, a non destructive procedure, neurosurgeons are also performing internal neurolysis and partial sensory rhizotomy, both of which damage the trigeminal nerve. These can have good initial success, but long term results are not as good. Neurostimulation is the latest technique to be developed.

After a joint lunch with the patients and their carers, the healthcare professionals started with a diagnostic quiz on 7 case histories, the theme being unilateral episodic facial pain. These were all patients seen by Prof Zakrzewska and she provided her diagnosis and their follow up response to her management plan. The new International Headache Classification was used and it was highlighted how little high quality evidence is available for the diagnosis of rare headache conditions. This was followed by Prof Zakrzewska reminding the audience of the lack of high quality evidence in the field of trigeminal neuralgia and providing some reasons why this is the case. She provided early results of a phase 2 trial for a new drug for TN, which has not previously been used in epilepsy. She mentioned the difficulties in recruiting patients into the study, however, early results show a positive response to the new drug.

Following afternoon tea, the healthcare professionals and patients joined together to listen to Dr Adeline Crawford, Clinical Psychologist within the facial pain services at the Eastman Dental Hospital, speaking about mindfulness. She directed the delegates to carry out mindfulness, which teaches us to be open to all emotions and not to push away those feelings we don't like, "staying with this moment".

The last event of the day was a question and answer session. The patients had submitted questions in writing throughout the day and these were then answered by the panel of speakers. It was also an opportunity for the Health Care Professionals (HCPs) to ask questions and get answers through a show of hands. The questions were varied, from the use of drugs and surgery to questions on the role of psychology in trigeminal neuralgia.

The evaluations were highly positive with the talks being given a high rating both for content and usefulness. Important skills that were learnt related to the practise of mindfulness and the need for improved communication in order to improve diagnostic skills. The variety of specialists present added interest and the patients' talks where highly valued. As usual various comments re venue, visibility of slides, lack of microphones were received but these were outweighed by the positive comments. Overall a very useful Study Day that should be attended by more healthcare professionals who treat this rare disorder.

Senior Appointments at BIS Burton Park

Partnerships in Care Brain Injury Services is pleased to announce the appointment of Louise Smith, Hospital Director and Dr Caroline Knight, Lead Consultant Clinical Neuropsychologist at the new brain injury service, Burton Park in Melton Mowbray, Leicestershire.

Dr Caroline Knight has over twenty years' experience in working with people with neurological conditions including ABI, dementia and Huntington's disease and has helped to develop nationally acclaimed psychometric assessment tools with Professor Alderman. Louise Smith is a specialist in developing and leading neurobehavioural rehabilitation and challenging behaviour services having developed the first female only neurorehabilitation unit in the country as well as leading a neuropsychiatric service.

Professor Nick Alderman, Director of Clinical Services, PiC Brain Injury Services said:

"Louise and Caroline bring a wealth of experience to Burton Park which is the only specialist neurobehavioural rehabilitation service in the area. We are working together to further develop our extensive clinical programmes as well as our vocational and educational facilities. Burton Park is the one stop shop for ABI services in the Midlands".

John Hardy awarded 2015 Robert A. Pritzker Prize for Leadership in Parkinson's Research

Professor John Hardy has been awarded the 2015 Robert A. Pritzker Prize for his leadership in Parkinson's genetics research. The award was presented by Michael J Fox at a ceremony in New York on April 15.

An expert in Alzheimer's genetic, Hardy, who is a professor at UCL, led a team toward a pathological discovery that revolutionised Parkinson's drug development. Moreover, he is regarded as an influential thought leader in driving the exploration of genetics for a causal role in Parkinson's disease, an area given little merit only 20 years ago.

The Pritzker Prize has been awarded annually since 2011 by MJFF to recognise researchers who make an exceptional contribution to Parkinson's research and exhibit a commitment to mentoring the next generation of Parkinson's scientists. Hardy will receive a $100,000 grant to advance his research in neurodegenerative diseases.

Professor Anthony Holland Awarded the CBE

Congratulations to Professor Anthony John Holland who has been awarded a CBE for his services to psychiatry. Professor Holland is the Professor of the Psychiatry of Learning Disabilities and Head of the Cambridge Intellectual and Developmental Disabilities Research Group in the Department of Psychiatry. His main areas of research include the relationship between genetic syndromes and associated psychiatric and behavioural disorders, and clinico-legal studies. He is also Chair in Learning Disabilities at the Health Foundation, Fellow and Vice-President of the International Association for the Scientific Study of Intellectual Disability, President of the UK Prader-Willi Association, and President of Cambridge MENCAP.

Student Essay Awards 2015

We are pleased to announce the launch of three Student Essay Prizes. If you are a student yourself, or have contact with medical students, please take a look at the awards and how to submit an entry. There is a £500 prize in each of the three categories. These are:

1. **Medical Student Essay.** Open to all UK medical school students (undergraduate and postgraduate) and we are looking for an essay on any aspect of Encephalitis. The winner will also be given a one year elective on to our Professional Advisory Panel.
2. **The Professor Barbara Wilson OBE Neuropsychology Student Essay Prize.** This is open to any psychology student at postgraduate level and the essay can be on any aspect of the neuropsychology of Encephalitis. The winner will also be given a one year elective on to our Professional Advisory Panel.
3. **The Johnny Sutton Student Travel Bursary.** Any student in medicine or neuropsychology can apply for this and the bursary will be used to support his/her work relating to Encephalitis.

Full details and information on how to apply are at www.encephalitis.info/research/grants-and-awards/. These prizes are an excellent opportunity for students to advance their learning and development and to make a contribution to understanding of Encephalitis. Thank you for your support – The Encephalitis Society team.

NeuroVive´s Clinical Phase II study for traumatic brain injury passes safety evaluation

The Swedish biotechnology company NeuroVive Pharmaceutical recently announced that the ongoing clinical Phase IIa study for traumatic brain injury with the company's drug candidate NeuroSTAT® passed a safety evaluation and is moving on to the higher dosage group with the last 10 of 20 patients. The interim analysis included an evaluation of blood concentrations of cyclosporin A (the active substance in NeuroSTAT®) and changes in intracranial pressure and blood samples collected to analyze possible organ injury.

"We've now obtained important safety data on the lower dose of NeuroSTAT® for treating patients with traumatic brain injury and can now move on to treat patients with the higher dose. This means that the study has reached an important milestone in the clinical trial program of NeuroSTAT®," commented NeuroVive's CEO Mikael Brönnegård.

More information about the study can be found at: https://clinicaltrials.gov/ct2/show/NCT01825044

NeuroVive´s project for the treatment of stroke enters new phase with Isomerase Therapeutics

NeuroVive Pharmaceutical, a Swedish biotechnology company focusing on mitochondrial medicine, is entering a new phase in the company´s development project NVP014 for the treatment of ischaemic stroke in collaboration with UK partner Isomerase Therapeutics. The former collaboration with to-BBB of the Netherlands concluded at the end of 2014 and on the basis of the results obtained, NeuroVive is now developing new molecules and a more effective method for penetrating the blood-brain barrier.

The collaboration with Isomerase has already generated new lead compounds that are in pre-clinical evaluation.

"The initiative we've now begun with Isomerase Therapeutics is based on the same chemistry platform as our NVP018/NVP019 compounds, which we view as the next generation cyclophilin inhibitor. We're also developing a new method for improved penetration across the blood-brain barrier," commented Magnus Hansson, Senior Scientist at NeuroVive.

Innovative MR technology puts the University of Glasgow at forefront of brain imaging research

Two high-resolution imaging systems from Siemens Healthcare will be installed on the South Glasgow University Hospital campus, including a MAGNETOM 7T MR system in the Imaging Centre of Excellence Building.

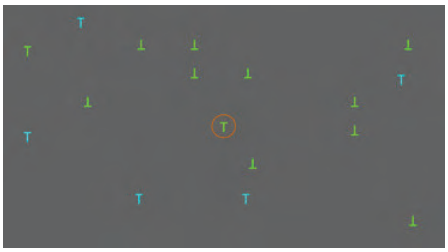
The University of Glasgow has recently received significant external funding to support investment in state-of-the-art research facilities. This includes two high-resolution imaging systems from Siemens Healthcare with a primary initial focus on brain research. The technology will provide detailed insights into the brain's structure, function and biochemistry in order to find causes and new treatments into various conditions. The technology includes a powerful MAGNETOM® 7T MR system and a MAGNETOM 3T MR.

Professor Anna Dominiczak, Vice Principal and Head of the College of Medical, Veterinary and Life Sciences at the University of Glasgow said: "These systems will provide us with unrivalled imaging capability and drastically enhance the quality of research carried out in Glasgow. This initiative is testament to the strength of the partnership between academia, the NHS and industry that we have in the city."

w. www.siemens.co.uk/press
Follow Siemens on Twitter at:
www.twitter.com/siemensuknews

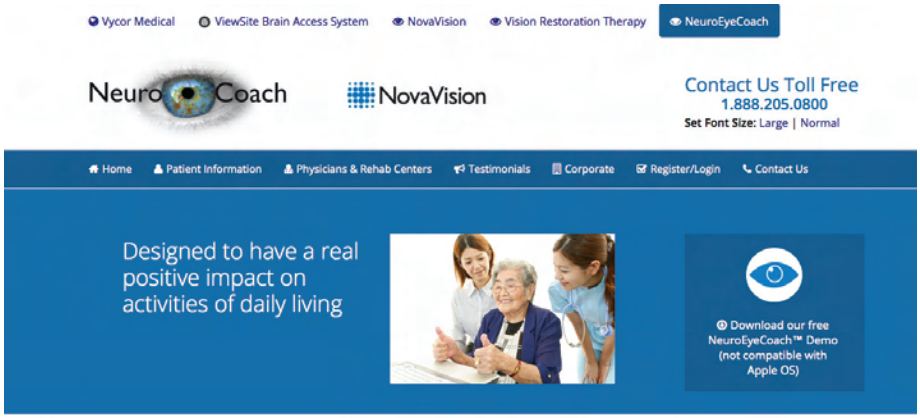
Eye-movement training therapy for visual field deficits

Sight Science, a NovaVision company (OTCQB–VYCO), is bringing to the UK its NeuroEyeCoach eye-movement training therapy for those suffering from visual field deficits as a result of stroke or brain injury. NeuroEyeCoach (www.neuroeyecoach.com) is designed to re-train the ability of a patient to scan the environment and make the most of their remaining visual field. The program is self-adaptive and adjusts the task difficulty to the patient's deficits and progress while encouraging eye movement efficiency.



NeuroEyeCoach was developed by Professor Josef Zihl of the Max Planck Institute based on his original research that has been the subject of 14 clinical studies on a total of 591 patients, along with Professor Arash Sahraie of the University of Aberdeen; both are scientific advisors to NovaVision.

This evidence-based therapy computer program will be available for clinics and also Internet-delivered to patients at home, and can be completed in 2-4 weeks.



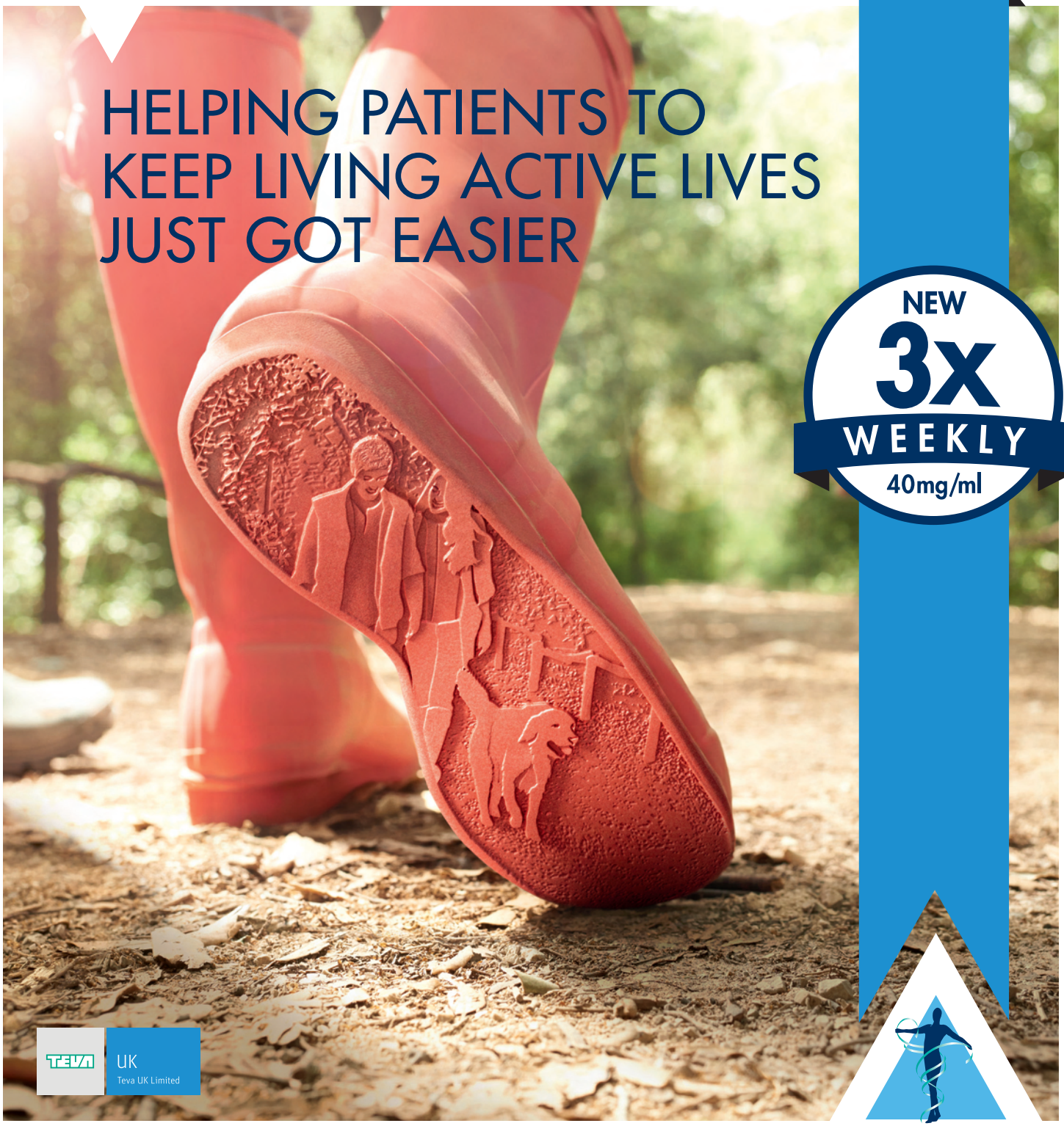
New Copaxone® (glatiramer acetate) formulation launched in UK

Teva UK Limited ("Teva") has launched Copaxone® 40mg/ml three-times weekly injection. Copaxone® 20mg/ml is currently approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). With this new formulation, patients will only have to inject themselves three times per week – compared to daily injections with the existing formulation.

Approval was granted in December 2014 and was based on the findings from Teva's Phase III Glatiramer Acetate Low-Frequency Administration (GALA) study, which involved over 1,400 patients. Results demonstrated that patients dosed three-times weekly with Copaxone® 40 mg/ml experienced significantly reduced relapse rates compared to placebo at 12 months, with a safety and tolerability profile similar to that of Copaxone® 20mg/ml daily.

Dr Ewan Walters, Teva UK's Medical Director, said: "Teva has been committed to the pursuit of MS research, and the development of Copaxone®, for more than 20 years. We are proud to be able to bring to patients in the UK the option of this new, three-times weekly Copaxone® 40 mg/ml formulation which we believe will offer patients and their healthcare professionals flexibility in choosing a dosing regimen that works best for them."

Copaxone has been available in the UK since 2000. The three-times weekly 40 mg/ml formulation gives patients a convenient treatment option. Clinical studies have shown three-times weekly Copaxone® can maintain the benefits of relapse reduction of the once-a-day formulation, with 57 percent fewer injections.



IT'S ABOUT GOOD DAYS, NOT LOST DAYS

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 and 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:** Not to be used 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/15/0066. **Date of Preparation:** May 2015.

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

UK/UKCPX/15/0012a
Date of Preparation: June 2015