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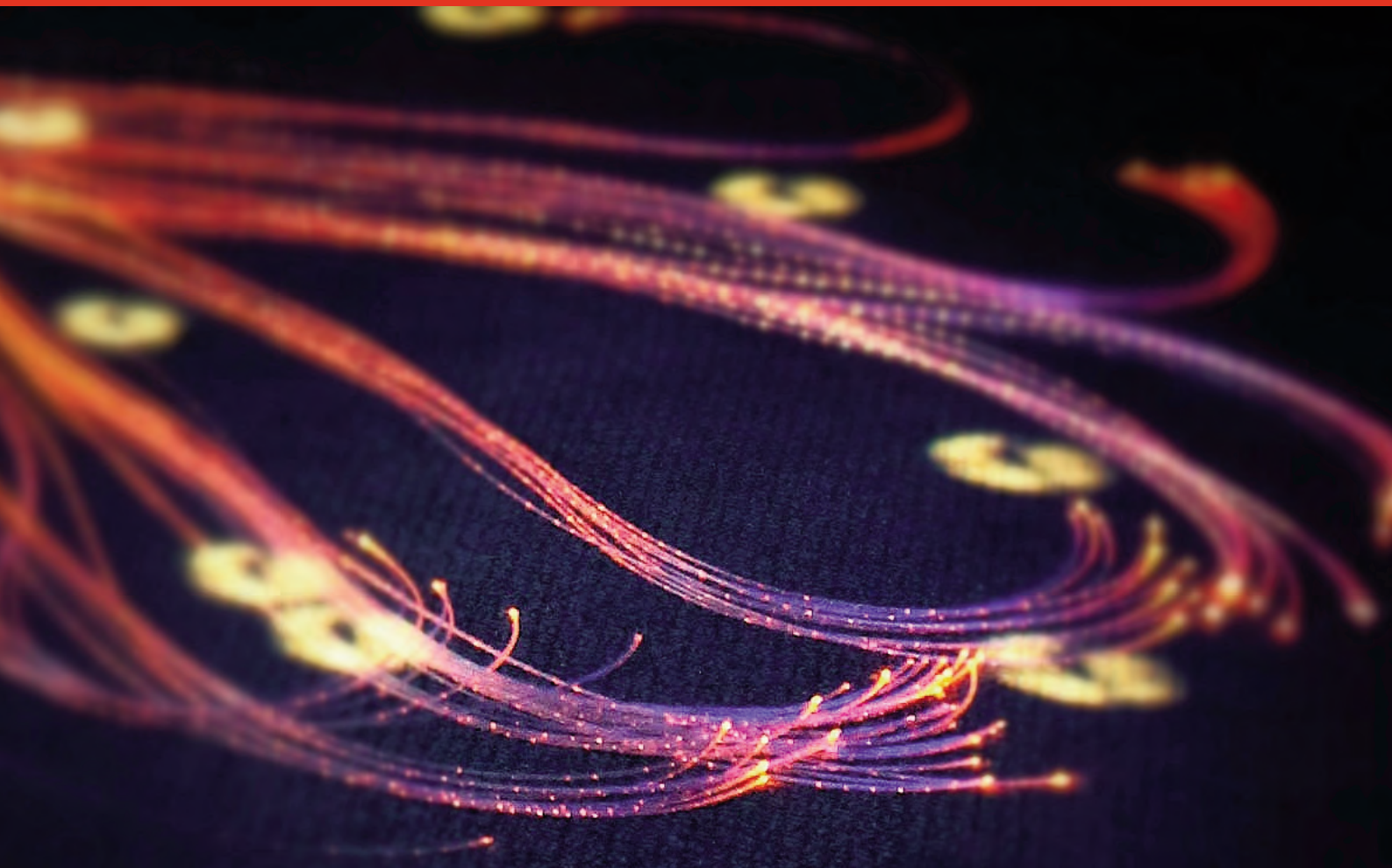
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



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Titleworth Neuro Awarded University Accreditation for Training Programme

Specialist provider of brain injury rehabilitation services, Titleworth Neuro, has developed a comprehensive in-house staff training programme accredited by the University of Brighton. Designed by Titleworth Neuro's Director of Clinical Services and Consultant Neuropsychologist, Dr Anita Rose (pictured), the course will consist of 18 modules in three learning units. Completion of the training will mean that staff not only achieve consistent, high quality standards, but will also know that their workplace learning is recognised as having academic quality. Dr Rose has created three assessment based learning units, each with six modules. The first core unit captures the basic elements of understanding Acquired Brain Injury (ABI) and neuro rehabilitation. The second has six more modules related to the use of multi-disciplinary therapies in ABI neuro rehabilitation and, in the final learning unit, staff will study psychosocial issues commonly experienced in neuro rehabilitation. The first part of the course will run from January 2013, with the aim of putting all current Titleworth Neuro staff through the full programme by mid 2014.

More information about the accreditation is available at: www.titleworthneuro.com/news/

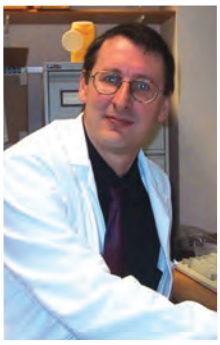
Lifetime Acheivement Award for Professor Thompson's MS work

Professor Alan Thompson has been awarded a lifetime Honorary Membership from the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) at its 28th Congress in Lyon, France. This is the first time this award has been given in the 28-year history of the largest international multiple sclerosis (MS) organisation and reflects Professor Thompson's outstanding international reputation within the field of MS research and his extraordinary contributions to ECTRIMS, an organization which brings together European researchers in MS and connects MS researchers worldwide. Professor Thompson has been crucial to the creation of ECTRIMS as a legal entity, and has established fruitful collaborations between ECTRIMS, ACTRIMS (American Committee for Treatment and Research in Multiple Sclerosis) and LACTRIMS (Latin-American Committee for Treatment and Research in Multiple Sclerosis), and between ECTRIMS and the *Multiple Sclerosis* Journal, of which he is editor-in-chief.

For more information about this prestigious award visit: www.ucl.ac.uk

Professor Dimitri Kullmann elected Editor of Brain

Professor Dimitri Kullmann, based in the Department for Clinical and Experimental Epilepsy, at the UCL Institute of Neurology, has been elected as the new Editor of *Brain*. This neurology journal provides researchers and clinicians with the finest original contributions in the field. Professor Kullmann's appointment reflects his standing in the academic neurology community.



Roger Barker, Co-Editor.

Sanjeev Rajakulendran and Dimitri Kullmann review the inherited ion channel disorders of the brain, an area that is constantly evolving. As an undergraduate I learnt about the sodium, potassium and calcium ion channels simply to understand the basis of the resting membrane potential; action potentials and muscle contraction with no real reference to clinical neurology. Over time this has changed and highlights that the seemingly academic studies of our preclinical days can help understand the clinical problems of tomorrow. This is a clear and insightful article with a number of highly informative summary tables.

In our article in the series on Norwegian Discoveries in Neuroscience, Krisztina Kunszt Johansen and Jan Olav Aasly explore the genetic basis of Parkinson's Disease (PD). In this article they highlight how well characterised cohorts of large numbers of "sporadic" PD can reveal new genes especially as we move into the era of next generation sequencing. They also highlight their own contributions to the genetic basis of some familial forms of PD and how the move towards international collaborations is set to revolutionise this whole field of neurogenetics.

Mark Bovey discusses the value of acupuncture for the treatment of migraine. This takes us through the Gallbladder channel and the various different approaches (both practically and theoretically) and the challenge of defining measures of success which can be very difficult in therapies such as this.

Who wrote the first paper on Alzheimer's Disease in the English language? Andrew Larner tells us in his stimulating account on the life and works of Solomon Carter Fuller, and how his work evolved in its description and importance in the early part of the 20th century with publications in journals such as the American Journal of Insanity!

Pes Cavus is a condition that is not uncommon and is defined as a deformity of "a high arched, relatively stiff foot", as Ball et al discuss in their article in our Rehabilitation Section. There are many causes of this condition and many variants each of which is a consequence in some way of weakness of muscles associated with the foot. This in turn changes the dynamic forces acting on the foot and thus a deformity ensues which brings challenges for the surgeon trying to correct it. This is a very clearly written account that offers much sound advice.

I would like to thank Stephen Kirker for all he has brought to the journal as the Editor of the Rehabilitation Section, as he has now decided to step down from this position. It has been wonderful working with him since the journal came into being in 2001, and he has done an incredible job in ensuring we have always had a first rate article that is interesting and written by the relevant expert. Thank you Stephen. In his place we are delighted to welcome Andrew Bateman (see page 6).

Mark Manford describes the treat that lies in store for 2013 in a new series on Epilepsy. As Mark states, he wrote one of our very first series of articles a decade ago. Indeed ACNR has now been going for 12 years. As the founder (with Rach Hansford) and Co-Editor in chief I am especially grateful for all the support and help I have had in taking this journal from an idea to a regular, much read publication. However, all good things must come to an end, and so I have decided that it is now time to hand it over to my colleague Mike Zandi. I will continue in an advisory capacity, but I think it is time for new ideas and leadership. Happy New Year! ◆

Roger Barker, Co-Editor,
Email. Rachael@acnr.co.uk

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Welcome to ACNR's new team members

New Rehabilitation editor

Andrew Bateman is Clinical Lead for NeuroRehab in Cambridgeshire Community Services NHS Trust, Affiliated Lecturer in Dept of Psychiatry at University of Cambridge. Since 2002 he has been Head of Department at the Oliver Zangwill Centre for Neuropsychological Rehabilitation, where alongside clinical work he has led research & educational activity. He has contributed to publications in topics concerning outcome measurement, cognitive assessment, and emotion, executive function and memory rehabilitation.

New Web editor

We would like to welcome Stevan Wing, the new web and digital editor for ACNR. He is a Specialist Neurology Registrar at Addenbrooke's Hospital, working on dementia and movement disorders at the University of Cambridge.

Stevan is overseeing the launch of our new website at www.acnr.co.uk which should be live by the time you read this. He has also set up a Facebook page, so do join in the conversation.

Inherited Ion Channel Disorders of the Brain

Sanjeev Rajakulendran
is currently a Specialist Registrar at the National Hospital for Neurology and Neurosurgery, Queen Square and an honorary research fellow at the Institute of Neurology. His research interests are in the genetics and electrophysiology of inherited neurological ion channel disorders.

Prof Dimitri Kullmann
is a Professor of Neurology at the Institute of Neurology and an honorary Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, Queen Square. His research interests span the fundamental mechanisms of synaptic transmission and alterations in neuronal and circuit excitability in epilepsy and other neurological disorders. The core methods in his laboratory include in vitro electrophysiology and pharmacology, heterologous and neuronal expression of mutated ion channels, confocal and two-photon laser scanning microscopy and computational simulations.

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The last two decades have witnessed a rapid increase in the number of inherited disorders caused by ion channel mutations. One of the major challenges is to delineate the full clinical spectrum of these 'channelopathies'. Among this expanding group, neurological ion channel disorders are among the best characterised, reflecting the fundamental importance of electrical excitability in the membranes of nerve and muscle cells. The neurological ion channelopathies may be divided into those that affect skeletal muscle and those that affect neurons. A common feature is that they often manifest clinically as paroxysmal attacks of paralysis, myotonia, or brain, spinal cord and nerve dysfunction. This review focuses on CNS channelopathies with the aim of providing an overview of recent advances and identifying gaps in our knowledge of disease mechanisms.

Introduction

Neurological ion channel diseases may be broadly classified as 'acquired'or 'genetic'. Acquired channelopathies are generally caused by antibodies which target specific ion channels or by toxins and venoms which block voltage-gated ion channels. Altered transcription, assembly and membrane trafficking of ion channels may also contribute to many acquired neurological ion channel disorders. The acquired channelopathies are not the subject of this article. Instead, this review is focused on the genetic neuronal ion channel disorders and specifically, those inherited or *de novo* mutations in ion channel subunits which result in brain dysfunction. The genetic skeletal muscle channelopathies, which lie at the other end of the anatomical spectrum and which are characterised by myotonia or periodic paralysis have been comprehensively reviewed elsewhere.[1]

A striking feature of most of the known CNS channelopathies is that they manifest as paroxysms of disturbed function against a background of normal development. Genetic ion channel disorders of the brain generally manifest as epilepsy, migraine, paroxysmal dyskinesia or episodic ataxia. Although individually rare, the expectation is that the study of these monogenic disorders will help to illuminate the pathophysiological basis of paroxysmal disorders in general and in particular the mechanistic pathways involved in common forms of epilepsy and migraine. Whilst a comprehensive review of the brain ion channel disorders is beyond the ambition of this article, our aim is to provide a brief overview of the field and consider the most recent advances, especially from a mechanistic point of view.

Brain ion channels and disease

Epilepsy

Although the genetic basis of idiopathic generalised epilepsy (IGE) remains a mystery, our understanding of the Mendelian or monogenic epilepsies has in contrast progressed considerably. Mutations in genes which encode subunits of CNS sodium, potassium, calcium channels, $GABA_A$ and nicotinic receptors have been reported in association with various epilepsy syndromes[2,3] (Table 1).

Benign familial neonatal convulsions (BFNC) is a disorder characterised by frequent brief attacks of partial and generalised seizures which typically resolve by six weeks of age. It was the first epilepsy disorder for which gene linkage studies established a disease locus, and subsequently identified a pair of potassium channel genes that had not previously been cloned. Mutations in both *KCNQ2* and to a lesser extent in *KCNQ3* have been reported with BFNC.[2] Some cases of severe epileptic encephalopathy have recently been linked to mutations of *KCNQ2*. Other potassium channel genes implicated in epilepsy include *KCNMA1* in which a dominant missense change was identified in a single large family with paroxysmal dyskinesia and epilepsy,[4] and *KCNA1*, the gene mutated in episodic ataxia type 1 (EA1 – see below) which not uncommonly is complicated by seizures.[5]

Generalised epilepsy with febrile seizures plus (GEFS+) is a clinically and genetically heterogeneous epilepsy disorder which manifests in childhood as febrile seizures which may be atypical (hence '+'), afebrile generalised seizures, and in rare cases myoclonic astatic epilepsy. Kindreds with GEFS+ show dominant inheritance but different affected members can present with strikingly different seizure types and severities. Although, the first disease-causing mutation was identified in *SCN1B*, which encodes the β1 auxiliary subunit of the voltage-gated sodium channel,[6] mutations in *SCN1A*, which encodes the pore-forming α subunit of the neuronal sodium channel NaV1.1, have since been identified.[7] GEFS+ can also be caused by heterozygous missense mutations in *GABRG2* which encodes the γ2 subunit of the $GABA_A$ receptor, which mediates fast inhibitory neurotransmission in the CNS. The mechanisms underlying epilepsy associated with γ2 subunit mutations remain unclear.

Mutations in the *SCN1A* gene may also lead to severe myoclonic epilepsy of infancy (SMEI or Dravet syndrome).[2] Affected individuals present in the first year of life with prolonged clonic or tonic-clonic seizures associated with febrile illness, and subsequently develop other seizure

Table 1: Ion channels and epilepsy.

ADNFLE = autosomal dominant nocturnal frontal lobe epilepsy, AR = autosomal recessive, BFNC = benign familial neonatal convulsions, BFNIS = benign familial neonatal-infantile seizures, CAE = childhood absence epilepsy, GEFS+ = generalised epilepsy with febrile seizures+, JME = juvenile myoclonic epilepsy, SMEI = severe myoclonic epilepsy of infancy.

Channel	Gene	Protein	Epilepsy type	Functional effects
Sodium channel	*SCN1A*	α1 subunit of $Na_V1.1$	GEFS+	Impaired inactivation leading to a gain of function
			SMEI	↓ sodium current in GABAergic inhibitory neurons
	SCN1B	β1 subunit of $Na_V1.1$	GEFS+	Impaired inactivation leading to a gain of function
			SMEI	SMEI: AR; loss of function
	SCN2A	α2 subunit of $Na_V1.2$	BFNIS	BFNIS: partial loss of function
			SMEI-like	SMEI-like: Gain of function
	SCN3A	α3 subunit of $Na_V1.3$	Partial epilepsy	↓ sodium persistent current
	SCN8A	α8 subunit of $Na_V1.6$	Infantile epileptic encephalopathy	Impaired inactivation leading to a gain of function
Potassium channel	*KCNQ2*	Subunit of M-channel	BFNC	Interference with channel assembly; ↓ potassium current density;
	KCNQ3	Subunit of M-channel	BFNC	
	KCNMA1	BK Ca^{2+} -activated potassium channel	Paroxysmal dyskinesia and epilepsy	Gain of function (negative shift in opening potential)
Calcium channel	*CACNA1H*	α1H subunit of $Ca_V3.2$ (T-type)	CAE	Gain of function
Nicotinic acetylcholine receptor	*CHRNA2*	α2 subunit of nAChR	ADNFLE	Mutation specific alteration in current density, Ach affinity and ↓ in permeability to calcium
	CHRNA4	α4 subunit of nAChR	ADNFLE	
	CHRNB2	β2 subunit of nAChR	ADNFLE	
GABA receptor	*GABRA1*	α1 subunit of $GABA_A$	JME	↓ in GABA-induced current
	GABRG2	γ2 subunit of $GABA_A$	GEFS+	↓ in GABA-induced current; ↓ sensitivity to diazepam
	GABRB3	β3 subunit of $GABA_A$	CAE	↓ surface expression of $GABA_A$ receptors

types including myoclonic and absence seizures. In addition, speech and motor development is impaired and ataxia occurs. Seizures often respond poorly to antiepileptic drugs. Approximately 70% of patients with SMEI have missense or nonsense mutations of *SCNA1*, and several hundred different mutations have now been identified. These tend to be *de novo* mutations leading to haploinsufficiency. That loss of function of a sodium channel gene should lead to epilepsy is paradoxical. A novel insight into disease mechanisms in this disorder came from a mouse model of SMEI which revealed a reduction in sodium current density in inhibitory interneurons, resulting in circuit disinhibition.[8] This model also accounts for worsening of seizures with anti-epileptic drugs that target sodium channels. SMEI has also been reported, albeit rarely, in association with mutations in *SCN1B*, which encodes the β1 subunit of the voltage-gated sodium channel[9] and *SCN2A*, which encodes the α2 subunit of $Na_V1.2$.[10]. Missense mutations in *SCN2A* are also associated with benign familial neonatal-infantile seizures (BFNIS) in a few families. BFNIS is characterised by tonic or clonic partial and generalised seizures with onset between 2 days and 3.5 months. Recently, a gain of function mutation in *SCN8A*, which encodes $Na_V1.6$, was identified in a family affected by infantile epileptic encephalopathy.[11]

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a rare disorder characterised by frequent short-lived seizures during sleep with a prominent motor component, usually consisting of violent movements and dystonic posturing of the limbs, often with preserved consciousness. Mutations in *CHRNA4*, *CHRNA2* and *CHRNB2* which encode the α4, α2 and β2 subunits of the neuronal nicotinic acetylcholine receptor (nAChR) respectively are associated with ADNFLE. The mechanisms linking altered nAChR function to focal neocortical seizures remain poorly understood.

Heterozygous mutations in *GABRB3*, which encodes the β3 subunit of $GABA_A$ are associated with childhood absence epilepsy, and one loss of function mutation in *GABRA1*, which encodes the α-subunit of the $GABA_A$ was identified in a large family with juvenile myoclonic epilepsy.[12]

Finally, genetic defects, including rare variants in calcium channel genes such as *CACNA1H*, which encodes the α1H subunit of a T-type calcium channel ($Ca_V3.2$) which is highly expressed in the thalamus, and in *CACNA1A* (see below and Tables 2 and 3), have been associated with childhood absence epilepsy[13] and EA2 with epilepsy respectively.[14] However these tend not to co-segregate with epilepsy and so they may be considered susceptibility factors.

Ataxia

Ion channel mutations cause both episodic and progressive forms of ataxia. With regard to the former, dominantly inherited episodic ataxia types 1 (EA1) and 2 (EA2) are the most common types[15] (Table 2). EA3 – EA8 are rare, having generally only been reported in single families, and will not be discussed further.

Attacks in EA1 are short-lived (seconds to minutes) and affected individuals are normal interictally, although may exhibit neuromyotonia – a consequence of peripheral nerve hyperexcitability. In contrast, the attacks in EA2 are more severe, and can last from hours to days and may be associated with vertigo, vomiting and oscillopsia. The interictal examination may reveal deficits in oculomotor function, including gaze-evoked nystagmus. In addition, approximately 30-50% of genetically confirmed EA2 cases develop a progressive cerebellar syndrome.

EA1 is associated with heterozygous missense changes in *KCNA1*, although a premature stop codon has been identified in one family. *KCNA1* encodes Kv1.1, a potassium channel subunit that occurs throughout the nervous system but is especially abundant in the terminals of inhibitory interneurons in the cerebellar cortex, as well as in motor axons. Channels containing Kv1.1 are thought to regulate axonal excitability and neurotransmitter release, and mutant subunits generally exert a dominant-negative effect on wild type subunits with which they co-assemble. Why EA1 is paroxysmal is not known.

A wide range of heterozygous mutations in *CACNA1A* have been identified in EA2, ranging from missense substitutions to splice site mutations and stop codons that are predicted to truncate the peptide. Large scale deletions

Table 2: A comparison of EA1 and EA2. ACZ = Acetazolamide.

	Episodic ataxia type 1	Episodic ataxia type 2
Gene affected	*KCNA1*	*CACNA1A*
Gene expression	Purkinje cells of the cerebellum; Juxta-paranodal regions of motor axons	Cerebellum, neocortex, pre-synaptic
Protein	$K_V1.1$ (shaker orthologue)	$Ca_V2.1$(P/Q-type)
Protein function	Stabilisation of resting membrane potential	links pre-synaptic calcium influx to vesicular exocytosis; Post-synaptic role in cerebellar plasticity
Inheritance	Autosomal dominant	Autosomal dominant
Mutation Spectrum	Missense, one premature stop codon (R417X)	Missense, nonsense, large deletions, small insertions
Mutation mechanism	Loss of function; Dominant-negative suppression of WT by mutant	Loss of function Haploinsufficiency
Age of onset	1st to 2nd decade	2nd to 3rd decade
Prevalence	Rare	More common
Attack duration	Seconds to minutes	Hours to days
Attack precipitants	Stress, infection, sudden movements (kinesigenic), caffeine, alcohol	Stress, infection
Attack resolution	–	Sleep
Interictal features	Myokymia	Downbeating nystagmus (late onset fixed cerebellar syndrome)
ACZ response	Good	Excellent
Migraine?	No	~ 50%
Additional clinical features	contractures; distal wasting; epilepsy	Vertigo; nausea & vomiting; epilepsy; migraines; tremor; dystonia; torticollis

Table 3: The clinical and genetic features of the EA2, FHM and SCA6. The effect of mutations on $Ca_V2.1$ channel function is stated. MA, migraine with aura.* The CAG repeat in the C-terminus is only present in certain splice variants.

	Episodic ataxia type 2 (EA2)	Familial hemiplegic migraine type 1 (FHM1)	Spinocerebellar ataxia type 6 (SCA6)
Genetics	Point mutations resulting in premature stop codons; small deletions/insertions, missense mutations; large deletions	Missense mutations affecting conserved amino acid residues; T666M most common mutation	CAG expansion in C-terminus of peptide
Age of symptom onset	1st – 2nd decade	1st – 2nd decade	5th-6th decade
Clinical features	Episodes of ataxia, nausea and vomiting, vertigo, oscillopsia lasting hours to days;	Episodes of hemiparesis and hemisensory disturbance lasting hours to days	Progressive cerebellar ataxia
Additional features	Epilepsy; migraine (50%); muscle weakness; dystonia; tremor; cognitive impairment; 30-50% develop progressive cerebellar ataxia	Coma after minor head injury; encephalopathy, epilepsy; cerebellar ataxia	Relatively 'pure' cerebellar syndrome; some individuals may experience vertigo
Examination findings	Interictal nystagmus (down-beating); cerebellar signs (30-50%)	20% may have cerebellar signs	Cerebellar signs
Acetazolamide response	Highly effective in reducing frequency and severity of attacks	–	–
Functional effect of mutations	Loss of $Ca_V2.1$ channel function	Gain of $Ca_V2.1$ channel function	Polyglutamine toxicity

of multiple exons have recently also been identified to cause EA2 in patients previously reported as '*CACNA1A*-negative'.[16] The gene encodes the α1A subunit of the Cav2.1 calcium channel, also known as the P/Q-type channel. This channel is abundantly expressed at most presynaptic terminals throughout the nervous system, where it plays an important role in triggering neurotransmitter release. It is also expressed at high levels in the dendrites and somata of cerebellar Purkinje and granule cells.

Mutations in *CACNA1A* also underlie spinocerebellar ataxia type 6 (SCA6), a relatively 'pure' progressive degenerative disease of the cerebellum without paroxysmal features. This is caused by an expansion of a polyglutamine (CAG) repeat in the intracellular C-terminus of the α_{1A}channel peptide, although missense mutations have also been identified.[17] A toxic gain of function has been suggested to underlie the disease mechanism, akin to that observed in Huntington's disease, but the evidence is indirect. The mechanism of cell death induced by the polyQ tract remains unclear although it has been suggested that cerebellar dysfunction in a related disorder, SCA2, may arise from aberrant activation of type 1 inositol 1,4,5-trisphosphate receptors (IPTRs) in Purkinje cells by the glutamine tracts themselves.[18] More recently, heterozygous mutations in *KCNC3*, which encodes the potassium channel, $K_V3.2$, have been identified in association with early and adult-onset progressive ataxia and neurodevelopmental delay, termed SCA13. The pathological mechanism is unclear.[19]

Migraine

Heterozygous missense mutations in *CACNA1A* underlie Familial Hemiplegic migraine type 1 (FHM 1), a severe subtype of migraine with aura causing disabling attacks of hemiplegia, paraesthesia and visual disturbance which may last from hours to days. Additional features

rarely include delayed cerebral oedema and coma after a minor head injury, confusion, encephalopathy, and a cerebellar syndrome in approximately 20% of cases. Mechanistically, the mutations are thought to result in a gain of function, with a knock-in mouse model of FHM1 exhibiting enhanced spontaneous transmission at the neuromuscular junction and a lower threshold for inducing cortical spreading depression (CSD), the physiological substrate for the aura of migraine.[20] Genetic heterogeneity is also a feature of FHM. Apart from *CACNA1A*, two other genes have been associated with Mendelian hemiplegic migraine: FHM2 is caused by loss-of-function mutations in *ATP1A2*, which encodes the alpha subunit of a sodium/potassium ATPase which helps maintain transmembrane ion gradients. FHM3 is caused by mutations in the neuronal sodium channel gene, *SCN1A*, which is also affected in GEFS+ and SMEI (see above). It is not clear why some *SCN1A* mutations lead to migraine rather than epilepsy.

Hyperekplexia

Familial Hyperekplexia (FH) was the first CNS ion channel disorder in which a mutation was identified.[21] It is characterised clinically by stiffness and an exaggerated startle reaction to sensory or auditory stimuli, which is thought to have its origin in the brainstem reticular formation. The disorder presents in infancy and can result in life-threatening apnoeic spells, although treatment with benzodiazepines is helpful and attacks become less marked with age. FH generally arises from missense mutations in the *GLRA1* gene, which encodes the α1 subunit of the glycine receptor that contributes to fast inhibition in the brainstem and spinal cord. Impairment of inhibition is thought to result in excessive motor activity, explaining the exaggerated startle response and co-contraction of muscles. Although most cases are autosomal dominant, sporadic cases and recessive mutations have also been described. Compound heterozygous mutations in *GLRB*, which encodes the β-subunit of the glycine receptor, have been identified in association with a few cases of hyperekplexia, as have mutations of the glycine transporter GlyT2.

Conclusion

Although individually rare, the channelopathies are of growing importance in neurological disease, not least because of the key insights they provide about the function of ion channels, their roles in membrane excitability and their interactions with various signalling cascades. Such knowledge will not only lead to a greater understanding of the basis of common paroxysmal disorders but may in time provide important therapeutic avenues. Furthermore, because of the direct evidence that their dysfunction gives rise to migraine, epilepsy and movement disorders, ion channel genes are the best candidate loci for polygenic inheritance of common forms of these diseases. However, many challenges lie ahead. From a mechanistic point of view, whilst electrophysiological techniques have demonstrated changes in the biophysical parameters of mutant channels, how these alterations lead to paroxysmal or progressive symptoms is largely unknown. Indeed why symptoms are classically paroxysmal in the first place when the genetic lesion is constant is still unclear, as are the reasons why certain disorders such as BNFC have an early onset and run a benign course whereas others such as SMEI or KCNC3-related channelopathies exhibit a more severe and progressive phenotype. ◆

REFERENCES

1. Cannon SC. *Pathomechanisms in channelopathies of skeletal muscle and brain.* Annu Rev Neurosci, 2006;29:387-415.
2. Gourfinkel-An I, et al. *Monogenic idiopathic epilepsies.* Lancet Neurol, 2004;3(4):209-18.
3. Kullmann DM. *Neurological channelopathies.* Annu Rev Neurosci, 2010;33:151-72.
4. Du W, et al. *Calcium-sensitive potassium channelopathy in human epilepsy and paroxysmal movement disorder.* Nat Genet, 2005;37(7):733-8.
5. Rajakulendran S, et al. *Episodic ataxia type 1: a neuronal potassium channelopathy.* Neurotherapeutics, 2007;4(2):258-66.
6. Wallace RH, et al. *Febrile seizures and generalized epilepsy associated with a mutation in the Na+-channel beta1 subunit gene SCN1B.* Nat Genet, 1998;19(4):366-70.
7. Escayg A, et al. *Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+2.* Nat Genet, 2000;24(4):343-5.
8. Yu FH, et al. *Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy.* Nat Neurosci, 2006;9(9):1142-9.
9. Patino GA, et al. *A functional null mutation of SCN1B in a patient with Dravet syndrome.* J Neurosci, 2009;29(34):10764-78.
10. Shi X, et al. *Clinical spectrum of SCN2A mutations.* Brain Dev, 2012;34(7):541-5.
11. Veeramah KR, et al. *De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP.* Am J Hum Genet, 2012;90(3):502-10.
12. Cossette P, et al. *Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy.* Nat Genet, 2002;31(2):184-9.
13. Khosravani H and Zamponi GW, *Voltage-gated calcium channels and idiopathic generalized epilepsies.* Physiol Rev, 2006;86(3):941-66.
14. Rajakulendran S, et al. *Genetic and functional characterisation of the P/Q calcium channel in episodic ataxia with epilepsy.* J Physiol, 2010;588(Pt 11):1905-13.
15. Jen JC, et al. *Primary episodic ataxias: diagnosis, pathogenesis and treatment.* Brain, 2007;130(Pt 10):2484-93.
16. Labrum RW, et al. *Large scale calcium channel gene rearrangements in episodic ataxia and hemiplegic migraine: implications for diagnostic testing.* J Med Genet, 2009;46(11):786-91.
17. Zhuchenko, O., et al., *Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage-dependent calcium channel.* Nat Genet, 1997;15(1):62-9.
18. Liu J, et al. *Deranged calcium signaling and neurodegeneration in spinocerebellar ataxia type 2.* J Neurosci, 2009;29(29):9148-62.
19. Waters MF, et al. *Mutations in voltage-gated potassium channel KCNC3 cause degenerative and developmental central nervous system phenotypes.* Nat Genet, 2006;38(4):447-51.
20. van den Maagdenberg AM, et al. *A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression.* Neuron, 2004;41(5):701-10.
21. Shiang R, et al. *Mutations in the alpha 1 subunit of the inhibitory glycine receptor cause the dominant neurologic disorder, hyperekplexia.* Nat Genet, 1993;5(4):351-8.

Management Topics in Epilepsy

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In the first volume of ACNR, the young and naïve editors invited me to write a series of articles discussing specific management topics in epilepsy. Ten years later, they are older and a little wiser. This time, rather than writing them myself, I have been asked to commission proper experts to write the articles. Consequently there will be some real pearls laid before you. Last time, I considered refractory epilepsy and the latest kid on the block was levetiracetam, now an established treatment and vagus nerve stimulation was also relatively new. I was a cynic but have had to change my view as VNS has found its niche, the only epilepsy treatment to be awarded the accolade of Grade A evidence by NICE in 2004. Now there are more clever boxes of tricks used in the treatment of epilepsy. This is an expanding area with a variety of intracranial and extracerebral devices triggering the migration of my cynicism more rostrally from the vagus nerve. Perhaps in another ten years, I shall be eating humble pie once again. By that time the wisdom of the editors will be so well developed that somebody else will be writing this article. In my view, at least as exciting is the prospect of devices enabling seizure detection, something which remains at an early stage. This offers the opportunity to intervene in cases of potential SUDEP, one of the great tragedies of epilepsy and an issue which rightly has come to the fore in the last decade and about which we shall be hearing more. Prof Mark Cook from Melbourne will tell us about developments in clinically relevant seizure detection.

Introduction

Epilepsy specialists can reasonably be accused of not knowing whether to lump or to split, both in terms of diagnosis and of treatment. In the current series of articles, we shall be doing a little splitting, looking at the specific issues and needs of selected groups of patients. Enough about women's issues I hear you call, we shall burn our boxers and strike a blow for masculinism. In the true spirit of egalitarianism with an article about men's issues in epilepsy, written by a woman, Susan Duncan, from Edinburgh. Another group with specific needs is the elderly for whom a diagnosis of epilepsy may cause particular social isolation and in whom it is more often a marker of serious underlying neurological disease. Choice of antiepileptic drugs is complicated by comorbidities and drug interactions and may be different from younger patients. Erica Chisanga, our very own Cambridge Nurse Consultant in Epilepsy will give us her knowledge of the particular issues faced by this group. Epilepsy is, of course, especially common in those with learning disability, from whom it may be difficult to obtain a history and who may express a variety of problems with attacks of one sort or another, making the diagnosis of epilepsy a particular challenge. They are also especially likely to have complex genetic disorders, which have been identified in the last decade. The management of epilepsy and related disorders in this group is becoming a subspecialty in its own right. These patients sit uncomfortably between neurology and learning disability specialties in this country. A select group with the balance and anatomical resilience to straddle this particular fence includes Howard Ring, also from Cambridge, who will expound on the issues.

Disappointingly, the explosion of new antiepileptic drugs has not seen the number of seizure-free patients grow appreciably in the last twenty years. Increasingly, we recognise that the agents we are currently using are seizure suppressing drugs; treating the symptom, like analgesia for a headache, but not addressing the cause. The current choice of drug in the management of epilepsy, centres more frequently around adverse effect profile and interactions than on the efficacy of particular drugs, as it is often hard to choose between them on this criterion. This tells us exactly how poor is our intelligence with regard to choosing the right drug for the right patient. Researchers have struggled to find a new conceptual approach and new paradigms, which may reflect more fundamentally, the underlying processes. Inflammatory molecules such interleukin-1 and key enzymes such as caspase may be targets but there is also a more sophisticated understanding of channels and their changes in regulation in epileptogenesis. They may be a target for gene therapy for example with viral vectors and the Holy Grail is to find an "epileptogenic" target which can be influenced after the epilepsy has started. Prof Dimitri Kullmann from Queen Square has pioneered work in this area and I am especially pleased that his team will be able to contribute to this series.

Status epilepticus, termed the maximum expression of epilepsy, is terrifying for those who observe it and is potentially rapidy fatal. Whilst treatment has existed for many years, it is of varying success and the evidence underlying treatment choices is poor. Increasingly we are starting to understand how the mechanisms of seizures evolve during status epilepticus, explaining why our treatments may not work in particular cases and how we might use existing drugs or design new drugs which take account of the changes in neuronal physiology and chemistry which occur minute by minute in this emergency. Prof Matthew Walker from Queen Square will tell us how his work and that of others is bringing science and clinical practice together in this neurological emergency.

I am delighted that you will be hearing from this group of people on new and exciting issues in epilepsy, as well as reviewing key areas of clinical difficulty over the coming months. I hope you will learn from them and enjoy their contributions as much as I shall – good decision Ed! ◆

Acupuncture for Headache

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Acupuncture has a long history as part of Chinese medicine. In Western countries it is now one of the major complementary therapies, with lifetime use in adult populations as high as 34%.[1] Headache is one of the more common presenting conditions in acupuncture general practice[2] and use of the therapy by headache sufferers in tertiary care has been reported at 58% in German and Austrian outpatient clinics.[3]

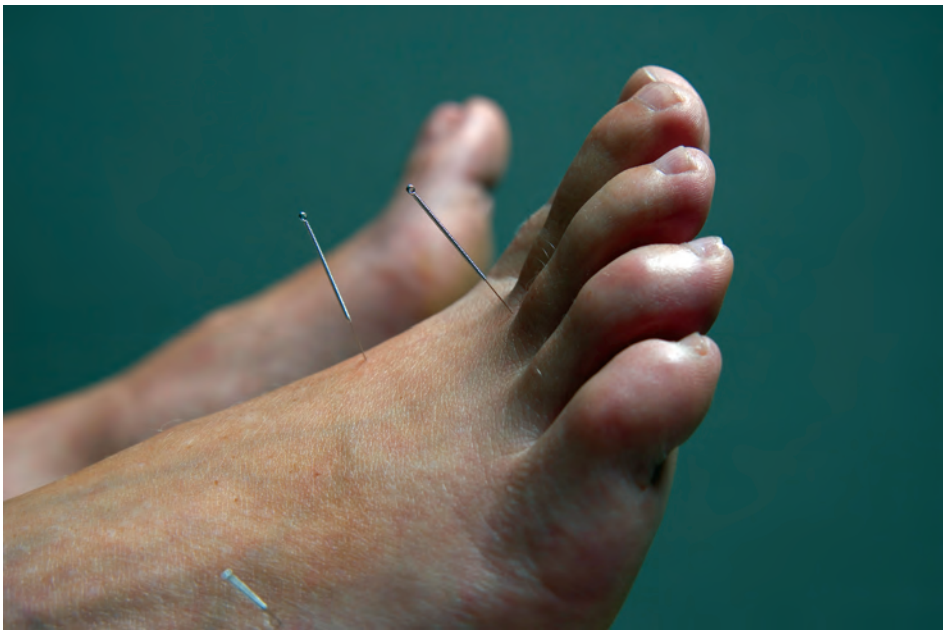
Acupuncture is practiced in many different forms, often conveniently distilled down to 'traditional' and 'medical' versions, but the distinctions are blurred and each of these itself embraces a multiplicity of styles. Typically patients with the same biomedical diagnosis would receive treatment that varied with their own individual presentation, as well as the practitioner's background. Also this would evolve from one session to the next. For headache in particular the exact location of the symptoms is an important pointer to choosing the appropriate pathway and points to needle, both local (around the head and neck) and distal (in the limbs). In addition, traditional acupuncturists may differentiate by Chinese medicine syndrome: identifying patterns from the symptoms and a wider range of physical and mental/emotional characteristics, and by radial pulse palpation and tongue inspection. There may be other layers of diagnosis and treatment too, according to the practitioner's particular training style.

Taking migraine as an example, there has been a consistent focus from ancient to modern times on the Gallbladder channel, which runs over the lateral and postero-lateral aspects of the body from head to foot. The most frequently cited point for migraine in published protocols, Western and Chinese, is GB20, lying in the hollow inferior to the occiput and lateral to the trapezius. Of the five most popular points in Chinese migraine trials three were on the head/neck and one each on the hand and foot;[4] however, treatments in normal practice may not use local points at all (see Figure 1). Some styles even place the main emphasis on the patient's underlying constitutional characteristics and don't respond directly to the symptoms.

Systematic reviews of randomised controlled trials (RCTs) of acupuncture for headache indicate that most of the Chinese studies have used a fixed treatment protocol whereas those in the West have tended to be semi-standardised.[4] There may be socio-political as well as scientific reasons for this distinction but an important point to note is that external validity may be compromised in both cases. Most trials do not evaluate acupuncture as it is actually practised. 'Pragmatic' RCTs would fit with the current impetus towards Comparative Effectiveness Research[5] and are better suited than 'explanatory' trials to informing clinicians and service commissioners. For headache, there are two high-quality examples, that also come with full economic evaluation.[6,7]

A host of physiological mechanisms appear to be associated with acupuncture analgesia, involving for example, segmental modulation via

Acupuncture points on the feet are used commonly with headache patients.



descending inhibitory pathways, regulation within the limbic system, and diffuse noxious inhibitory control. Whilst these are now well established, and genomic/proteomic/metabolomic research is opening new avenues, there is as yet little indication of their clinical significance. We are still largely ignorant of the mechanisms by which acupuncture mediates symptom relief in chronic illness. For headache, the possible physiological pathways that have been identified come mainly from laboratory animal studies.[4]

To be inclusive of all styles of acupuncture it may be defined minimally as the insertion of needles into points on the skin for therapeutic purposes. However, for those who practice according to a traditionally-based East Asian model acupuncture is much more than this, a complex intervention where so-called contextual effects are integral to the therapy, where specific and non-specific effects are inextricably intertwined and where working with 'qi' (usually translated as energy) is both a theoretical concept and a practical experience.[8] This raises serious obstacles for those who wish to evaluate acupuncture in placebo-controlled trials. Since we have neither isolated the specific effects nor identified the causal mechanisms we cannot design a placebo around them. Acupuncture treatment is much more akin to physiotherapy, psychotherapy, even surgery, than it is to pharmaceutical intervention. Despite this, active controls have been used extensively in acupuncture RCTs. This sham acupuncture takes many forms, the gold standard involving a device like a stage dagger that does not pierce the skin. However, as with other sham forms this cannot be assumed to be physiologically inert.[9] In particular, it stimulates nerve fibres in the same way as mild forms of verum acupuncture, so it is not surprising that sham acupuncture is usually an effective treatment in its own right.

There have been Cochrane systematic reviews for both migraine[10] and tension headache.[11] The authors recommended acupuncture as a treatment option, especially for those patients refusing drug treatment or suffering side effects from it. Results from trials, case reports and very large prospective observational studies all indicate acupuncture to be safe when carried out by trained practitioners.[4] In the most robust evidence to date on chronic pain conditions, including headache (individual patient meta-analysis on 29 trials and 18,000 patients), acupuncture was significantly superior to sham by a small margin (effect size 0.15 to 0.23 standard deviations), and more substantially superior to no treatment/usual care (0.42 to 0.57 SD).[12]

It is then disappointing to see that NICE included only sham-controlled RCTs as clinical evidence in their guidance on the use of acupuncture for headache treatment (in contrast to their approach with exercise or manual therapy).[13] They compounded this error by using the sham comparison effectiveness data in the economic modelling, leading to incremental cost-effectiveness ratio estimates that are more than twice as high (i.e. worse) as those from high quality UK and German comparisons against no treatment/usual care.[6,7] Whilst topiramate topped the NICE economic evaluation, and is the frontline recommendation for migraine prophylaxis, it was less effective than acupuncture in a recent head-to-head trial and associated with more than ten times the rate of adverse events.[14] That NICE still opted to recommend acupuncture is testament to:

a) the innate effectiveness of the therapy for headache. It is believed by traditional practitioners to be one of the conditions most amenable to treatment, and a survey of neurologist acupuncturists reported that tension headache and migraine gave the best results, with improvements of more than 50% in 70% of cases.[15]

b) the paucity of good quality clinical research, especially for cost-effectiveness, not only amongst other complementary therapies but also most orthodox ones. Note that NICE was unable to recommend anything other than acupuncture for the prophylaxis of tension headache. ◆

It is believed by traditional practitioners to be one of the conditions most amenable to treatment, and a survey of neurologist acupuncturists reported that tension headache and migraine gave the best results, with improvements of more than 50% in 70% of cases

REFERENCES

1. Bücker B, Groenewold M, Schoefer Y, Schäfer T. *The use of complementary alternative medicine (CAM) in 1 001 German adults: results of a population-based telephone survey.* Gesundheitswesen. 2008 Aug-Sep;70(8-9):e29-36
2. Hopton AK, Curnoe S, Kanaan M, Macpherson H. *Acupuncture in practice: mapping the providers, the patients and the settings in a national cross-sectional survey.* BMJ Open. 2012 Jan 11;2(1):e000456. http://bmjopen.bmj.com/content/2/1/e000456.long
3. Gaul C, Eismann R, Schmidt T, May A, Leinisch E, Wieser T, Evers S, Henkel K, Franz G, Zierz S. *Use of complementary and alternative medicine in patients suffering from primary headache disorders.* Cephalalgia. 2009 Oct;29(10):1069-78.
4. Chmelik S, Bovey M. *Acupuncture and Traditional Chinese Medicine for treating migraine.* In: Fernández-de-las-Peñas C, Chaitow L, Schoenen J (eds) Multidisciplinary management of migraine: pharmacological, manual and other therapies. 2012. Jones & Bartlett Learning, Sudbury, MA.
5. Witt CM, Huang WJ, Lao L, Berman B. *Which research is needed to support clinical decision-making on integrative medicine?-Can comparative effectiveness research close the gap?* Chin J Integr Med. 2012 Oct;18(10):723-9
6. Wonderling D, Vickers AJ, Grieve R, McCarney R. *Cost effectiveness analysis of a randomised trial of acupuncture for chronic headache in primary care.* BMJ. 2004 Mar 27;328(7442):747 http://www.bmj.com/content/328/7442/747?view=long&pmid=15023830
7. Jena S, Witt CM, Brinkhaus B, Wegscheider K, Willich SN. Acupuncture in patients with headache. Cephalalgia. 2008 Sep;28(9):969-79.
8. Paterson C, Dieppe P. *Characteristic and incidental (placebo) effects in complex interventions such as acupuncture.* BMJ. 2005 May 21;330(7501):1202-5. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC558023/
9. Lundeberg T, Lund I, Sing A, Näslund J. *Is Placebo Acupuncture What It is Intended to Be?* Evid Based Complement Alternat Med. 2011;2011:932407 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3139519/
10. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. *Acupuncture for migraine prophylaxis.* Cochrane Database Syst Rev. 2009 Jan 21;(1):CD001218. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3099267/
11. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. *Acupuncture for tension-type headache.* Cochrane Database Syst Rev. 2009 Jan 21;(1):CD007587. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3099266/
12. Vickers AJ, Cronin AM, Maschino AC, Lewith G, Macpherson H, Foster NE, Sherman KJ, Witt CM, Linde K. *Acupuncture for Chronic Pain: Individual Patient Data Meta-analysis.* Arch Intern Med. 2012 Sep 10:1-10.
13. National Institute for Health and Clinical Excellence. *Headaches. Diagnosis and management of headaches in young people and adults.* CG150. 2012. London: National Institute for Health and Clinical Excellence http://guidance.nice.org.uk/CG150/Guidance
14. Yang CP, Chang MH, Liu PE, Li TC, Hsieh CL, Hwang KL, Chang HH. *Acupuncture versus topiramate in chronic migraine prophylaxis: a randomized clinical trial.* Cephalalgia. 2011;31(15):1510-21.
15. Bijak M. *What can be achieved by using acupuncture and related techniques in neurology? Expert evidence.* Revista Internacional de Acupuntura. 2008;2(4):231-7.

Norwegian leading discoveries in neurology and neuroscience are presented in a series of short articles in ACNR, initiated by the journal. All the selected discoveries have links to ongoing research projects in leading groups. They span from clinical to more basic topics. The discoveries are all relevant for clinicians evaluating and treating patients with brain and nervous system disease. Neuroscience with a clinical focus has been a priority for Norwegian research. Further expansion is planned in cooperation between the universities, the university hospitals, the Research Council of Norway, and the Norwegian Brain Council. Although the discoveries in this series are presented as Norwegian, they all appear in an international context. They represent small pieces fitting into the bigger puzzle, but contribute in elucidating mechanisms for brain and neuromuscular function, thus laying foundations for improved treatment of human disease.

Genetic Causes of Sporadic Parkinson's Disease

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Familial occurrence of Parkinson's disease (PD) has been observed ever since the disease was first described almost two centuries ago. In 1903 William Gowers reported that 15% of his patients had a positive family history of PD which is about the same percentage of familial occurance reported in most studies today. The first major genetic study in PD was performed by Henry Mjønes in the late 1940s. He found secondary cases of parkinsonism in up to 40% of his PD patients and concluded that PD was an autosomal dominant disease with 60% penetrance. David Marsden and colleagues came to similar conclusions when studying large multi-incident PD families in the late 1980s. Despite the convincing evidence of inheritance sporadic PD remained a disease in which the role of genetic factors in the cause of PD was 'negligible'. In the early 1990s Duvoisin and colleagues studied multiple PD cases in the Contursi kindred originating from southern Italy and in 1997 they published the first gene for Parkinson's disease which coded for alfa-synuclein.[1] Although mutations in the alfa-synuclein gene are very rare causes of PD this was a major discovery for understanding PD pathology. Lewy body inclusions consist of aggregated α-synuclein and PD is pathologically classified as a synucleinopathy.[1] In the following year the gene for autosomal recessive juvenile parkinsonism was located in the *parkin* gene.[2] Over the next years several important PD genes were discovered. Mutations in the LRRK2 gene represent the most common causes for autosomal dominant PD and mutations in PTEN-induced putative kinase 1 (*PINK1*) are the second most common cause of recessive PD.[3] A few more genes have recently been reported in some large PD families. These discoveries include mutations in vacuolar protein sorting 35 (*VPS35*),[4] eukaryotic translation initiation factor 4 gamma 1 (*eIF4G1*),[5] as well as dynactin p150Glued mutations in Perry syndrome patients (depression and parkinsonism with hypoventilation).

Most cases of Parkinson's disease are sporadic and several susceptibility genes have been described. There is a documented association between parkinsonism and the gene encoding the lysosomal enzyme glucocerebrosidase (*GBA*), in Gaucher's disease, and GBA heterozygotes have an increased incidence of PD.[6] Genetic studies for new PD genes are possible only in relatives of patients with known diseases or in multi-incident PD families. In true sporadic PD cases where many rare mutations may be involved a very large number of cases are needed to demonstrate a correlation between rare genetic variants and a disease. There are other genetic diseases as well which may mimic parkinsonism and should not be misdiagnosed as PD. These include tremor and bradykinesia in spinocerebellar ataxia 2 and 3, (SCA2 and SCA3) whereas fragile X mental retardation 1 (*FRM1*) premutations may manifest as fragile X tremor/ataxia syndrome (FXTAS).

In Central Norway the reported frequency of familial PD is about the same as in other centers around the world which is around 15% with a mean age of onset around 60 years. The Norwegian population has been stable with low degree of mobility and until recent years also with a low rate of immigration. The movement disorder clinic at the University hospital in Trondheim has collected clinical data and DNA from more than 800 PD patients. This population has been extensively tested for genetic causes as part of a very good collaboration with the Farrer lab (Mayo clinic, Jacksonville, Fl, and recently Vancouver, University of British Columbia, Vancouver, Canada).

The PD material from Central Norway has been central in finding new genes in so-called sporadic PD. The clinical features of the LRRK2 G2019S PD was first described in this material.[7] Although this is an autosomal dominant disease with high penetrance about one third of our LRRK2 cases appear to be so-called sporadic without any known relatives suffering from the same disease. The low mobility in the population became evident in the genealogical studies in LRRK2 families. All Norwegian LRRK2 G2019S cases were traced back to a relatively small geographical area in Central Norway and the pedigrees showed one common ancestor born around 1580.[8] We suggest that the G2019S mutation was imported to Norway, probably through a tradesman from Europe in the late mediaeval time who travelled up to settlements along the Norwegian coast-line. Recently we reported a severe LRRK2 variant, the N1437N mutation, representing only a few kindreds.[9] This gene

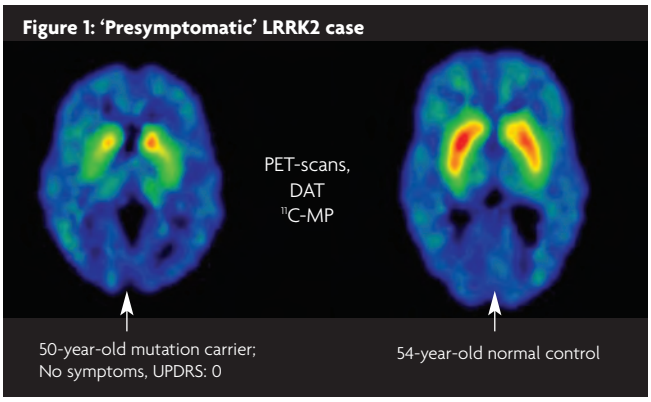

Fig. 1: PET scan, Healthy LRRK2 mutation carrier, UPDRS: 0 (left), normal control (right). Dr. Vesna Stossi, UBC, Vancouver, Canada.

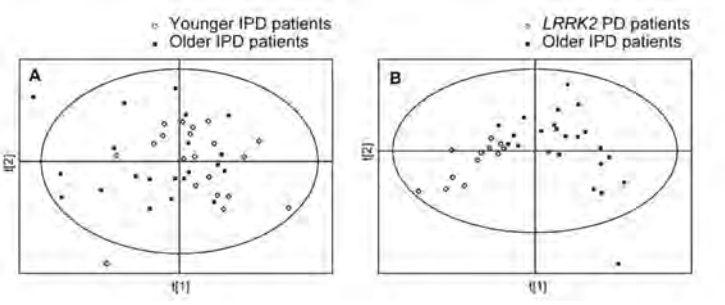

Figure 2: Age effects on metabolomic profiles of IPD patients and LRRK2 PD patients. (A) PLS-DA scores plot showing lack of separation between younger (57.365.6 years old, n = 19, mean6SD) and older (71.463.3 years old, n = 22, mean6SD) idiopathic PD patients. (B) PLS-DA scores plot showing a significant separation between older idiopathic PD patients (71.463.3 years old, n = 22, mean6SD) and LRRK2 patients (72.8611.2 years old, n = 12, mean6SD). The analytes discriminating between all IPD patients and LRRK2 patients were used for this analysis.
From Johansen et al. 2009.[13]

was also found in familial cases located in a very small geographical area although quite distant to other LRRK2 families.

Clinical characteristics of the LRRK2 G2019S patients do not phenotypically differ from any other sporadic PD cases and studies in healthy LRRK2 mutation carriers has told us that the onset of PD is probably a rather slow process.

Carriers of PD mutations enter the pre-clinical phase defined by abnormal images, PET or SPECT scans, probably many years before onset of clinical symptoms. It may resemble that which is seen in PD twins. Although the age of onset in twins may vary considerably PET scans often show that the unaffected sibling has ongoing dopaminergic deficits, (Figure 1). It is more likely a slowly progressing chronic disease which can be split in several phases, the pre-physiological, pre-clinical, the pre-motor and the pre-diagnostic phase.[10] In healthy LRRK2 mutation carriers the initial part of the disease is characterised by an increased dopamine turnover and changes in cerebrospinal fluid markers.[11,12] Biomarker studies using metabolomic techniques in blood samples are able to separate carriers from PD cases even in the pre-motor phase,[13] (Figure 2).

In the pre-motor phase neuronal inclusion bodies are found in the olfactory bulb and in the autonomic nervous system. Olfactory testing is easily obtainable and inexpensive but the results may be quite unspecific. There are wide overlaps between normal controls and individuals at risk and this tool is not suitable for pre-motor identification of PD. Autonomic disturbances may manifest as significant reduction of the frequency of bowel movements but is observed only in a minority of cases prior to PD onset. REM sleep behaviour disorder (RBD) may also be observed early in PD but like constipation and anosmia it is only of significance in those who report this disorder. In the pre-diagnostic phase which is the last phase before the patient develop PD bradykinesia and rigidity are easily detected when examining the patients[14]. Tremor is rarely observed because this often makes the patients aware of the symptoms and PD is readily diagnosed.

Genes for sporadic PD may sound like a contradiction. It implies that these genes have a low penetrance or an age of onset late in life which makes any familial occurrence less obvious. The PD biobank in Central Norway has a high number of cases from a homogenous population covering most of the PD cases in that area. This material will then also include many distant relatives. The reliability of family history information of PD in distant relatives of PD cases is low but may be considerably increased by longitudinal studies performed by a team of neurologists who are well informed on local kindreds. Distant relatives share less genetic material than first degree relatives and is optimal for next generation gene sequencing searching for genes with low penetrance and late onset of disease. Large cohorts in low mobility populations and thorough genealogical screening will reveal cases from kindreds where familial cases may be easily over-looked.

Genes for sporadic PD are biomarkers for early or pre-clinical PD. Low penetrance autosomal dominant late onset PD mutations may simulate sporadic cases and true family occurrence may only be detected in large genealogical studies. Large disease populations from multiethnic cohorts may preclude or mismanage rare genetic causes from being discovered. The Norwegian LRRK2 families have been thoroughly studied in terms of their premotor features. The LRRK2 carriers, as other PD patients, develop their symptoms over a long period, probably over many years.[10,15]

So far all studies with so-called neuroprotective agents have been negative. Many future neuroprotective agents will have to be started before the patients enter a more advanced stage of the disease. An inexpensive and non-toxic agent would be optimal for early treatment and subjects who never enter the clinical phase of PD need to be included in such studies.

Next generation sequencing in multi-incident PD families followed longitudinally by the Trondheim PD cohort team has recently found 3 more PD genes (Matt Farrer, personal communication). Family members at risk for developing PD are excellent candidates for developing biomarkers for PD. They should also be offered the possibility of testing new future neuroprotective drugs since this type of treatment probably should be initiated many years prior to disease onset. By identifying more genes for sporadic PD it will enhance our knowledge of PD and enable more cases to be included in trials for more efficient drugs which may delay the progression of the disease. ◆

REFERENCES

1. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. Nature 1997;388:839-40.
2. Hattori N, Kitada T, Matsumine H, et al. Molecular genetic analysis of a novel Parkin gene in Japanese families with autosomal recessive juvenile parkinsonism: evidence for variable homozygous deletions in the Parkin gene in affected individuals. Ann Neurol 1998;44:935-41.
3. Toft M, Myhre R, Pielsticker L, White LR, Aasly JO, Farrer MJ. PINK1 mutation heterozygosity and the risk of Parkinson's disease. J Neurol Neurosurg Psychiatry 2007;78:82-4.
4. Vilarino-Guell C, Wider C, Ross OA, et al. VPS35 mutations in Parkinson disease. Am J Hum Genet 2011;89:162-7.
5. Chartier-Harlin MC, Dachsel JC, Vilarino-Guell C, et al. Translation initiator EIF4G1 mutations in familial Parkinson disease. Am J Hum Genet 2011;89:398-406.
6. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 2009;361:1651-61.
7. Aasly JO, Toft M, Fernandez-Mata I, et al. Clinical features of LRRK2-associated Parkinson's disease in central Norway. Ann Neurol 2005;57:762-5.
8. Johansen KK, Hasselberg K, White LR, Farrer MJ, Aasly JO. Genealogical studies in LRRK2-associated Parkinson's disease in central Norway. Parkinsonism Relat Disord 2010;16:527-30.
9. Aasly JO, Vilariño-Güell C, Dachsel JC, et al. Novel Pathogenic Lrrk2 p.Asn1437His substitution in familial Parkinson's disease. Mov Disord 2010;In press.
10. Stephenson R, Siderowf A, Stern MB. Premotor Parkinson's disease: clinical features and detection strategies. Mov Disord 2009;24 Suppl 2:S665-70.
11. Sossi V, de la Fuente-Fernandez R, Nandhagopal R, et al. Dopamine turnover increases in asymptomatic LRRK2 mutations carriers. Mov Disord 2010;25:2717-23.
12. Aasly JO, Shi M, Sossi V, et al. Cerebrospinal fluid amyloid beta and tau in LRRK2 mutation carriers. Neurology 2012;78:55-61.
13. Johansen KK, Wang L, Aasly JO, et al. Metabolomic profiling in LRRK2-related Parkinson's disease. PLoS One 2009;4:e7551.
14. Johansen KK, White LR, Farrer MJ, Aasly JO. Subclinical signs in LRRK2 mutation carriers. Parkinsonism Relat Disord 2011;17:528-32.
15. Johansen KK, Jorgensen JV, White LR, Farrer MJ, Aasly JO. Parkinson-related genetics in patients treated with deep brain stimulation. Acta Neurol Scand 2011;123:201-6.

Pes Cavus – Not Just a Clinical Sign

Diagnosis, Aetiology and Management

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The term *Pes cavus* describes the deformity of a high arched, relatively stiff foot. It has a variety of neurological and other causes. Management depends on the aetiology, rapidity of progression and the severity of symptoms.

Definition

Pes cavus is an umbrella term describing a spectrum of foot shapes with a high arch.[1] Pure *Pes cavus* occurs when the metatarsal bones are plantarflexed relative to the hindfoot – described as 'forefoot plantaris' – which increases the height and curvature of the medial longitudinal arch (Figure 1). When the patient weight-bears, the hindfoot is pushed into dorsiflexion by the plantarflexed forefoot (Figure 2).

A high arch accompanied by a medially angulated heel is termed *pes cavovarus* (Figure 3). When this is complicated by foot drop and equinus of the ankle, it is described as *pes equinocavovarus*. Another variant, *pes calcaneovarus*, occurs when the primary deformity is excessive ankle and hindfoot dorsiflexion; in order to place the foot flat on the ground, the forefoot plantarflexes, leading to a high arch.

On radiographs, a high arch manifests as a Meary's angle of over 5 degrees – the angle between the long axis of the talus and the first metatarsal in the lateral view (Figure XR 4). The talus and the calcaneum are dorsiflexed, with calcaneal pitch exceeding 30 degrees.[1] The calcaneum appears shortened when in varus. On the dorso-plantar view, supination is seen as a narrow talo-calcaneal angle (Figure XR 5).

The wide spectrum of normality leads to controversy over the inclusion of milder variants in the definition of *pes cavus*. An objective measure of the degree of supination or pronation, the Foot Posture Index (FPI), has been developed and validated.[2] However, while the FPI describes and quantifies foot shape, it does not delineate the normal foot from *pes cavus*.

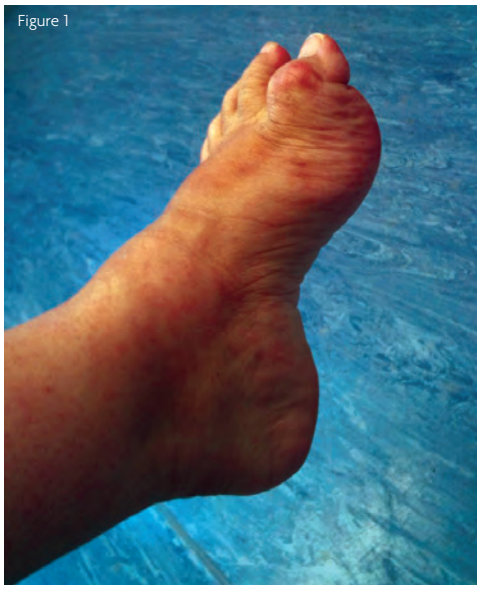
In practice, what is important is that subtle cases of *pes cavus* are identified and that potential pathology is considered.

Aetiology, classification and pathophysiology

A list of causes is given in box 1. These conditions have differing pathophysiology, but unbalanced muscular forces are almost always at the root of cavus feet.

The sole of the foot can be conceived as a tripod, consisting of the first metatarsal head, fifth metatarsal head and heel. All three points should be in contact with the ground during stance, with the ankle balanced over the triangular base that they form.

Figure 1



Box 1: Causes of Pes cavus

Progressive neurological disorders

- Hereditary Sensorimotor Neuropathies (HSMN) or Charcot-Marie-Tooth disease (CMT) (78%)[3]
- Hereditary sensory and autonomic neuropathies
- Friedreich ataxia
- Spinal or brain Tumour
- Spinal muscular atrophy
- Spinal trauma
- Syringomyelia
- Myelodysplasia
- Spinal dysraphism: spina bifida, spina bifida occulta, diastematomyelia[4]
- Muscular dystrophy

Static neurological disorders

- Cerebral palsy
- Stroke
- Poliomyelitis
- Spinal nerve root injury
- Peroneal nerve injury[4]

Other causes

- Scarring of the deep posterior compartment after compartment syndrome[5]
- Foot trauma
- Tarsal coalition
- Under-corrected congenital talipes equinovarus
- Iatrogenic (e.g. overzealous surgery for pes planus)
- Idiopathic / familial

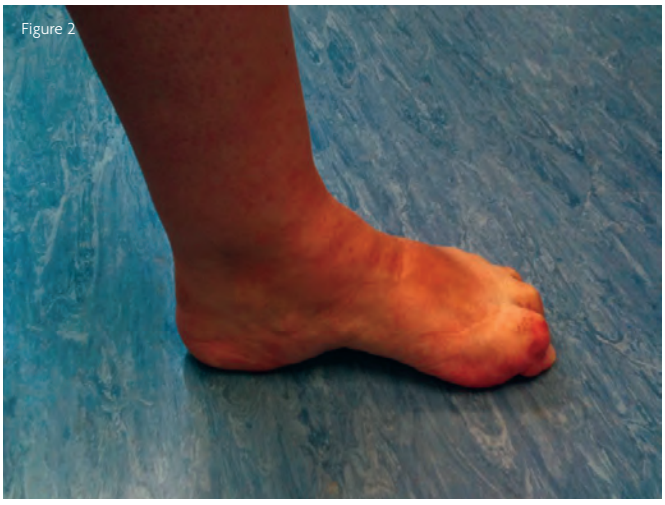


Figure 2

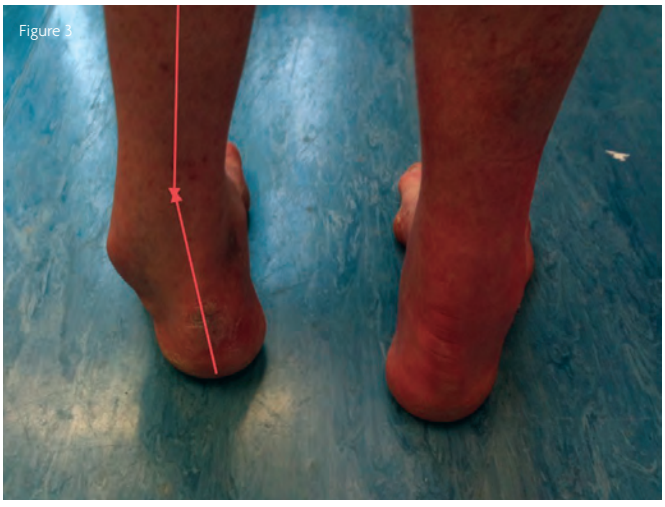


Figure 3

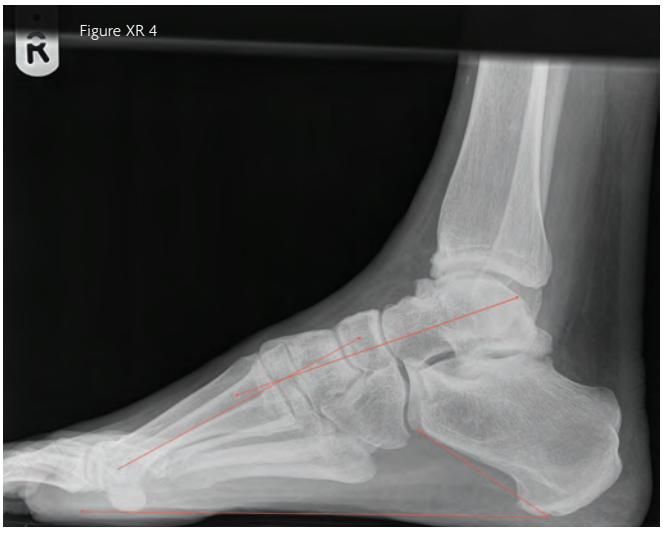


Figure XR 4

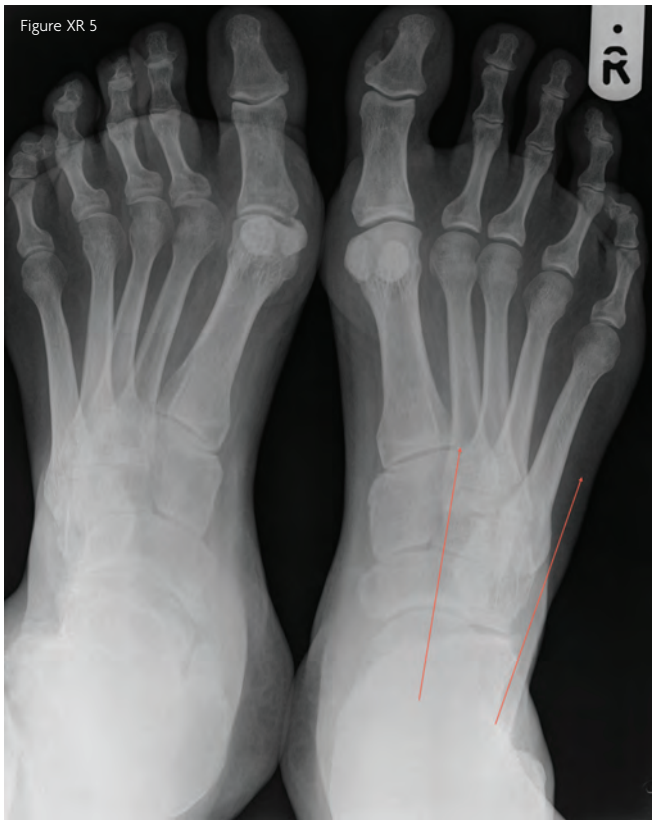


Figure XR 5

In typical cases of *pes cavovarus* associated with HSMN,[3] tibialis posterior and peroneus longus are consistently stronger than tibialis anterior (TA) and peroneus brevis,[6] resulting in plantarflexion of the first ray and adduction of the forefoot.[4,7] This creates pronation of the forefoot relative to the hindfoot.[8] The plantar fascia contracts, further depressing the first metatarsal head. To keep the tripod flat on the ground, the hindfoot dorsiflexes and supinates into varus.

Hindfoot varus may be flexible at first but becomes progressively fixed.[1,8] Once the heel's point of contact is medial to the centre of the ankle, there is a moment that tends to exacerbate the hindfoot varus. The Achilles tendon's insertion is medialised and it becomes a secondary inverter.[1] Thus *pes cavovarus* may start as a *forefoot-driven* phenomenon and later become *hindfoot-driven*.

Frequent toe deformities are partly caused by weak intrinsic foot muscles. They are overcome by the extrinsic muscles: extensor digitorum longus (EDL), flexor digitorum longus (FDL), extensor hallucis longus (EHL) and flexor hallucis longus (FHL). The imbalance leads to hyperextension of the metatarso-phalangeal joints (MTPJs) and flexion of the interphalangeal joints, or 'clawing'. This is made worse when EHL and EDL are recruited to aid a weak TA in dorsiflexing the foot.[4] The plantar fascia, attached to the proximal phalanges, tightens when they hyperextend. This exaggerates the medial longitudinal arch via the windlass mechanism.[1] Eventually the slips of plantar fascia toes become dorsal to the centre of the MTPJ, thus becoming a perverse extensor. A theory that weak intrinsic muscles account for all the deformities of *pes cavus*[9] cannot, however, be sustained.[10,6]

The Equino-cavovarus deformity is seen as the end stage of HSMN-induced *pes cavus*. Once there is no active dorsiflexion, the ankle plantarflexes, the calf muscles and posterior joint capsule contract, and equinus ensues.

The calcaneovarus variant is seen in poliomyelitis, low spinal dysraphism or after overzealous surgical lengthening of the Achilles tendon. Paralysis of the calf muscles leads to excessive ankle dorsiflexion and compensatory forefoot plantaris.

In children, the skeleton reacts to the forces upon it, with differential growth at the physis, according to Wolff's law. The muscle imbalances cause deformities that initially occurred through the joints to become fixed in the bony architecture of the mature foot.

Epidemiology and Genetics

Some authors quote the prevalence of high-arched feet as 8-15% in the population;[11,12] but the true prevalence of *pes cavus* associated with pathology is much lower. About 37 in 100,000 people are affected by CMT.[7] A recent review has summarised our knowledge of the varied phenotypes and their genetic basis.[13] In the UK, 90% of patients have autosomal CMT type 1 (demyelinating) or type 2 (axonal). Most mutations involve the *peripheral myelin protein 22* gene on chromosome 17. Genetic testing has progressed such that 70% of patients can be given a genetic diagnosis. Our ability to relate the different forms of these genes

to their variable phenotypic expression is still limited, although mRNA levels of some lipid metabolism genes in skin biopsies may offer a way to predict phenotypic expression.[13] CMT type 2 seems to produce milder symptoms with a slower progression than type 1.[7]

Symptoms and signs, and their relationship to biomechanics

The foot serves as an organ of load distribution, shock absorption, balance and propulsion. *Pes cavus* interferes with all of these functions.[1]

Supination of the hindfoot normally results in a change of the foot from a loosely packed, flexible, energy absorbing structure to a tightly packed, stiffer lever. This change occurs naturally during the gait cycle. When the hindfoot remains supinated throughout the gait cycle, however, the reduced flexibility lessens the foot's capability as a shock absorber[1] and diminishes its ability to balance on uneven ground.

Hindfoot varus also leads to an increased moment on the ankle,[11] making ankle inversion injuries common.[14] Eventually there may be dramatic varus tilting of the ankle and secondary osteoarthritis.[15]

Forefoot plantaris leads to increased pressure on the metatarsal heads. This pressure is maintained for a greater proportion of the gait cycle than in normal feet.[16,17] A high arch reduces the size of the footprint and increases plantar pressure. Plantar pain and callus formation may give way to ulceration, particularly in the neuropathic patient who lacks protective sensation.

Neuropathies may be accompanied by neuropathic pain. It is essential that mechanical symptoms, which can be treated by orthoses or surgery, are distinguished from neuropathic pain, which cannot.

With progression, deformity and rigidity become more severe. This leads to overload of the lateral side of the foot and stress fractures of the fifth metatarsal.[14] Peroneal tendinopathy, Achilles tendon disorders, plantar fasciitis, and ankle impingement are also more common in the cavus foot.[5]

Clinical evaluation & investigation

It is critical to establish whether there is a neurological diagnosis and whether it is progressive or static.[18] In the growing foot, the deformity may be progressive although the neurological impairment may be static.

The history should cover the onset of foot problems and how they have progressed. Pain, instability, difficulty walking or running and problems with footwear are frequent complaints. Neurological symptoms, such as sensory changes, weakness and clumsiness should be sought. Back pain or headaches may signify a central cause. Family history may suggest a hereditary cause.

Box 2: Symptoms of pes cavus

- Metatarsal overload
- Heel pain
- Lateral overload
- Stiffness
- Ankle sprains
- Ill-fitting footwear, toes rubbing
- Ulceration

General examination may reveal features of neurological conditions such as "champagne bottle legs" (Charcot-Marie-Tooth disease), scoliosis in Friedreich ataxia, or a naevus, dimple or patch of hair over the spine in spina bifida occulta. The neurological examination should include a search for signs of peripheral nervous disease, such as muscle wasting, weakness and sensory deficit, and signs of central nervous disease, such as pyramidal signs, cerebellar signs or cranial nerve abnormalities. Accurate serial recording of power in individual muscle groups will allow the clinician to follow the disease over time and detect neurological progression.

The key in examining the foot is to determine to what extent deformities are fixed or flexible. This guides orthotic and surgical treatment. Gait is inspected; in HSMN the typical gait is high-stepping because of foot-drop, with the toe striking the ground before or with the heel.[17] Foot shape is best assessed with the patient standing.[4,5] The soles are inspected for calluses and the shoes for differential wear (indicating sites of excessive pressure). Tender areas, such as the metatarsal heads or base of the fifth metatarsal, are palpated. Passive movements should be assessed, looking for joint contractures. Testing active movements detects muscle weakness. The Coleman block test[8] is one way to determine whether the hindfoot is flexible. With the patient standing, the heel and fifth ray are placed on a wooden block, permitting the forefoot to pronate. If the hindfoot also pronates, it is flexible; if not, it is in fixed varus.

Investigations will be guided by the suspected aetiology. Weight-bearing radiographs are performed to assess the degree of bony deformity and look for arthritic changes. In cases of suspected HSMN, nerve conduction testing and electromyography may be useful. A CMT DNA duplication detection test may be performed for confirmation. If the onset is during adulthood, and especially if rapidly progressive or unilateral, a central disorder such as spinal dysraphism or a space occupying lesion must be excluded by magnetic resonance imaging of the brain and spinal cord.

Treatment

Non-surgical treatments

Non-surgical treatment is instituted early and is chiefly delivered by podiatrists and orthotists, preferably working alongside doctors in a foot and ankle clinic. Orthotic treatment can broadly be separated into four types: pressure relief, correction of deformity, accommodation of deformity, and splinting. Chiropodists and podiatrists can provide simple devices, but more involved orthoses are made by an orthotist.

A simple cushioning orthosis alone may help symptoms from pressure overload.[12] Pressure on the metatarsal heads is alleviated by a total contact orthosis that widens the contact area.[11,19] One randomised controlled trial[12] has compared custom-molded, semi-rigid orthoses with soft, sham inserts. The custom inserts caused a clinically and statistically significant reduction in foot pain scores and peak plantar pressure at three months, and a significant increase in quality of life measures.

If a considerable part of the deformity is flexible, a corrective orthosis should be used. For example, in forefoot-driven cavovarus, the hindfoot is flexible, and so an orthotic shoe insert incorporating lateral forefoot posting (support) and recessing under the first metatarsal will allow the hindfoot to correct.[5] For ankle instability, the lateral side of the hindfoot post can be built up as well as the lateral forefoot post,[11] creating a pronatory moment on the forefoot that counteracts the excessive supinatory moment in the hindfoot.

Any fixed deformity must be accommodated, for example by cupping and supporting the varus heel and providing a small heel raise to compensate for forefoot plantaris. It has been shown that an orthosis that allows the first metatarsal to drop can decrease calcaneal dorsiflexion, and that this coincides with a reduction in foot pain.[20]

With increasing paralysis, splints or appliances are used. If there is a degree of flexibility in the deformity, semi-rigid custom-made ankle-foot orthoses (AFO) can both correct and stabilise the foot and ankle, but can be worn inside a normal shoe and are thus preferred by many patients. If swelling or a fixed deformity cause rubbing and pressure in an AFO, custom-made boots are an alternative. For very severe deformity and refractory ankle instability, in a patient who cannot tolerate an AFO, a caliper incorporating an inside iron

The foot serves as an organ of load distribution, shock absorption, balance and propulsion. Pes cavus interferes with all of these functions

and outside T strap may be prescribed.

Physiotherapy is often directed at maximising muscle power[21] and stretching stiff joints. A typical program would aim at strengthening dorsiflexors and everters (EHL, TA, peroneus brevis) and stretching inverters (tibialis posterior). A review of the two published randomised controlled trials of night time ankle bracing found that it had no effect on ankle flexibility in patients with CMT1A.[22] Thus, in the face of a pronounced or progressive neurological deficit, efforts are probably best directed towards providing aids that optimise function.

Botulinum toxin type A injections into peroneus longus and tibialis posterior have been trialled in patients with CMT1A without success.[23]

If non-invasive treatment alleviates symptoms and can delay progression, it is clearly preferable to surgery. However, there are no longitudinal studies showing that conservative treatments alter the course of *pes cavus*.[7]

Surgical treatment

Surgery is a last resort if the above conservative measures fail to control symptoms. Surgery is only justified when deformity is so pronounced or progressive that symptoms are intrusive and unresponsive to conservative treatments. On the other hand, surgery should not be delayed so long that severe ulceration develops or the patient cannot ambulate. A timely, limited surgical intervention, while the foot is still flexible, can re-balance the foot and prevent the need for a larger, more technically demanding procedure later on.[15]

The aims of surgery are threefold:

- To correct deformity, thereby placing a balanced, stable, plantigrade foot on the ground with even plantar pressures between heel, first ray and fifth ray.
- To relieve pain due to overloaded or arthritic joints, while preserving joint motion where possible.
- To re-balance muscle forces, aiding in gait and preventing progression or recurrence of deformity.

In principle, these aims are achieved by means of:[15]

- Joint releases and tendon lengthening.
- Tendon transfers, taking over-powerful, mechanically advantaged tendons and transferring them to weaker, disadvantaged tendons.
- Osteotomies: dividing and re-aligning bones, and stabilising with plaster or internal fixation.
- Arthrodeses: fusing stiff, painful joints

A critical element of any attempted surgery is re-balancing the forces across the foot. A common example is the Bridle procedure, splitting tibialis posterior and transferring half to tibialis anterior and half to the lateral side of the dorsum of the foot. Peroneus longus is commonly transferred to augment peroneus brevis.[4] Soft tissue procedures are occasionally performed in isolation in the paediatric foot.

When there is limited deformity and rigidity, osteotomies are preferred to arthrodesis if possible, as they preserve motion. The first metatarsal is often treated with a dorsal closing wedge osteotomy, and the heel is lateralised with a sliding osteotomy.[24] Even after a good correction with well-healed osteotomies, neurological progression may cause recurrent deformity, typically five to ten years later,[15] necessitating arthrodesis.[18]

Toe deformities can be effectively treated with the Jones[25] and Hibbs procedures. These correct the cock-up deformities by fusion of the interphalangeal (IP) joints, combined with transfer of the EHL and EDL tendons to the metatarsal necks to assist with ankle dorsiflexion.[4] The EHL and EDL transfers remove the deforming force on the MTP joint, and relax the plantar fascia.

In patients with inflexibility, arthrodesis sacrifices little, and relieves joint pain. The foot can be re-orientated by excising wedge shaped portions of the joints. The triple arthrodesis of subtalar, talonavicular and calcaneocuboid joints is very commonly used.[24,15] Midfoot arthrodeses may be more appropriate, depending on the maximum site of pain and deformity.

Finally, the arthritic ankle may require arthrodesis or replacement. However, this is doomed to failure unless the foot position is corrected and the muscles re-balanced at the same time.[15]

While these general principles have evolved from collective experience and discussions between expert commentators, there is a distinct lack of good quality level I and level II evidence comparing different treatments.[7] In this relatively rare disorder with a heterogeneous presentation, treated by various surgeons in different ways, randomised controlled trials are for the moment elusive.

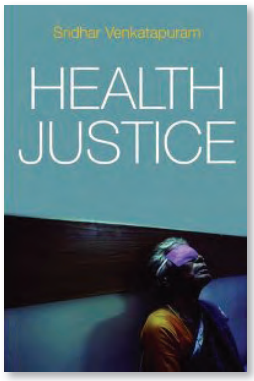
Summary

Pes cavus is a complex deformity, which can arise from neurological aetiology. Despite centuries of experience, controversies still exist as to its precise definition, pathophysiology, prognosis and treatment. The clinician should always identify the cause, whether it is progressive or static, and address the symptoms, tailoring conservative treatment according to the degree of flexibility. The objective of surgical treatment is a plantigrade, stable, flexible foot, in order to improve mechanical symptoms. Neuropathic pain needs to be distinguished from mechanical pain in order to avoid inappropriate surgical interventions.

REFERENCES

1. Aminian A, Sangeorzan BJ. *The anatomy of cavus foot deformity.* Foot Ankle Clin 2008;13:191-8, v.
2. Redmond AC, Crosbie J, Ouvrier RA. *Development and validation of a novel rating system for scoring standing foot posture: the Foot Posture Index.* Clin Biomech (Bristol, Avon) 2006;21:89-98.
3. Nagai MK CG, Guille JT et al. *Prevalence of Charcot-Marie-Tooth disease in patients who have bilateral cavovarus feet.* J Pediatr Orthop 2006;26:438-43.
4. Marks RM. *Midfoot and forefoot issues cavovarus foot: assessment and treatment issues.* Foot Ankle Clin 2008;13:229-41, vi.
5. Chilvers M, Manoli An. *The subtle cavus foot and association with ankle instability and lateral foot overload.* Foot Ankle Clin 2008;13:315-324.
6. Burns J, Redmond A, Ouvrier R et al. *Quantification of muscle strength and imbalance in neurogenic pes cavus, compared to health controls, using hand-held dynamometry.* Foot Ankle Int 2005;26:540-544.
7. Beals TC, Nickisch F. *Charcot-Marie-Tooth disease and the cavovarus foot.* Foot Ankle Clin 2008;13:259-74, vi-vii.
8. Coleman SS, Chesnut WJ. *A simple test for hindfoot flexibility in the cavovarus foot.* Clin Orthop Relat Res 1977;60-62.
9. Gallardo E, Garcia A, Combarros O et al. *Charcot-Marie-Tooth disease type 1A duplication: spectrum of clinical and magnetic resonance imaging features in leg and foot muscles.* Brain 2006;129:426-437.
10. Burns J, Ouvrier R. *Pes cavus pathogenesis in Charcot-Marie-Tooth disease type 1A.* Brain 2006;129:E50; author reply E51.
11. Scherer PR. *Orthotic management of the pes cavus foot.* Lower Extremity Review Magazine 2011
12. Burns J, Crosbie J, Ouvrier R et al. *Effective orthotic therapy for the painful cavus foot: a randomized controlled trial.* J Am Podiatr Med Assoc 2006;96:205-211.
13. Pandraud A LY, Houlden H. *of Peripheral Nerve Advances in the genetics of peripheral nerve Disorders.* ACNR 2012;12:8-13.
14. Williams DSr, McClay IS, Hamill J. *Arch structure and injury patterns in runners.* Clin Biomech (Bristol, Avon) 2001;16:341-347.
15. Sraj SA, Saghieh S, Abdulmassih S et al. *Medium to long-term follow-up following correction of pes cavus deformity.* J Foot Ankle Surg 2008;47:527-532.
16. Burns J, Crosbie J, Hunt A et al. *The effect of pes cavus on foot pain and plantar pressure.* Clin Biomech (Bristol, Avon) 2005;20:877-882.
17. Crosbie J, Burns J, Ouvrier RA. *Pressure characteristics in painful pes cavus feet resulting from Charcot-Marie-Tooth disease.* Gait Posture 2008;28:545-551.
18. McCluskey WP, Lovell WW, Cummings RJ. *The cavovarus foot deformity.* Etiology and management. Clin Orthop Relat Res 1989;27-37.
19. Benedetti MG CF, Ceccarelli F et al. *Gait analysis in pes cavus.* Gait Posture 1997;5:169.
20. Eslami M, Tanaka C, Hinse S et al. *Acute effect of orthoses on foot orientation and perceived comfort in individuals with pes cavus during standing.* Foot (Edinb) 2009;19:1-6.
21. Sackley C DPB, Turner-Stokes L et al. *Rehabilitation interventions for foot drop in neuromuscular disease.* Cochrane Database Syst Rev 2007;18:CD003908.
22. Rose KJ, Burns J, Wheeler DM et al. *Interventions for increasing ankle range of motion in patients with neuromuscular disease.* Cochrane Database Syst Rev 2010;CD006973.
23. Burns J, Scheinberg A, Ryan MM et al. *Randomized trial of botulinum toxin to prevent pes cavus progression in pediatric Charcot-Marie-Tooth disease type 1A.* Muscle Nerve 2010;42:262-267.
24. Klaue K. *Hindfoot issues in the treatment of the cavovarus foot.* Foot Ankle Clin 2008;13:221-7, vi.
25. Tynan MC, Klenerman L. *The modified Robert Jones tendon transfer in cases of pes cavus and clawed hallux.* Foot Ankle Int 1994;15:68-71.

Health Justice: an argument from the Capabilities approach



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Reviewed by: Rhys Davies,
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Health Justice by Sridhar Venkatapuram will do you good. It is good to read scholarly material in a field that is related to one's own but separate from it. It is also good for clinicians, used to treating relatively rare disorders in individual patients, to look across to the subject of 'Health' as opposed to the 'Medicine' of their professional life.

Comments on the volume's back cover include the assertion 'Do not mistake Sridhar Venkatapuram's *Health Justice* for an arcane treatise of interest to a small number of political philosophers'. Only a political philosopher could conclude that the volume does not read rather like a thesis but, at about 270 pages of text, it is short enough (just occasionally one feels it might have been shorter) and the writing style is clear, if not impeccably elegant and engaging.

Technical (philosophical) terms inevitably feature (always with some explanation). Of course, most just add a little to reading effort for a non-philosopher, although some add to the enjoyment. I am glad to know that 'meta-right' refers to the right to have policies formulated such that a 'primary' right comes closer to being achieved. In the festive season full of brands and commercialism, I was glad to be reminded that etymologically 'cosmopolitan' refers to the 'universal city' and that 'cosmopolitanism' is the philosophy that all human groups belong to a single community with shared morality.

At the core of Venkatapuram's argument is the idea that 'Capabilities' for health should be regarded as fundamental human rights. That is, factors that undermine health in the biological, physical and social environment (HIV policy, poverty etc) may usefully be addressed on the international stage by judicial and political processes alongside issues of abuse and general inequity. This contrasts with the more traditional view in Philosophy whereby diseases, and disease risk, were regarded as too unpredictable to underpin any system of ideas that, in turn, might aspire to inform international Politics and Law.

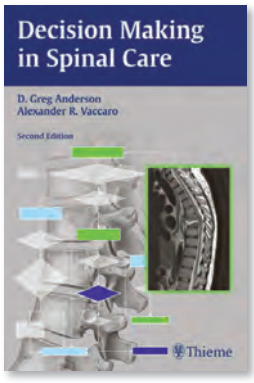
It is only after setting the book aside for a while that clinicians, for whom the morality of striving for the health of their patients underpins daily life, may realize that Venkatapuram's writing is rather bold, and appealing. Personally, I see parallels with the recent furore concerning British prisoners' voting 'rights': my original sense that the human rights adjudication on this point was irrelevant, if not counter-productive, has evolved. We should expect the consensus on human morality to evolve, as the scientific/neuroscientific consensus does. And as clinicians we may be expected to have greater clarity of thought on the matter, certainly, than I usually would at the end of a morning in the Outpatient department.

Health Justice would be an eminently justifiable medical library purchase. ◆

> ***Health Justice by Sridhar Venkatapuram will do you good. It is good to read scholarly material in a field that is related to one's own but separate from it.***

Decision Making in Spinal Care

(Second edition)



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Reviewed by:
Simon Clarke,
Consultant Neurosurgeon,
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Decision making in Spinal Care is another product of the prolific Anderson-Vaccaro lineage. The volume follows the whole of 'Spine' in 15 chapters and then gives a 16th chapter covering miscellaneous topics such as spinal cord stimulation, bone grafts, bracing, penetration injuries to the spine and spine emergencies which would not have fitted-in elsewhere.

A particular strength is the layout of the chapters, consistent throughout the whole text. Each chapter is nicely laid out with a brief preamble followed by a classification and 'work up' encompassing history, examination, imaging, other diagnostic tests, treatment, outcome and complications. Then there is a useful bibliography, referencing the major papers in the field. In addition to the bare citation, the authors nicely provide a line or two describing the paper's overall content.

The presentation style is didactic and very systematic which gives it to a wide target readership. It could be equally valuable to experienced surgeons as a quick reference as to surgeons in training and allied health professionals, in need of a concise but comprehensive account of spinal disorders (with the caveat that a certain degree of core knowledge and skill is assumed).

As a neurosurgeon with a 'Complex Spine' interest, I will find this a handy book to have on my desk. It covers the current management of spinal disorders very well. It is strong on the key principles of decision-making, and provides the references for those who require greater depth and detail. Whilst the book does not cross any frontiers in terms of complex techniques or scientific understanding, this was never its remit.

Even as spinal neurosurgery texts go, you would not find this to be much of page-turner if you mistakenly took it with you on holiday. However, all in all, the authors have comfortably attained their goal: as a quick reference for spinal disorders, this book certainly hits the mark and, as such, I would recommend it. ◆

Solomon Carter Fuller (1872-1953) and the Early History of Alzheimer's Disease

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Whilst the name of Alois Alzheimer (1864-1915) is familiar to every neurologist, if not every schoolboy, and the 100th anniversary of his seminal publications[1,2] on the disease which came to bear his name, courtesy of Kraepelin's systematising, attracted much attention,[3-5] it is unlikely that the name of Dr Solomon Carter Fuller (Figure 1) will be known to any but a handful of Alzheimer's disease (AD) cognoscenti. This obscurity prevails despite the fact that Fuller published what was probably the first paper on AD to appear in the English language.

Fuller's distinguished biography, beginning in Liberia as the grandson of a freed slave and culminating as the first African-American to practice as a psychiatrist in the United States of America, for many years at the Westborough Insane Hospital and at Boston University School of Medicine, has been well documented.[6-8] He was granted leave of absence from his post at Westborough for postgraduate studies with Emil Kraepelin (1856-1926) in Munich for two semesters in 1904-5, and here he was one of only five 'privalesmus' admitted to the course run by Alzheimer, his acceptance perhaps facilitated by his prior experience in histology and his working knowledge of the German language.[8]

Little is known about Fuller's work in Alzheimer's laboratory, for example it is not clear if he knew of 'Alzheimer's first case', Auguste D. Nevertheless, it is evident from his subsequent work that Fuller took an interest in Alzheimer's publications, not surprisingly. The purpose of this article is to look again at Fuller's major publications related to AD and its pathology[9-12] which appeared in the *American Journal of Insanity* and the *Journal of Nervous and Mental Disease* between 1907 and 1912.

Fuller's 1907 *American Journal of Insanity* paper[9] was a histological study of neurofibrils in various conditions, including three cases of 'dementia senilis' as well as cases of dementia paralytica and chronic alcoholism, using the Bielschowsky silver impregnation method. At the outset (416), Fuller acknowledged his "indebtedness to Prof. Kraepelin for his kind permission to use the facilities of the Munich Psychiatric Clinic, where most of our preliminary work was done, and also to Dr Alzheimer, of the same institution, under whose direction we began the study of the neurofibrils". The three patients reported (cases VIII, IX, and X; 444-447) were all elderly males (8th decade). Macroscopic atrophy of the cerebral convolutions was noted in two cases. Diffuse alterations in neurofibrils in the cerebral cortex were noted in all cases: "The cells present a somewhat shrunken appearance and fragmentation, granulation and disappearance of the fibrils are common" (447). Fuller concluded that "diffuse destruction of intercellular [sic] fibrils ... is the rule in dementia senilis" (460) and that silver impregnation for neurofibrils might be used to differentiate dementia paralytica "from a disease with a dystrophic substratum such as dementia senilis" (461). There is no account or illustration (Figures 16 and 21, not 20 as reported in text) which resembles or could be recognised as the neurofibrillary tangle which had been delineated by Alzheimer in his first case, and no mention of Alzheimer's first papers.[1,2] It may be that at this time Fuller was not aware of these publications.

In his 1912 paper (in two parts) in the *Journal of Nervous and Mental Disease*,[10,11] Fuller used the term Alzheimer's disease, acknowledging: "The first published case presenting the combination of clinical and microscopical changes discussed in this paper was reported by Alzheimer in 1906" (440). Fuller cited Alzheimer's 1907 paper[2] (incorrectly as 1906) and included a translation of this case (452-454), as well as material from 11 other papers in the literature reporting similar cases, including Alzheimer's 1911 publication (541-543), the 'second case' of Johann F.[13,14] Fuller's patient was a man in his 50s with symptoms which, with hindsight, seem consistent with amnesia, aphasia without anomia, apraxia and possibly agnosia. At autopsy he was noted to have "regional atrophies of cerebrum" (444). With the Bielschowsky method "easily the most characteristic findings are the presence of a great number of plaques" (448) which are illustrated (Figures 1, 2, and 4, the latter with surrounding neuritic change, described as "Alzheimer degeneration", 449). Furthermore, "many ganglion cells ... exhibit the Alzheimer type of degeneration. This degeneration consists of a tangled mass of thick, darkly staining snarls and whirls of the intracellular fibrils" (451), the illustration of which (Figure 3, 448) is typical of neurofibrillary tangles. Glial proliferation was also reported (454). Of note, Fuller used the term "senium praecox" for this

REFERENCES

1. Alzheimer A. *Über den Abbau des Nervengewebes.* Centralblatt fur Nervenheilkunde und Psychiatrie 1906;29:526-8.
2. Alzheimer A. *Über eine eigenartige Erkrankung der Himrinde.* Allgemeine Zeitschrift fur Psychiatrie und Psychisch-Gerichtlich Medizine 1907;64:146-8.
3. Hodges JR. *Alzheimer's centennial legacy: origins, landmarks and the current status of knowledge concerning cognitive aspects.* Brain 2006;129:2811-2822.
4. Perry G, Avila J, Kinoshita J, Smith M (eds.). *Alzheimer's disease. A century of scientific and clinical research.* Amsterdam: IOS Press, 2006.
5. Larner AJ. *Alzheimer 100.* Adv Clin Neurosci Rehabil 2006;6(5):24.
6. Cobb WM. *Solomon Carter Fuller, 1872-1953.* J Natl Med Assoc 1954;46:370-2.
7. Kaplan M, Henderson AR. *Solomon Carter Fuller, M.D. (1872-1953): American pioneer in Alzheimer's disease research.* J Hist Neurosci 2000;9:250-61.
8. Kaplan M. *Solomon Carter Fuller. Where my caravan has rested.* Lanham: University Press of America, 2005.
9. Fuller SC. *A study of the neurofibrils in dementia paralytica, dementia senilis, chronic alcoholism, cerebral lues and microcephalic idiocy.* Am J Insanity 1907;63:415-68.
10. Fuller SC. *Alzheimer's disease (senium praecox): the report of a case and review of published cases.* J Nerv Ment Dis 1912;39:440-55.
11. Fuller SC. *Alzheimer's disease (senium praecox): the report of a case and review of published cases.* J Nerv Ment Dis 1912;39:536-57.
12. Fuller SC, Klopp HI. *Further observations on Alzheimer's disease.* Am J Insanity 1912;69:17-29.
13. Alzheimer A. *Über eigenartige Krankheitsfalle des spateren Alters.* Zeitschrift fur die gesamte Neurologie und Psychiatrie 1911;4:356-85.
14. Klünemann HH, Fronhöfer W, Wurster H, Fischer W, Ibach B, Klein HE. *Alzheimer's second patient: Johann F. and his family.* Ann Neurol 2002;52:520-3.
15. Allison RS. *The senile brain. A clinical study.* London: Edward Arnold, 1962:118.
16. Larner AJ. *Epileptic seizures in AD patients.* Neuromolecular Med 2010;12:71-7.
17. Friedman D, Honig LS, Scarmeas N. *Seizures and epilepsy in Alzheimer's disease.* CNS Neurosci Ther 2012;18:285-94.


Dr Solomon Carter Fuller

case (which he believed to be the 8th recorded case of Alzheimer's disease[12]) and the other cases from the literature which he reviewed, this term apparently synonymous with 'Alzheimer's disease' (440,452), presumably to distinguish these cases from 'dementia senilis'.

Some fifty years later, Allison[15] claimed that in this paper Fuller noted convulsive fits in a confirmed case of Alzheimer's disease in the later stages, if so a most interesting observation in view of current interest in the occurrence of epileptic seizures in AD.[16,17] Reading Fuller's lengthy case report,[10] I can only presume that Allison refers to the "short periods of unconsciousness or dream-like states" which occurred in the two years before the patient's 'final breakdown' (441), but no account of convulsion has been found. However, in his summary of previously published cases,[11] Fuller noted that "In a few of the cases motor disturbances have been noted as residua of epileptiform convulsions. Convulsions with loss of consciousness, however, have not been observed, save in the terminal stage, epileptiform attacks and muscular twitchings being recorded" (554). It is now well-recognised that epileptic seizures and myoclonus become more evident with progression of AD.[16] In Fuller's review, most patients showed evidence of brain atrophy, either general or regional, all but one had evidence of plaques, and all but one had "peculiar basket-like alterations due to the presence of thick, darkly staining intracellular fibrils arranged in whorls or in a tangled mass" (555), the exception being Alzheimer's second case.[13]

With his colleague Henry Klopp, Fuller reported in the *American Journal of Insanity* in 1912 a second personally examined case believed to be an example of Alzheimer's disease.[12] This judgement was based on the clinical history and autopsy findings of plaques but "the Alzheimer degeneration of intracellular neurofibrils ... was not exhibited" (24), as in Alzheimer's second case[13] and differing from the first Westborough case.[10] The nosological position of "Alzheimer's disease" vis-a-vis senile dementia was discussed, the former being conceived of as an "atypical form of senile dementia" (26).

Fuller's diligence, industry and skill are readily apparent from his papers. Evidently he was in the right place at the right time and possessed the right skills to contribute to the contemporaneous debate on the new diagnostic entity of Alzheimer's disease. In retrospect it is puzzling that he reported nothing resembling neurofibrillary tangles in the brains of patients with "dementia senilis" in his 1907 paper. One may surmise that his views evolved between 1906 and 1912, perhaps as a result of his ongoing studies and his reading of Alzheimer's papers.[1,2,13] Fuller's position as a pioneer of Alzheimer's disease studies in the English language is unquestionable and he deserves to be more widely known. ◆

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th February, 2013

2013

January

RCP/BAD Medical Dermatology Meeting – Neurology
10 January, 2013; London, UK
E. Dawn.Moore@theabn.org

February

Biomarkers for Brain Disorders: Challenges and Opportunities
3-5 February, 2013; Cambridge, UK
https://registration.hinxton.wellcome.ac.uk/display_info.asp?id=303
E. Lucy Criddle, l.criddle@hinxton.wellcome.ac.uk

BNPA 26th Annual General Meeting
7-8 February, 2013; London, UK
T. 020 8878 0573,
E. admin@bnpa.org.uk or jashmenall@yahoo.com

Dementias 2013
7-8 February, 2013; London, UK
www.mahealthcareevents.co.uk/dementias2013 or
T. 020 7501 6762.

Basic Applied Neurophysiology
13th Feb. 2013; Derby, UK
T. 01332 254679
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

8th Essential Neuro MRI Study Day – One day course in how to interperet MRI Brain & Spine
Liverpool Medical Institute
– Sat 17th Nov 2012 – Limited places
Kath Tyler
T. 07799 723 925
E. essentialneuromri@hotmail.co.uk

Understanding and Management of Fatigue and Sleep Disorders following Acquired Brain Injury
22nd February 2013; The Oliver Zangwill Centre, Ely, Cambridgeshire, UK
T. 01353 652173
E. rachel.everett@ozc.nhs.uk

March

Glia and Neurons: a symbiotic partnership
20-22 March, 2013; Cambridge, UK
T. 01223 331160
E. skt37@cam.ac.uk

April

5th Parkinson's Advanced Masterclass
4 April, 2013; Marriott Hotel, Leeds City Centre, UK
Neuropsychiatric and complex management issues
Early bird booking by 17th December £40 per attendee.
Programme and booking www.redpublish.co.uk, **Festival of Neuroscience 2013**
7-10 April, 2013, London, UK
T. 0208 166 8713
E. office@bna.org.uk

Research for Clinicians – Integrating Research into Day to Day Practice
19th April, 2013: The Oliver Zangwill Centre, Ely, Cambridgeshire, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

3rd Essential Stroke Imaging Course
Saturday 20 April, 2013; Liverpool, UK
Intensive 1 day course aimed at clinicians and trainees, covering the essentialaspects of stroke imaging & image interpretation.
Contact: Kath Tyler
T. 07799 723 925
E. essentialcourses@hotmail.com

Ketogenic Dietary Therapies Matthew's Friends UK & European Dietitian's Conference
25th and 26th April 2013 Lingfield Park Marriott, Lingfield, Surrey
www.matthewsfriends.org
T. 01342 836571
E. Julie@matthewsfriends.org

May

Magstim Neuroenhancement Conference & Workshop 2013
4-5 May, 2013; Oxford, UK
For more information see www.magstim.com/events-courses

The 11th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD™)
6-10 May, 2013; Florence, Italy
T. + 41 22 906 0488
E. reg_adpd2013@kenes.com

NeuroID 2013: Liverpool Neurological Infectious Diseases Course
9-10 May, 2013, Liverpool, UK
For more information and to register see
www.liv.ac.uk/neuroidcourse

MS Frontiers
9-10 May, 2013; London, UK
www.mssociety.org.uk/msfrontiers
or call 020 8438 0941

ABN Annual Meeting
21-24 May, 2013; Glasgow, UK
www.abn.org.uk
T. 020 7405 4060
E. info@theabn.org

ASNR 2013
18-23 May, 2013; San Diego, USA
T. (630) 574 0020
www.asnr.org/

June

Consultant & final year SpR Parkinson's Masterclass
Module 1 - Bristol City Centre, 3rd - 5th June 2013,
Module 2 - London, 28th November (1 day) for further details and booking www.redpublish.co.uk

ENS 2013
8-11 June, 2013; Barcelona, Spain
E. info@ensinfo.org

New Avenues for Brain Repair: Programming and Reprogramming the Central Nervous System
June 10-11, 2013; Cambridge, US
E: events@abcam.com

17th International Congress of Parkinson's Disease and Movement Disorders
16-20 June, 2013, Sydney, Australia
T. +1 414 276 2145
E. info@movementdisorders.org
www.movementdisorders.org

The Advanced Balance Course
19-21 June, 2013; Chilworth Manor, Southampton, UK
Fiona Barker,
T. 0790 779 1619
E. fiona.barker@windsor-ent.co.uk

4th Oxford Neurology Course
26-28 June, 2013; Oxford, UK
E. events@ndcn.ox.ac.uk

July

Human Brain Anatomy
15-17 July, 2013; London, UK
Book online at www.neurocourses.com

September

XXI World Congress of Neurology
21-26 September, 2012; Vienna, Austria
T. +41 22 9080488
E. Dnuriel@kenes.com
www2.kenes.com/wcn

October

3rd World Parkinson Congress
1-4 October, 2013; Montreal, Canada
T. (+001) 800.457.6676
E. info@worldpdcongress.org
www.worldpdcongress.org

A Special Relationship: The joint American Neurological Association and Association of British Neurologists meeting

Conference details: 7-9 October 2012, Boston, USA. ***Reviewed by:*** Rubika Balendra, King's College London; Timothy Rittman, Addenbrookes Hospital, Cambridge, UK.

New England in the Fall, and members of the Association of British Neurologists crossed the Atlantic to join the American Neurological Association for their Annual Meeting. The seniority and experience of many who attended was evident in high quality academic lectures and intelligent, clinically relevant discussions. However, it was not a meeting where senior neurologists kept themselves apart; instead they constantly interacted with junior colleagues.

Lectures and symposia

A series of named lectures and well organised symposia showcased the best of current clinical neuroscience research and gave the floor to work developed over a number of years. Alastair Compston (University of Cambridge) gave the Soriano lecture, presenting a body of work in multiple sclerosis stretching back to the 1990's bringing Alemtuzumab from the theoretical early days, through failures and successes to a phase III trial. He looked to the future of multiple sclerosis work, to find effective treatments with better side effect profiles.

More recent work was presented by Bryan Traynor, (National Institute on Aging) who received a Neurological Scholar Award. He described his 'eureka' moment in 2011 on realising that a hexanucleotide repeat expansion in the C9orf72 gene was responsible for a large proportion of familial ALS in Northern Europe. Sydney Cash, (Massachusetts General Hospital, Boston) talked on using EEG, MEG and intracranial electrodes to explore neuronal activity during normal cognition, sleep and seizures. He demonstrated that superior temporal gyrus recordings reveal individual neuronal responses to specific word sounds.

Presentations from two studies of disease modifying drugs targeting the beta-amyloid pathway in Alzheimer's disease shifted the meeting to another level, bringing the largest audience of the conference. Rachelle Doody (Baylor College of Medicine, Houston) presented modest but encouraging results from Solanezumab in Alzheimer's disease. She reported an independent study of data provided by Lilly, showing a 1.41 point advantage of Solanezumab over placebo on the ADAS-COG ($p=0.009$) in mild and moderate Alzheimer's disease on data pooled from North American and European studies. There was a small effect on decline in daily function (ADCS-ADL) only for mildly affected patients.

By contrast Reisa Sperling (Brigham and Women's Hospital, Boston) presented disappointing results from Bapineuzumab, showing no effect on clinical scores, and a concerning increased rate of whole brain atrophy in the treatment group.

Alastair Compston, awarded the Soriano Lectureship, discusses Phase III Trials of Alemtuzumab in Relapsing-Remitting Multiple Sclerosis.

Eva Feldman (ANA President) and Martin Rossor (ABN President) exchange gifts of appreciation between the organisations.

Both studies will undoubtedly provide insights in to the mechanisms of Alzheimer's disease and shape future drug studies and trial design, but the general feeling was that we will have to wait a little longer for a truly effective therapy which is ready to take to the clinic.

Special Interest Groups

The breadth of smaller special interest group sessions offered an opportunity to learn about a broad range of topics in neurology. The symposium on health services research was one such session. Strategies to solve inequalities in the American healthcare system formed the basis for the meeting. 'Can Corporate America Solve Health Disparities' was a provocative title from Lewis Morgenstein (University of Michigan, Ann Arbor), who discussed the advantages and disadvantages of encouraging companies to provide targeted health promotion for minority groups within their workforce.

A Special Interest Symposium on Sleep Disorders was also informative. Thomas Scammell (Harvard Medical School, Boston), discussed the narcolepsy orexin knockout mice his group uses to study the neurobiology of the disease. These mice respond to rewarding stimuli in the same way as humans with narcolepsy, with increased cataplexy to the rewarding stimuli of running wheels, 'sociable' group housing and chocolate. By inducing focal expression of orexin they can identify which brain regions are essential for orexin's wake-promoting effects.

Lunch worshops

The new interactive lunch workshops certainly sparked debate and controversy. In one workshop continuous EEG monitoring in the ICU was advocated for patients in whom non-convulsive seizures are suspected, as a one hour EEG misses 50% of such cases. This provoked intense discussion on how to facilitate the necessary technical support, staffing and expertise, and how aggressively seizures should be treated if detected.

Faculty Development course

A welcome addition to the programme this year was the excellent daily Faculty Development courses. Strands for Junior and Senior Faculty members and Department Chairs aimed to nurture the careers of academic neurologists at all levels. Although some sessions were more relevant to those seeking NIH funding, the final session entitled 'Getting Published' was enlightening. We were treated to behind closed doors insights from Alastair Compston (Editor, Brain) and Stephen Hauser (Editor, Annals of Neurology) who described in detail how the review process functions. Their overriding message was that juniors should strive towards creative, interesting and novel research with relevance to medicine and health.

Art, culture and the city

A display of brain inspired art provided a splash of colour to the meeting. 'Valentine' showed a heart shaped sulci in a sagittal brain slice, whilst 'Emerging' explored the shape of cortical folds as they appeared to swirl outwards away from the underlying white matter.

Boston is what the Americans call a 'walkable' city, small enough to wander around and find parks, American historical sites, university campuses and great restaurants. The famous freedom trail takes many tourists around the main sites of the city. And this time of year 'leaf-peepers' descend on New England as the leaves start turning to deep reds and yellows. Overall it was an educational and enjoyable meeting, in a friendly city between two organisations who have met together many times over the years, and know each other perhaps a little better than before. ◆

The 34th Advanced Clinical Neurology Course

Conference details: 10-11 September 2012, John McIntyre Centre, Edinburgh First, Edinburgh.
Reviewed by: Dr Louise Davidson, Research Registrar, National CJD Research and Surveillance Unit, Western General Hospital, Crewe Road, Edinburgh

Background

2012 marked the 34th anniversary of the Advanced Clinical Neurology course in Edinburgh. Initially established by Professor Charles Warlow over three decades ago and now organised by Dr Richard Davenport, this highly successful course has carved a reputation for its relaxed, informal atmosphere and practical approach to neurology. The course gathered together over 60 participants, attracting medical students, trainees, consultants and neurology veterans. Lively discussion and interaction was encouraged, particularly from junior attendees. This year saw a change in venue to Edinburgh First, based at the university campus in the purpose built conference facilities. A variety of general topics were organised into six sessions, compacted into two days.

Course organisers: From left - Dr Richard Davenport (Consultant Neurologist, Edinburgh), Judi Clarke (Academic Personal Assistant), Professor Charles Warlow (Emeritus Professor of Neurology, Edinburgh).

Day one

The course opened on Monday 10th September with a welcome address by Dr Richard Davenport followed by the first morning session entitled 'Mostly Peripheral Nerves'. Dr Tim Williams (Newcastle) gave an excellent overview on motor neuron disease with an emphasis on the common mimickers of the condition and the potential for misdiagnosis. This was followed by Dr Arup Mallik's (Glasgow) discussion of the common entrapment neuropathies including anterior/posterior interosseous neuropathies, carpal tunnel syndrome and ulnar neuropathy. A clear and concise guide to the localisation of lesions was presented with particular reference made to the importance of good clinical skills.

The second morning session concentrated on epilepsy with Professor John Duncan (London) delivering an informative talk on the importance of the classification of seizures. The discussion centred on focal seizures and included their recognition as well as localisation. Dr Hannah Cock (London) followed with a presentation on mortality in epilepsy. There was emphasis placed on SUDEP with a general overview including incidence, risk factors, suggested mechanisms and prevention. Dr Chris Derry (Edinburgh) gave the final talk of the session with a highly educational presentation on sleep and epilepsy. A series of patient videos were used to illustrate the differences between nocturnal frontal lobe seizures and various parasomnias. The audience had the opportunity to participate which made for enjoyable and effective learning. It was highlighted that a detailed and accurate history is key to the diagnosis as investigations are often normal.

Following the lunch break, Dr Huw Morris (Cardiff) opened the first afternoon session which covered movement disorders. An update on Progressive Supranuclear Palsy (PSP) was presented and detailed the diagnostic challenges of the condition. The limitations in the current diagnostic criteria were highlighted. Features that distinguished PSP from Parkinson's disease (PD) were discussed including the pattern of bradykinesia, distinctive gait and posture as well as saccadic eye movements. The genetic predisposition to the condition was also covered. Dr Carl Counsell (Aberdeen) delivered a talk entitled 'Ten things I wish I had known about PD when I started'. Primarily directed at trainees, this was a fantastic presentation of the difficulties posed by PD, particularly with regard to early diagnosis and subsequent management. We learnt not to be afraid of reviewing patients over time and to monitor their symptoms before committing to the diagnosis as it may not be obvious at initial presentation. The role of FP-CIT scans was discussed although it was emphasised that they are not a substitute for clinical skill or experience.

Day 2

The final session of the day commenced with an invited lecture from Dr Alastair Compston (Cambridge) who gave a fascinating talk on the history of BRAIN. The clinicopathological conference concluded the day with a complex case expertly discussed by Dr Hadi Manji (London). The diagnosis of paraneoplastic limbic encephalitis associated with a neuroendocrine tumour eluded all participants. This was followed by an evening of dinner and drinks.

Day two was opened by Dr Edward Fathers (Taunton) who turned the direction of discussion to presentations in general and how to give a good talk. Tips were given on style, content and how to captivate the audience as well as common pitfalls and habits to be avoided. The founder of the course, Professor Charles Warlow (Edinburgh), followed with invaluable advice on how to write a good paper. Emphasis was placed on the importance of writing clearly, concisely and consistently with examples provided to highlight a variety of 'do's and don'ts'.

The final session covered a medley of topics beginning with Dr Miles Connor (Fife) presenting the challenges facing sub-Saharan Africa in delivering a neurology service. We learnt about the burden of neurological disease and the difficulties in accessing neurologists, particularly in rural areas. The limitations in diagnostic tools and the reliance on excellent clinical skills were highlighted. Initiatives to improve neurological services were also covered. Dr Peter Enevoldson (Liverpool) gave a highly educational talk on 'top-tips in neuro-opthalmology'. Red flag symptoms that suggest an underlying neurological problem and key points to aid localisation of lesions were discussed. Transient monocular blindness and its potential causes were discussed with amaurosis fugax considered in detail. Dr Alok Tyagi (Glasgow) delivered an excellent overview on spontaneous intracranial hypotension. Causes, associations and complications were covered with a helpful algorithm on diagnosis and management.

Professor Tom Warner (London) gave an illustrative teaching session on dystonia with an overview of primary and secondary cases. The course concluded with talks focused on muscle. Dr Cheryl Longman (Glasgow) concentrated on the genetic aspects of muscle disease followed by an informative overview of acute and chronic myopathies by Dr James Miller (Newcastle).

Concluding remarks

This is an organised, high quality course with an excellent standard of presentations addressing a number of neurological topics. It offers a fantastic opportunity to keep updated with general knowledge and advances in neurology. The relaxed and enthusiastic approach to learning along with plenty of opportunity for discussion and interaction make this course highly enjoyable and not to be missed. ◆

Seeing Beyond the Gene – Second National Conference on Huntington's Disease

Conference details: 26 April, 2012, Stoke-on-Trent, UK. ***Reviewed by:*** Dr George El-Nimr, Consultant Neuropsychiatrist/Clinical Tutor. Clinical Lead for Neuropsychiatry and Older Adult Psychiatry.

Having received overwhelming support and approval of the first national conference in 2010, the second event did not disappoint! With more than 160 attendees from all over the UK and Europe from a wide range of sectors, the attendance exceeded expectation. The conference was sponsored by a number of organisations from various fields, ranging from health care groups, support organisations and technical experts; both from the UK and other European countries. Excellent support and input were also received from relevant voluntary organisations.

Dr George El-Nimr, Consultant Psychiatrist and the conference organiser, began the day by presenting an overview of the epidemiology of Huntington's Disease (HD) in a talk entitled "HD around the World". This highlighted the importance of epidemiology in informing service planning and also to assist with the interpretation of potential preventative methods. He went on to discuss the change in attitudes towards positive predictive testing over time and across different countries. Increased testing will shed more light on the service needs of at risk individuals and asymptomatic abnormal gene carriers.

Charles Sabine, TV journalist, along with a carer from the neuropsychiatry HD services in Stoke-on-Trent delivered a session entitled "Personal perspectives, living with genetic test results". Personal views of the different challenges raised by positive and negative HD test results were discussed in an interactive session that received excellent feedback. During this session the importance of collaborative working between patients, families, researchers and clinicians was emphasised.

Dr Oliver Quarrell, Clinical Geneticist, talked about predictive and pre-natal genetic testing in HD: practical and ethical challenges. The identification of the gene in 1993 allowed more widespread predictive testing and the guidelines for genetic testing were modified. Issues surrounding disclosure of reduced penetrance and intermediate allele results were also presented.

Dr David Craufurd, Consultant Neuropsychiatrist and Senior Lecturer in Medical Genetics at the University of Manchester talked about neuropsychiatric symptoms and their treatment. Dr Craufurd focused on mood changes, irritability and loss of motivation (apathy) being the most common and troublesome behavioural changes. There is some evidence that apathy and irritability are a direct consequence of the underlying neurodegenerative process, while depression and psychotic symptoms may reflect a distinct genetic predisposition for these disorders.

The afternoon session started with Mr Doug Feery, Barrister, who is a specialist in Court of Protection matters and has a particular interest in cases where there is a human rights element. The unprecedented change in the law affecting adults who lack capacity was presented. The introduction of the Human Rights Act, amendments to the Mental Health Act and the introduction of the Mental Capacity Act were discussed with special reference to patients with HD.

Dr George El-Nimr, conference organiser (in the middle) with the conference speakers.

The conference attracted a number of national and international sponsors and exhibitors.

Professor Sarah Tabrizi, Professor of Clinical Neurology at UCL Institute of Neurology, talked about the TRACK-HD Study which commenced in 2008. TRACK-HD was designed to observe natural disease progression in premanifest and early stage HD with the aim of establishing sensitive and specific clinical and biological markers of disease progression. A new study, namely Track-On HD was also discussed. The aim of that study is to identify neural compensatory networks that may occur in the premanifest phase of neurodegeneration in HD.

Dr Hugh Rickards, Consultant Neuropsychiatrist and Honorary Reader at Birmingham University talked about the theoretical basis of abnormal behaviour. He highlighted the fact that the striatum is a "neuropsychiatric" brain region which contains neurons related to mood, cognition and movement. The issue of excluding HD patients from mainstream psychiatric services in the last 20 years was highlighted as a matter that will need addressing.

Professor Bernhard Landwehrmeyer, Professor of Neurology at Ulm University and the Chair of European Huntington's Disease Network presented a talk entitled "Finding a Cure; Hopes and Challenges". Professor Landwehrmeyer indicated that insight into critical mechanisms of disease derived from studies of experimental model systems of HD are important to study. He also discussed ENROLL-HD, a global prospective natural history study of people affected by HD that will accelerate research in the field of HD.

Professor Anne Rosser, Professor of Clinical Neuroscience and Joint Director of the University's Brain Repair Group at Cardiff University, presented a talk on cell and tissue transplantation as a potential therapeutic strategy in neurodegenerative disorders, which offers to replace cells lost during the disease process.

The conference was a great success in supporting patients and families, informing professionals and raising awareness. The programme flowed excellently with a great mix of professional presentations from field experts to local carers and well known Huntington's disease gene carriers who are dealing with the ramifications of being in such a difficult position.

Concurrent and subsequent feedback from delegates, sponsors and speakers was quite encouraging. This led to the ongoing planning for the third national conference that will take place next year. All presentations and videos from the day were made available for delegates after the event. ◆

4th Annual UKABIF Conference

Conference details: 13 November 2012, National Motorcycle Museum, UK. ***Reviewed by:*** Louise Blakeborough on behalf of UKABIF.

Over 150 doctors, case managers, personal injury lawyers, social care workers, voluntary organisations and care providers attended the meeting. The programme highlighted the need for long-term rehabilitation following a brain injury to maximise optimal patient recovery – a key message that is generally not accepted by funders.

Professor Michael Thaut from the Centre for Biomedical Research in Music at Colorado State University, USA began the day with a stimulating presentation on the role of music in rehabilitating people with brain injury. Research has demonstrated that auditory rhythm has a profound effect on the motor system and a large number of clinical studies have looked at the effectiveness of rhythm and music to produce functional change in motor therapy for stroke, traumatic brain injury (TBI), Parkinson's disease and other conditions. Professor Thaut illustrated his talk with several video case studies to show the positive effect of rhythmic auditory stimulation in improving gait and upper extremity function.

Dr David Sharp, NIHR Research Professor and Consultant Neurologist at Imperial College, London discussed the use of advanced neuroimaging to diagnose the underlying causes of common cognitive impairments such as memory and attention.

"TBI is a massive clinical, social and economic problem which isn't reflected in funding for research in the UK" said Dr Sharpe. He discussed a study where head injury was found to be associated with an increased vulnerability to death from a variety of causes, for at least 13 years after hospital admission. From the cohort of 767 people, 40% had died after 13 years. Dr Sharpe focused on the common cognitive impairments in areas such as memory and attention which limit recovery and are difficult to treat. Advanced MRI techniques such as diffusion tensor imaging can now facilitate identification of those areas in the white matter where damage has occurred.

The use of psychological tests to assess executive function and the development of techniques and technologies to aid rehabilitation were discussed by Dr Andrew Worthington, Clinical Neuropsychologist and Director of Headwise. One project underway to assist executive problems is 'CogWatch', a European Commission funded research project involving six partners including Headwise, for the rehabilitation of stroke patients. Co-ordinated by the University of Birmingham, CogWatch is developing advanced and intelligent common objects and tools which will help to re-train patients on how to carry out activities in their daily life by providing persistent multimodal feedback. The CogWatch tools will be part of a personalised home rehabilitation system and silently monitor the patient as they complete tasks. When an error is detected, CogWatch will provide helpful and relevant guidance cues to assist the patient in completing the activity.

Professor Michael Thaut, Colorado State University gave a stimulating presentation on the role of music in neurorehabilitation.

Sleep disorders are both under-recognised and under-reported and Professor Michael Barnes, UKABIF Chair said: "Overnight sleep disorders and excessive daytime tiredness are very common after a TBI; about 50% of people have some form of long-term sleep disorder". Professor Barnes discussed the range of sleep disorders including sleep disturbance, circadian rhythm disorders and hypersomnia. The most serious sleep disorder after TBI is obstructive sleep apnoea and one study found it occurred in nearly a quarter of people. This causes actual cessation of breathing during the sleep, often in association with snoring. The diagnosis of the nature and type of sleep disorder is a specialist area and most regional centres have a sleep clinic, usually run by neurologist or a sleep specialist.

Visual disturbances are another under-recognised aspect of ABI. "It is not just about vision because many people with TBI people have normal vision, but other visual issues can be hidden" said Mr Mark Menzes a neuro-developmental optometrist. Unfortunately, many patients with visual problems after a stroke or head injury fail to receive an accurate diagnosis. Each case is different and the difficulty each patient has depends on the severity and location of the injury. Some of the most common visual problems include loss of visual field, visual spatial disorders and visual neglect, vertigo, dizziness and impaired eye movements including double vision, eyestrain and difficulty in reading. The visual problems of ABI may affect nearly all aspects of vision and can hinder normal recovery; early vision evaluation is therefore crucial.

"The effect of peer support in recovery and rehabilitation is now well-proven" said Ava Easton, Chief Executive Officer of The Encephalitis Society in a presentation that was strongly endorsed by the audience. Peer support refers to initiatives where members of self-help organisations and others meet as equals to give each other support on a reciprocal basis to help one another through recovery and rehabilitation. Peer support does not exist in a clinical setting and given the current resource restraints then involvement of the voluntary sector is crucial.

Sue Thomas, Chief Executive of Neurological Commissioning Support delivered a comprehensive overview of the NHS changes. The commissioning of services for Acquired Brain Injury will be both specialised and commissioned by the clinicial Commissioning Groups (CCGs). A large element of neurology will be commissioned locally by CCGs and each CCG board must include GPs, at least one registered nurse and a doctor who is a secondary care specialist. Some CCGs already have a GP neurology lead but many do not. ◆

Over 150 doctors, case managers, personal injury lawyers, social care workers, voluntary organisations and care providers attended the meeting.

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3rd Annual Parkinson's Disease (PD) Expert Series Meeting

Conference details: 23-24 November 2012, London, UK. ***Reviewed by:*** Dr Deepti Zutshi, Neurology Specialist Registrar, Department of Neurology, Nottingham University Hospitals NHS Trust, Nottingham, UK.

The 3rd Annual PD-Expert Series Meeting took place from 23-24 November 2012 in London, UK. Over 150 delegates representing Consultant Neurologists and Elderly Care physicians, PD nurse specialists, GPs, specialist registrars (SpRs), physiotherapists and pharmacists, attended the conference at the Hilton Tower Bridge Hotel, located in the Borough district of London.

The meeting was chaired by Dr Nin Bajaj, Clinical Director of the National Parkinson Foundation International Centre of Excellence and Honorary Associate Professor in Neurology, University of Nottingham. The meeting was sponsored by UCB Pharma Ltd and 9 CPD points from the RCP was awarded to attendees. A wide range of topics, faculty debates and video case presentations, in conjunction with a 'real time analysis' audience voting system used for the first time in this meeting, provided an educational and engaging conference.

Professor Günther Deuschl, President of the International Movement Disorder Society, Christian-Albrechts-University in Kiel, Germany opened the start of the conference with a lecture on current topics in PD. He presented data on the EARLY-STIM study advocating the use of deep brain stimulation (DBS), which is currently a widely accepted practice in the treatment of advanced PD, to be considered in patients with early or moderate PD. The conference then proceeded with a lecture on the non-motor symptoms of PD, with a focus on pain and sleep, given by Professor K Ray Chaudhuri, Clinical Director of the National Parkinson Foundation International Centre of Excellence, Kings College, London. Citing several papers currently in-press, Professor Chaudhuri commented on the importance of healthcare workers asking patients about pain, especially during fluctuations OFF medications, as well as using a new PD pain score undergoing a multi-centre validation study to help investigators monitor pain. The second half of the lecture concentrated on various sleep disorders commonly seen in PD as well as excessive daytime somnolence, a non-motor symptom that often progresses with the disease.

The next two hours were spent with a dynamic interactive video session where a variety of classic and challenging movement disorder cases were presented by various neurology SpRs from all over the country. For the first time, an audience response system was used to provide an amiable but competitive challenge where each table had to compete for points against the meeting's faculty members. The cases included a diagnosis of aqueductal stenosis potentially causing parkinsonism, episodic ataxia type 2, progressive apraxia of speech, XXYY syndrome, PSP with chorea and finally acquired alien limb syndrome. The faculty was successfully able to defend their honour by a six point lead in this year's round of questions.

Professor K Ray Chaudhuri

Dr Nin Bajaj

A review on the imaging of motor and non-motor aspects of PD was given by Professor David J Brooks, Hartnett Professor of Neurology and Head of the Centre for Neuroscience, Imperial College, London. He mentioned the correlation between specialised scans (DAT, VMAT2 and DDC) reflecting the severity of disease. He also discussed the use of imaging in recognising the neuroanatomical connections of various motor and non-motor symptoms of PD, such as tremor, dementia, dyskinesia.

Dr Doug MacMahon, Consultant at University Hospitals of Coventry and Warwick NHS Trust presented some of the preliminary results of PD MED, a large multi-centre trial that is evaluating the cost-effectiveness of currently available treatment in early and late PD. After presentation of the preliminary data, many of the audience felt that level of impact in their own practice would be minimal, but the effect of these results on PCTs remains uncertain for the future.

Day one closed after a lively debate on the reliance of clinical acumen solely versus requirement of imaging to confirm the diagnosis of PD. Dr Richard Genever, Movement Disorder Lead, Chesterfield Royal Hospital argued for the former against his opponent, Dr Nin Bajaj. The winner of the debate was Dr Genever, convincing 57% of the audience to rely on clinical acumen solely for diagnosis.

The end of the day was followed by a scrumptious dinner and a lively speech on the future of general neurology by Dr John Paul Leach, Consultant Neurologist, Southern General Hospital, Glasgow.

At the dinner proceeds from the registration fees for the meeting were donated to Parkinson's UK and Cure Parkinsons by Mr Taco Van Tiel from UCB Pharma and Dr Nin Bajaj.

Saturday morning started out with the second debate, 'Drug Therapy in Parkinson's Disease should be given soon after diagnosis and titrated to symptom control.' Dr Paul Worth, Consultant Neurologist, Norfolk and Norwich University Hospital, argued to not delay treatment, citing that PD was a progressive disease and the goal should be to maintain the best quality of life for as long as possible. His opponent, Dr Romi Saha, Consultant Neurologist, Royal Sussex County Hospital, Brighton, argued against starting early and aggressive treatment, stating that there was no evidence for neuroprotection and there was a benefit of giving patients the time to understand, accept and educate themselves about the diagnosis prior to starting treatment. The final vote was close with 54% agreeing with Dr Worth's stance.

The second lecture was a very practical and useful topic on functional movement disorders by Dr Mark Edwards, Consultant Neurologist, The Sobell Department of Motor Neuroscience Foundation and Movement Disorders Institute of Neurology, London. Dr Edwards's talk went through several 'tricks of the trade' in evaluating functional patients in various diseases, medico-legal pitfalls and the paucity of available treatments. His lecture was followed by Dr Helen Roberts, Chair of the BGS Movement Disorders Section, Senior Lecturer and Honorary Consultant, University of Southampton on recognising key problems and treatments in Parkinsonism in the older patient.

The final two lectures of the conference gave an overview of PRoBaND (Parkinson's Repository of Biosamples and Networked Datasets), a large multi-centre biomarker study to prospectively observe patients diagnosed with PD. The primary investigator, Dr Donald Grosset, Consultant Neurologist, Institute of Neurological Sciences, Southern General Hospital, Glasgow discussed the recruitment criteria, the study endpoints and data collection methods as well as the possible applications and collaborations of the study. This was followed by the final lecture by Dr Bajaj on MRI studies looking at neuromelanin and the possibilities of 7T MRI in the evaluation of PD in collaboration with the PRoBaND study.

Overall, the conference was educational and interactive, and met with positive feedback from the multi-disciplinary audience. The controversial topics on the evaluation and treatment of PD and other movement disorders, as well as information on future studies, showcased the current challenges of matching clinical needs with further basic science work in order to provide well-balanced and individualised patient care. The 2013 meeting is certainly one to keep on the calendar for next year. ◆

The International Spinal Cord Society 51st Annual Scientific Meeting

Conference details: 3-5 September 2012, London, UK. ***Reviewed by:*** Susan Charlifue, PhD, FACRM, Senior Principal Investigator, Craig Hospital, Englewood, Colorado and Chair, ISCoS Scientific Committee

Background

The International Spinal Cord Society (ISCoS) returned to England, its founding nation in 2012 for the 51st Annual Scientific Meeting (ASM) on September 3rd-5th. With a backdrop of the Paralympic Games, the ISCoS meeting shared scientific, programmatic and educational advances in the management of spinal cord injury and spinal cord diseases (SCI/D) through a series of plenary talks, workshops, symposia, oral presentations and posters.

ISCoS (formerly the International Medical Society of Paraplegia – IMSOP), was founded in 1961 by doctors from around the world. In the early years, the ASM was held at Stoke Mandeville Hospital in the UK; however, over the past two decades, consistent with the international focus of ISCoS, the meetings have been hosted in numerous nations, most recently Italy in 2009, India in 2010 and the United States in 2011. The membership of ISCoS has grown rapidly and consists of physicians, allied health professionals and scientists involved in the management and study of SCI/D.

The 2012 meeting had an audience of nearly 1000 physicians, neuroscientists, physiotherapists, nurses, researchers and other health professionals as well as individuals with SCI/D themselves. The Queen Elizabeth II Conference Centre, adjacent to Westminster Abbey, served as the venue for this meeting. Themes for the meeting were Long-Term Outcomes of SCI, Putting Evidence into Practice, and Health Economics and Cost Management.

The talks

The annual Sir Ludwig Guttmann Lecture, named after the founder of the International Medical Society of Paraplegia, was given by one of Guttmann's most well-known and well-respected mentees – Dr Hans Frankel, OBE. Dr Frankel worked at the National Spinal Injuries Centre (NSIC) at Stoke Mandeville Hospital from 1957-2002 and is the developer of the Frankel Classification of Neurologic Injuries. This was later adapted by an international team and is now the gold standard of neurologic testing – the International Standards for the Neurologic Classification of Spinal Cord Injury. Dr Frankel, who still works as an Honorary Consultant at the NSIC, gave an eloquent and historically rich lecture titled 'The contribution of Stoke Mandeville Hospital to spinal cord injuries.'

A lecture on 'Global Disparities in Income and Care' was presented by Dr Hans Rosling from Sweden, in which he explained global trends in health and economics in a lively session, specifically highlighting and dispelling some long-held myths about the developing world. A professor of global health at the Karolinska Institute in Stockholm, Dr Rosling engaged the audience with solid statistics presented with informative visual effects.

In addition, this year marked the launch of 'The Global SCI Consumer Network' (www.globalsci.net) workshop, which will continue to be a feature of future ISCoS meetings. Led by Jane Horsewell, President of the European Spinal Cord Injury Federation, this workshop brought together a large international contingent of individuals living with SCI/D to discuss the ways in which they can work among themselves and with various stakeholders, including SCI healthcare professionals, the SCI research community and providers of healthcare and mobility aids. These partnerships are aimed at the goal of improving the quality of life of people with SCI all over the world.

Regular features of all ISCoS ASMs include a Prevention Symposium which, this year, focused specifically on road traffic accident prevention, prevention of unintentional injuries in teenagers, and approaches to preventing low velocity spinal cord injuries, such as those that occur during rugby matches.

Each year, ISCoS partners with the International Spinal Research Trust (ISRT) to bring in a guest speaker. This year, the ISRT lecture was delivered by Prof Michael Craggs, who spoke on 'Beyond the injury, before the cure: Neuroprostheses for function and health.'

Perhaps the most noteworthy activity during the meeting was the launch of www.elearnSCI.org: a global educational initiative of ISCoS

Launch of E-learn

Perhaps the most noteworthy activity during the meeting was the launch of www.elearnSCI.org: a global educational initiative of ISCoS. The launch was complimented by a series of workshops. The Asian Spinal Cord Network, Indian Spinal Injuries Centre, Livability Ireland and the New South Wales Lifetime Care and Support Scheme provided initial content support and website development, all with substantial financial support from Access to Health Care. As the project progressed, 332 experts from ISCoS and various affiliated societies in 36 countries worked together to develop the content through 28 sub-committees, each working on a particular sub-module. The basic content of each sub-module was developed from a 3-day workshop conducted after the 2010 ISCoS ASM titled "Comprehensive management of SCI". The presentations in this workshop were used as a draft by the sub-committees. The content of each sub-module developed by the sub-committees was ultimately reviewed and approved by the Education and Scientific Committees of ISCoS. The modules were then trialed at a workshop in New Delhi in April 2012 and feedback was taken from over 200 delegates. An Editorial Committee comprising 23 experts met simultaneously during the workshop to review and edit the sub-modules. Editorial work continued online thereafter. At www.elearnSCI.org, users can work through 7 learning modules that actively engage the users by providing information on the management of SCI for all clinical disciplines. The modules contain didactic presentations, activities, self-assessment questions and reference materials.

Conclusions

With 180 oral presentations and 251 posters to round out the full program, participants at the scientific meeting were treated to the latest information on optimal management of spinal cord SCI/D, ranging from basic science to rehabilitation, presented by an international team of the leading clinicians and scientists in the field. ◆

PREVIEW Modern Thinking in MS Management – Educational Meeting for Specialist Multiple Sclerosis Nurses, organised and funded by Teva UK Ltd

Course details: Friday 10th (evening) and Saturday 11th May 2013 ***Venue:*** Radisson Blu Portman Hotel, Portman Square, London W1, UK.

Teva UK Ltd would like to invite practising specialist Multiple Sclerosis nurses to the second 'Modern Thinking in MS Management' national educational meeting. This meeting aims to bring together around 100 nurses from across the UK providing a platform for discussion and review of the current and future management of MS.

With well established and emerging therapeutic options for MS treatment, this forum will allow delegates the opportunity to interact with a faculty of high calibre specialists. Throughout the day, delegates will be invited to review strategies through lively debate and informative discussion and to take part in interactive workshop sessions.

Event highlights include

- Developments and trends in MS diagnosis and management
- Presentation of ongoing research
- Interactive workshops and debates
- Hot topic sessions

To register your interest for this meeting:

Please email your name, job title, institutional affiliation and postal address to modernthinking@apothecom.com. There is no registration fee for the meeting. Please note that places for the meeting are limited and you will be contacted in due course if you have a place to confirm at the meeting.

We do hope that you are able to join us for this important review of current treatment and a look at the future of MS management. The second 'Modern Thinking in MS management' meeting promises to be an exciting, stimulating and informative event. CME accreditation is being sought.

Your personal details will only be used for the purposes of this meeting. Teva UK Limited or ApotheCom will not sell, share, or otherwise distribute your personal data to third parties outside Teva.

CPX/12/0003a – Date of preparation: November 2012

The use of Snoezelen in brain injury

Following the receipt of a donation of a significant amount of Snoezelen equipment, Mulberry House, one of the rehabilitation units owned by Titleworth Neuro, have developed a Sensory Room in order to provide sensory interventions for residents.

Snoezelen is described as a multi-sensory intervention providing sensory stimuli to an individual's primary senses of sight, hearing, touch, taste and smell. This is achieved using lighting effects, tactile apparatus, meditative music, and olfactory use of aromatherapy oils.

First used in the 1970's, it was introduced as an intervention for people with learning disabilities (LD), the rationale being intervention would reduce the effects of sensory deprivation. Expression of negative emotions, self-stimulating and disruptive behaviours are associated with a reduced ability in individuals with LD to explore and interact with their environment i.e. sensory deprivation. Therefore, such an environment offering fewer demands on their intellectual abilities whilst bringing to the fore residual sensorimotor abilities, would promote positive changes in emotion and behaviour. Research has highlighted positive outcomes in LD and dementia.

There has been significant debate over the last four decades as to whether Snoezelen is considered as a multisensory environment or as a therapeutic medium. Advocates of Snoezelen postulate Snoezelen is beneficial in promoting positive behavioural changes in LD and dementia. However reviews of the outcomes obtained from people with LD and dementia suggest caution.

A literature search around Snoezelen in Brain Injury highlighted very few studies. In 2006 a small reported study looked at use with children who had sustained a severe traumatic brain injury (TBI) and, in 2011, a study looked at the effect of Snoezelen on spectral patterns in adults with brain injury. Yet, to date, there appears to have been no empirical studies looking at its effect on social and emotional behaviour as well as adaptive and performance skills in adults with brain injuries.

In Mulberry House excellent results have already been achieved, in particular staff and family report positive social and behavioural changes in some residents receiving this intervention. Also, spouses have found benefit in being able to be physically close to their loved ones, as they lay on the floor together in the Sensory Room during the intervention. From the qualitative reports, this closeness appears to have led to lowering of caregiver burden and strain. Such an intervention has not been reported before in the research literature. As a result we are commencing some single case design studies in the hopes we can add to the paucity of research literature of the benefit of Snoezelen in Brain Injury, both for the individual with a brain injury and also for the caregiver.

Marketing Authorisation extension for Gadovist® 1.0 (gadobutrol) in the whole body

Bayer HealthCare's Radiology and Interventional division has completed the necessary UK variation procedure for Gadovist®1.0 (gadobutrol) for the diagnosis of diseases in the whole body with magnetic resonance imaging.

Based on the label extension, Gadovist 1.0 can be used in Europe for magnetic resonance imaging of the whole body (including brain and spine, head and neck region, lung, breast, abdomen, pelvis, kidney, extremities and musculoskeletal system as well as imaging of blood vessels). This also covers cardiac magnetic resonance imaging to diagnose coronary heart disease.

Gadovist 1.0 offers a quick (high resolution) magnetic resonance imaging procedure and is effective at providing detailed images of different organs without exposing the patient to ionising radiation.

"Early diagnosis is paramount for successful disease management and improved patient outcomes," said Nicole Farmer, Head of Bayer HealthCare Radiology and Interventional division in the UK. "This label extension strengthens Gadovist 1.0-enhanced magnetic resonance imaging as a radiation-free diagnostic modality to identify the early onset of diseases. Not only does it fulfil the promise of our Radiology and Interventional franchise to offer comprehensive solutions for our customers and their patients but, it will strengthen the Gadovist brand's market leading position."

New State-of-the-Art Ventilator Service at RHN

A new purpose-built ventilator service has opened at the Royal Hospital for Neuro-disability (RHN). The Jack Emerson Centre, named after the American inventor of artificial respiration John Haven 'Jack' Emerson, offers bespoke state-of-the-art services for people living on ventilatory support.

In a collaboration between RHN staff, Cowan Architects and existing patients, the service is designed to be homely whilst providing the optimal environment for facilitating rehabilitation, including colour-coding and clear signage to promote way-finding for patients with cognitive communication impairments. Specially adapted environmental controls mean that independence is maximised as the operation of windows, curtains, televisions and radios can be controlled by the patient.

Following more than a decade of care, providing specialist support to people living with a neurological injury or disease who are dependent on ventilatory support, the Jack Emerson Centre offers increased capacity of 16 beds, more single rooms and a greatly improved environment. The RHN's specialist ventilator team are able to care for complex patients requiring shorter stay neurological rehabilitation (including specialist wheelchairs and assistive technology) and residents requiring long term care.

At the Jack Emerson Centre, the multi-disciplinary team includes doctors, nursing staff, occupational therapists, speech and language therapists, physiotherapists, social workers, dieticians and assistive technologists. The RHN has a number of additional on-site services, from which patients can also benefit.

The new ventilator service has also been made possible by a generous donation of £500,000 by The Albert Reckitt Charitable Trust. The RHN is now taking referral enquiries, please contact: Carol Groves, Commissioning & Placement Liaison Manager. Tel: 020 8780 4513 Email: admissionsoffice@rhn.org.uk

UKABIF announce 2012 award winners

The winners of the Innovation and Inspiration awards were announced at the 4th UK Acquired Brain Injury Forum (UKABIF).

Gerry Roxburgh, a Senior Specialist Speech and Language Therapist, was presented with the Award for Innovation. The Award for Inspiration was presented to Louise Wilkinson, Training Manager at the Child Brain Injury Trust.

Gerry was presented with her award for implementing a fast track assessment and treatment pathway for the management of eating and drinking disorders in patients with acquired and traumatic brain injury.

Louise won the award because of her awareness raising work on behalf of young offenders affected by acquired brain injury, which includes setting up the Criminal Justice and Acquired Brain Injury Interest Group (CJABIIG). The UKABIF Award for Innovation and Inspiration are open to individuals or organisations that make a difference in ABI; be they a lawyer/law firm, clinician, care provider, social care worker, educational or voluntary sector provider or registered charity.

For further information, please contact: info@ukabif.org.uk

Launch of online National Brain Injury Service Directory

BrainNav
The National Brain Injury Service Directory

A new, online National Brain Injury Service Directory – ***BrainNav*** – is set to clear the road to rehabilitation for brain injury survivors across the country. BrainNav is a revolutionary tool that provides health professionals with a comprehensive database of rehabilitation centres, cognitive therapists, clinics, and other specialist facilities. The online portal has been designed to support those working in the field of acquired brain injury (ABI) and allows them to search relevant services either by what stage their patient is at on the rehabilitation pathway, or by their specific needs and wants.

BrainNav is a joint, not-for-profit venture between Thompsons Solicitors, UKABIF (UK Acquired Brain Injury Forum), and Optua UK; organisations that recognised the inadequacy of ABI information resources in the UK. Andrew Bateman, a leading NeuroRehab clinician and NHS business manager, says it will dramatically improve healthcare professionals' access to rehabilitation services.

"This is an important venture, and one that will become stronger the more services take part. This facility - which helps patients and clinicians navigate the complexities of different services - is a much-needed one, especially for the people who are living with the consequences of brain injury who otherwise might not even know a service exists. I have met, for example, many patients who did not know that services around the UK are available which can help overcome emotional, cognitive, vocational or behavioural problems. As a result they are at risk of being mismanaged. I have also met clinicians who are, by nature of their more generic roles, unaware of all the possible problems that follow brain injury and ways of managing them. I envisage that, in due course, BrainNav will help in the mission to overcome regional inequalities - a dream of all who work in this sector and a vital step for the UK as a whole."

An additional purpose of the site is to help ease the strain on the public purse; PCTs were tasked with setting up directories to map trauma services, but few had the resources to follow this through. Now that PCTs are being disbanded, BrainNav will support NHS commissioners in meeting their obligations by taking up this responsibility, thereby helping clinicians deliver the quality of service that is required of them.

Professor Mike Barnes, former chief executive for the NHS, founding member of the Northern Acquired Brain Injury Forum and Chair of UKABIF – which aims to raise awareness of acquired brain injury – commented, "The need for a directory of services for brain injury has been recognised for a long time. BrainNav has achieved this goal using local professionals to source information about the services available in their area. We think this resource – which has already proven valuable in designing a regional model of care - will become an essential tool for all working in the field."

For more information visit www.brainnav.info

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MS Frontiers brings together experts from across the world to speak on MS research.

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- **Professor Frauke Zipp**, Johannes Gutenberg University Main speaking on Inflammation and axonal damage: protective vs detrimental mechanisms
- **Professor John Saxton**, University of East Anglia presenting a Pragmatic Exercise Programme
- **David Ford**, Swansea University presenting The Achievements of the MS Register in the first three years and future plans
- **Professor Charles ffrench-Constant** speaking on the work of the Edinburgh Centre for translational research.
- **Ian McDonald** memorial lecture: Professor Hans Lassman.

CPD points applied for.

- Early bird conference fees are available until 8 February.
- Reduced conference fees and travel bursaries available for students.

Please visit our website: www.mssociety.org.uk/msfrontiers for more details or call 020 8438 0941.